

CHAPTER 8

EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS ASSOCIATED WITH AMBIENT PARTICULATE MATTER

Table of Contents

	<u>Page</u>
8. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS ASSOCIATED WITH AMBIENT PARTICULATE MATTER	8-1
8.1 INTRODUCTION	8-1
8.1.1 Approaches for Identifying, Presenting, and Assessing Studies	8-2
8.1.2 Types of Epidemiologic Studies Reviewed	8-5
8.1.3 Overview of Key Methodological Issues	8-8
8.1.3.1 Issues Related to Use of General Additive Models (GAM) in PM Epidemiology	8-8
8.1.3.2 Confounding and Effect Modification	8-9
8.1.4 Approach to Assessing Epidemiologic Evidence	8-15
8.2 MORTALITY EFFECTS ASSOCIATED WITH AIRBORNE PARTICULATE MATTER EXPOSURE	8-18
8.2.1 Introduction	8-18
8.2.2 Mortality Effects of Short-Term Particulate Matter Exposure	8-18
8.2.2.1 Summary of 1996 Particulate Matter Criteria Document Findings and Key Issues	8-18
8.2.2.2 Newly Available Information on Short-Term Mortality Effects	8-23
8.2.2.3 New Multi-City Studies	8-29
8.2.2.4 U.S. Single-City Studies	8-49
8.2.2.5 The Role of Particulate Matter Components	8-54
8.2.2.6 New Assessments of Cause-Specific Mortality	8-74
8.2.2.7 Salient Points Derived from Assessment of Studies of Short-Term Particulate Matter Exposure Effects on Mortality	8-80
8.2.3 Mortality Effects of Long-Term Exposure to Ambient Particulate Matter	8-83
8.2.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document	8-83
8.2.3.2 New Prospective Cohort Analyses of Mortality Related to Chronic Particulate Matter Exposures	8-87
8.2.3.3 Studies by Particulate Matter Size-Fraction and Composition	8-116
8.2.3.4 Recent PM-Mortality Intervention Studies	8-125
8.2.3.5 Salient Points Derived from Analyses of Chronic Particulate Matter Exposure Mortality Effects	8-130
8.3 MORBIDITY EFFECTS OF PARTICULATE MATTER EXPOSURE	8-134
8.3.1 Cardiovascular Morbidity Effects Associated with Acute Ambient Particulate Matter Exposure	8-134
8.3.1.1 Introduction	8-134
8.3.1.2 Summary of Key Findings on Cardiovascular Morbidity from the 1996 Particulate Matter Air Quality Criteria Document	8-135

Table of Contents
(cont'd)

		<u>Page</u>
	8.3.1.3 New Particulate Matter-Cardiovascular Morbidity Studies	8-135
	8.3.1.4 Issues in the Interpretation of Acute Cardiovascular Effects Studies	8-164
8.3.2	Effects of Short-Term Particulate Matter Exposure on the Incidence of Respiratory-Related Hospital Admissions and Medical Visits	8-165
	8.3.2.1 Introduction	8-165
	8.3.2.2 Summary of Key Respiratory Hospital Admissions Findings from the 1996 Particulate Matter Air Quality Criteria Document	8-166
	8.3.2.3 New Respiratory-Related Hospital Admissions Studies	8-167
	8.3.2.4 Key New Respiratory Medical Visits Studies	8-182
	8.3.2.5 Identification of Potential Susceptible Subpopulations	8-184
	8.3.2.6 Summary of Salient Findings on Acute Particulate Matter Exposure and Respiratory-Related Hospital Admissions and Medical Visits	8-186
8.3.3	Effects of Particulate Matter Exposure on Lung Function and Respiratory Symptoms	8-187
	8.3.3.1 Effects of Short-Term Particulate Matter Exposure on Lung Function and Respiratory Symptoms	8-188
	8.3.3.2 Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory Symptoms	8-205
8.3.4	Ambient PM Impacts on Fetal and/or Early Postnatal Development/Mortality	8-208
	8.3.4.1 PM Effects on Intrauterine Fetal Morbidity/Mortality ...	8-209
	8.3.4.2 PM Effects on Post-Neonatal Infant Mortality	8-212
	8.3.4.3 Summary of Salient Points on PM Effects on Fetal and/or Early Postnatal Development/Mortality	8-214
8.4	INTERPRETIVE ASSESSMENT OF THE EPIDEMIOLOGIC EVIDENCE	8-215
	8.4.1 Introduction	8-215
	8.4.2 GAM Issue and Reanalyses Studies	8-218
	8.4.2.1 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Mortality	8-219
	8.4.2.2 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Respiratory Hospital Admissions	8-223
	8.4.2.3 HEI Commentaries	8-227

Table of Contents
(cont'd)

		<u>Page</u>
8.4.3	Assessment of Confounding by Co-Pollutants and Adjustments for Meteorological Variables	8-229
8.4.3.1	Introduction to Assessment of Confounding by Co-Pollutants	8-229
8.4.3.2	Statistical Issues in the Use of Multi-Pollutant Models	8-231
8.4.3.3	Multipollutant Modeling Outcomes	8-236
8.4.3.4	Bioaerosols as Possible Confounders or Effect Modifiers in PM Epidemiologic Studies	8-245
8.4.3.5	Adjustments for Meteorological Variables	8-246
8.4.4	The Question of Lags	8-259
8.4.5	Measurement Error: Concepts and Consequences	8-271
8.4.5.1	Theoretical Framework for Assessment of Measurement Error	8-271
8.4.5.2	Measurement Error Issues Related to Divergence Between Monitors and to Monitoring Frequency	8-278
8.4.5.3	Measurement Error and the Assessment of Confounding by Co-Pollutants in Multi-Pollutant Models	8-288
8.4.6	Role of Particulate Matter Components	8-289
8.4.6.1	Thoracic Particle (PM ₁₀) Mortality/Morbidity Effects ...	8-290
8.4.6.2	Fine and Coarse Fraction Particle Effects on Mortality	8-291
8.4.6.3	Source-Oriented Analyses of PM and Mortality	8-295
8.4.6.4	Fine and Coarse Fraction Particle Effects on Morbidity	8-297
8.4.7	Concentration-Response Relationships for Ambient PM	8-306
8.4.8	The Question of Heterogeneity of Particulate Matter Effects Estimates	8-310
8.4.8.1	Evaluation of Heterogeneity in Time-Series Studies ...	8-311
8.4.8.2	Comparison of Spatial Relationships in the NMMAPS and Cohort Reanalyses Studies	8-314
8.4.9	Age-Related Differences in PM Effect Estimates	8-315
8.4.10	Implications of Airborne Particle Mortality Effects	8-316
8.4.10.1	Short-Term Exposure and Mortality Displacement	8-316
8.4.10.2	Life-Shortening Estimates Based on Prospective Cohort Study Results	8-322
8.4.10.3	Potential Effects of Infant Mortality on Life-Shortening Estimates	8-322
8.5	SUMMARY OF KEY FINDINGS AND CONCLUSIONS DERIVED FROM PARTICULATE MATTER EPIDEMIOLOGY STUDIES	8-323
	REFERENCES	8-336

List of Tables

<u>Number</u>		<u>Page</u>
8-1	Recent U.S. and Canadian Time-Series Studies of PM-Related Daily Mortality	8-24
8-2	Synopsis of Short-Term Mortality Studies that Examined Relative Importance of PM _{2.5} and PM _{10-2.5}	8-56
8-3	Newly Available Studies of Mortality Relationships to PM Chemical Components	8-67
8-4	Summary of Source-Oriented Evaluations of PM Components in Recent Studies	8-71
8-5	Comparison of Six Cities and American Cancer Society Study Findings from Original Investigators and Health Effects Institute Reanalysis	8-89
8-6	Relative Risk of All-Cause Mortality for Selected Indices of Exposure to Fine Particulate Matter (per 18.6 µg/m ³) Based on Multivariate Poisson Regression Analysis, by Age Group, for Harvard Six City Study Data	8-93
8-7	Summary of Results from the Extended ACS Study	8-95
8-8	Relative Risk of Mortality from all Nonexternal Causes, by Sex and Air Pollutant, for an Alternative Covariate Model in the ASHMOG Study	8-102
8-9	Relative Risk of Mortality from Cardiopulmonary Causes, by Sex and Air Pollutant, for an Alternative Covariate Model in the ASHMOG Study	8-103
8-10	Relative Risk of Mortality from Lung Cancer by Air Pollutant and by Gender for an Alternative Covariate Model	8-104
8-11	Particulate Matter Effects on Mortality by Exposure and Mortality Period with Ecological Variables for the Veterans Cohort Study Expressed as Excess Mortality	8-109
8-12	Comparison of Excess Relative Risks of Long-Term Mortality in the Harvard Six Cities, ACS, AHSMOG, and VA Studies	8-112
8-13	Comparison of Estimated Relative Risks for All-Cause Mortality in Six U.S. Cities Associated with the Reported Inter-City Range of Concentrations of Various Particulate Matter Metrics	8-117
8-14	Comparison of Reported SO ₄ ⁻ and PM _{2.5} Relative Risks for Various Mortality Causes in the American Cancer Society Study	8-118

List of Tables
(cont'd)

<u>Number</u>		<u>Page</u>
8-15	Comparison of Total Mortality Relative Risk Estimates and T-Statistics for Particulate Matter Components in Three Prospective Cohort Studies	8-119
8-16	Comparison of Cardiopulmonary Mortality Relative Risk Estimates and T-Statistics for Particulate Matter Components in Three Prospective Cohort Studies	8-120
8-17	Percent Attributable Risk of Mortality (from Lipfert and Morris, 2000) and Risk Estimates Calculated Per 10 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$	8-123
8-18	Summary of Studies of PM_{10} , $\text{PM}_{10-2.5}$, or $\text{PM}_{2.5}$ Effects on Total CVD Hospital Admissions and Emergency Visits	8-137
8-19	Summary of United States PM_{10} Respiratory-Related Hospital Admission Studies	8-168
8-20	Percent Increase in Hospital Admissions per 10- $\mu\text{g}/\text{m}^3$ Increase in PM_{10} in 14 U.S. Cities (original and reanalyzed results)	8-170
8-21	Summary of United States $\text{PM}_{2.5}$ Respiratory-Related Hospital Admission Studies	8-174
8-22	Summary of United States $\text{PM}_{10-2.5}$ Respiratory-Related Hospital Admission Studies	8-175
8-23	Intercomparison of Detroit Pneumonia Hospital Admission Relative Risks (\pm 95% CI below) of PM Indices (per 5 th -to-95 th percentile pollutant increment) for Various Model Specifications	8-176
8-24	Summary of United States PM_{10} , $\text{PM}_{2.5}$, and $\text{PM}_{10-2.5}$ Asthma Medical Visit Studies	8-182
8-25	Summary of Quantitative PFT Changes in Asthmatics per 50 $\mu\text{g}/\text{m}^3$ PM_{10} Increment	8-190
8-26	Summary of PFT Changes in Asthmatics per 25 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ Increment	8-191
8-27	Summary of Asthma PM_{10} Cough Studies	8-194
8-28	Summary of Asthma PM_{10} Phlegm Studies	8-195
8-29	Summary of Asthma PM_{10} Lower Respiratory Illness Studies	8-195

List of Tables
(cont'd)

<u>Number</u>		<u>Page</u>
8-30	Summary of Asthma PM ₁₀ Bronchodilator Use Studies	8-196
8-31	Summary of Asthma PM _{2.5} Respiratory Symptom Studies	8-199
8-32	Summary of Non-Asthma PM ₁₀ PFT Studies	8-200
8-33	Summary of Non-Asthma PM ₁₀ Respiratory Symptom Studies	8-201
8-34	Summary of Non-Asthma PM _{2.5} Respiratory Outcome Studies	8-203
8-35	Summary of Non-Asthma Coarse Fraction Studies of Respiratory Endpoints	8-204
8-36	PM ₁₀ Excess Risk Estimates from Reanalysis Studies for Total Non-Accidental Mortality per 50 µg/m ³ Increase in PM ₁₀	8-220
8-37	Comparison of Maximum Single Day Lag Effect Estimates for PM _{2.5} , PM _{2.5-10} , and PM ₁₀ for Seattle Asthma hospital Admissions Based on Original GAM Analyses using Default Convergence Criteria Versus Reanalyses using GAM with more Stringent Convergence Criteria and GLM	8-225
8-38	Comparison of Los Angeles COPD Hospital Admissions Maximum Single Day Lag Effect Estimates for PM _{2.5} and PM ₁₀ from the Original GAM Analyses Using Default Convergence Criteria Versus Effect Estimates Derived from Reanalyses using more Stringent Convergence Criteria and for Models Smoothed with more Degrees of Freedom	8-226
8-39	Effects of Different Models for Weather and Time Trends on Mortality in Utah Valley Study	8-251
8-40	Summary Statistics Showing Mean Site-Pair Pearson Correlation Coefficients, Annual Mean PM _{2.5} Concentrations (µg/m ³), the Range in Annual Mean Concentrations (µg/m ³), Mean of 90 th Percentile Differences in Concentrations Between All Site Pairs (µg/m ³), and Coefficients of Divergence for MSAs Meeting Selection Criteria given in Appendix 3A	8-281
8-41	Summary of Relative Homogeneity / Heterogeneity Characteristics for MSAs Given in Table 8-40	8-282
8-42	Summary of Past Ecologic and Case-Control Epidemiologic Studies of Outdoor Air and Lung Cancer	8-303

List of Figures

<u>Number</u>		<u>Page</u>
8-1	Estimated excess risks for PM mortality (1 day lag) for the 88 largest U.S. cities as shown in the revised NMMAPS analysis	8-32
8-2	Map of the United States showing the 88 cities (the 20 cities are circled) and the seven U.S. regions considered in the NMMAPS geographic analyses	8-33
8-3	Percent excess mortality risk (lagged 0, 1, or 2 days) estimated in the NMMAPS 90-City Study to be associated with 10- $\mu\text{g}/\text{m}^3$ increases in PM_{10} concentrations in cities aggregated within U.S. regions shown in Figure 8-4	8-34
8-4	Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1 with and without control for other pollutants, for the 90 cities	8-35
8-5	Percent excess risks estimated per 25 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ or $\text{PM}_{10-2.5}$ from new studies that evaluated both $\text{PM}_{2.5}$ and $\text{PM}_{10-2.5}$, based on single pollutant (PM only) models	8-58
8-6	Excess risks estimated per 5 $\mu\text{g}/\text{m}^3$ increase in sulfate, based on the studies in which both $\text{PM}_{2.5}$ and $\text{PM}_{10-2.5}$ data were available	8-70
8-7	Natural logarithm of relative risk for total and cause-specific mortality per 10 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ (approximately the excess relative risk as a fraction), with smoothed concentration-response functions	8-95
8-8	Relative risk of total and cause-specific mortality per 10 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$, derived for means of 1979-1983 $\text{PM}_{2.5}$ data for various cities, using alternative statistical models	8-96
8-9	Relative risk of total and cause-specific mortality for particle metrics and gaseous pollutants over different averaging periods (years 1979-2000 in parentheses)	8-97
8-10	Acuate cardiovascular hospitalizations and particulate matter exposure excess risk estimates derived from U.S. PM_{10} studies based on single-pollutant models from GAM strict convergence criteria reanalyses (2003 studies) or alternative (non-GAM) original analyses	8-153
8-11	Percent change in hospital admission rates and 95% CIs for an IQR increase in pollutants from single-pollutant models for asthma	8-178
8-12	Maximum excess risk of respiratory-related hospital admissions and visits per 50 $\mu\text{g}/\text{m}^3$ PM_{10} increment in studies of U.S. cities based on single-pollutant models	8-187

List of Figures
(cont'd)

<u>Number</u>	<u>Page</u>
8-13	8-192
8-14	8-197
8-15	8-221
8-16	8-238
8-17	8-239
8-18	8-240
8-19	8-241
8-20	8-255
8-21	8-256
8-22	8-260

List of Figures
(cont'd)

<u>Number</u>		<u>Page</u>
8-23	Marginal posterior distribution for effects of PM ₁₀ on all cause mortality at lag 0, 1, and 2 for the 90 cities	8-261
8-24	Excess risk estimates for associations between various health outcomes and PM ₁₀ (50 µg/m ³ increment) from different studies conducted in Cook County, IL	8-263
8-25	Excess risk estimates for associations between various health outcomes and PM ₁₀ (50 µg/m ³ increment) from studies conducted in Los Angeles County, CA	8-264
8-26	Excess risk estimates for associations between various health outcomes and PM ₁₀ (50 µg/m ³ increment) from studies conducted in Pittsburgh, PA	8-265
8-27	Excess risk estimates for associations between various health outcomes and PM ₁₀ (50 µg/m ³ increment) from studies conducted in Detroit, MI	8-266
8-28	Excess risk estimates for associations between various health outcomes and PM ₁₀ (50 µg/m ³ increment) from studies conducted in Seattle or King County, WA	8-267
8-29	Relative risk estimates and 95% confidence intervals for total mortality per 100 µg/m ³ increase in PM ₁₀ , adjusting for ozone, temperature, seasonal cycles, day of week, and linear trend for 1985-1990 in Cook County, IL	8-285
8-30	Concentration-response curves for PM ₁₀ mortality relationships in 20 largest U.S. cities (1987-1994), for total (TOTAL) mortality, cardiovascular and respiratory (CVDRESP) mortality, and other causes (Other) mortality	8-309
8-31	Posterior probabilities of thresholds for each cause-specific mortality and for mean PM ₁₀ , 20 largest U.S. cities, 1987-1994	8-309

8. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS ASSOCIATED WITH AMBIENT PARTICULATE MATTER

8.1 INTRODUCTION

Epidemiologic studies linking community ambient PM concentrations to health effects played an important role in the 1996 PM Air Quality Criteria Document (PM AQCD; U.S. Environmental Protection Agency, 1996a). Many of those studies reported that measurable excesses in pulmonary function decrements, respiratory symptoms, hospital and emergency department admissions, and mortality in human populations are associated with ambient levels of various indicators of PM exposure, including most notably PM_{10} as well as other indicators of fine-fraction particles (e.g., $PM_{2.5}$). Numerous more recent epidemiologic studies discussed in this chapter have also evaluated ambient PM relationships to morbidity and mortality, using various PM indicators, with greater emphasis on $PM_{2.5}$ and other indicators of fine-fraction particles and, to much less extent, $PM_{10-2.5}$.

The epidemiology studies assessed here are best considered in combination with information on ambient PM concentrations presented in Chapter 3, studies of human PM exposure (Chapter 5), and PM dosimetry and toxicology (Chapters 6 and 7). The epidemiology studies contribute important information on associations between health effects and exposures of human populations to “real-world” ambient PM and also help to identify susceptible subgroups and associated risk factors. Chapter 9 provides an interpretive synthesis of information drawn from this and other chapters.

This chapter opens with brief discussion of approaches used for identifying, presenting, and assessing studies; general features of the different types of epidemiologic studies assessed and key methodological issues that arise in analyzing and interpreting study results; and salient aspects of epidemiological evidence that are considered in their critical assessment. Section 8.2 and 8.3 present and assess epidemiologic studies of PM effects on mortality and morbidity, respectively. Section 8.4 then provides an interpretive assessment of the overall PM epidemiologic data base reviewed in Sections 8.2 and 8.3 in relation to various key issues and

1 aspects of the evidence. The overall key findings and conclusions for this chapter are then
2 summarized in Section 8.5.

3 4 **8.1.1 Approaches for Identifying, Presenting, and Assessing Studies**

5 Numerous PM epidemiologic papers have been published since completion of the 1996 PM
6 AQCD, and U.S. EPA (NCEA-RTP) has used a systematic approach to identifying pertinent
7 epidemiologic studies for consideration in this chapter. In general, an ongoing continuous
8 Medline search has been employed in conjunction with other strategies to identify PM literature
9 pertinent to developing criteria for PM NAAQS. The literature search method is similar to those
10 used by others (e.g., Basu and Samet, 1999). A publication base was first established by using
11 Medline and other data bases and a set of key words (particles, air pollution, mortality,
12 morbidity, cause of death, PM, etc.) in a search strategy which was later reexamined and
13 modified to enhance identification of pertinent published papers. Since literature searches
14 encounter not a static but a changing, growing stream of information, searches are not run just
15 for the most recent calendar quarter but are backdated in an attempt to capture references added
16 to that time period since the previous search was conducted. Papers were also added to the
17 publication base by EPA staff (a) through review of advance tables of contents of thirty journals
18 in which relevant papers are published and (b) by requesting scientists known to be active in the
19 field to identify papers recently accepted for publication.

20 While the above search regime builds a certain degree of redundancy into the system,
21 which ensures good coverage of the relevant literature and lessens the possibility of important
22 papers being missed, additional approaches have augmented traditional search methods. First, at
23 the beginning of the process, a Federal Register Notice was issued, requesting information and
24 published papers from the public at large. Next, non-EPA chapter authors are expert in this
25 field; and, while EPA provides them with the outcomes of searches, the authors are also charged
26 with identifying the literature on their own. Finally, a keystone in the literature identification
27 process is that, at several review stages in the process, both the public and CASAC offer
28 comments which may identify additional potentially relevant publications; and the combination
29 of these approaches is believed to produce a comprehensive collection of pertinent studies
30 appropriate for review and assessment here. This collection of studies includes pertinent new
31 studies accepted for publication through April, 2002, as well as some published since then (if

1 such recent new papers provide particularly important information helpful in addressing key
2 scientific issues).

3 Those epidemiologic studies that relate measures of ambient air PM to human health
4 outcomes are assessed in this chapter, whereas studies of (typically much higher) occupational
5 exposures are generally not considered here. Criteria used for selecting literature for the present
6 assessment include mainly whether a given study includes information on: (1) ambient PM
7 indices (e.g., PM₁₀, PM_{2.5}, PM_{10-2.5}, etc.) of short- and long-term exposures as a key element;
8 (2) analyses of health effects of specific PM chemical or physical constituents (e.g., metals,
9 sulfates, nitrates or ultrafine particles, etc.) or indicators related to PM sources (e.g., motor
10 vehicle emissions, combustion-related particles, earth crustal particles); (3) evaluation of health
11 endpoints and populations not previously extensively researched; (4) multiple pollutant analyses
12 and other approaches to addressing issues related to potential confounding of effects and effects
13 modification; and/or (5) studies addressing important methodological issues (e.g., lag structure,
14 model specification, thresholds, mortality displacement) related to PM exposure effects.

15 In assessing the evidence, key points derived from the 1996 PM AQCD assessment of the
16 available information are first concisely highlighted. Then, key new information is presented in
17 succinct text summary tables for important new studies that have become available since the
18 1996 PM AQCD. More detailed information on various methods and results for these and other
19 newly available studies are summarized in tabular form in Appendices 8A and 8B. These
20 appendix tables are generally organized to include: information about (1) study location and
21 ambient PM levels; (2) description of study methods employed; (3) results and comments; and
22 (4) quantitative outcomes for PM measures. In the main body of the chapter, greater emphasis is
23 placed on integrating and interpreting findings from the array of evidence provided by the more
24 important newer studies than on detailed evaluation of each of the numerous newly available
25 studies. In presenting quantitative effects estimates in tables in the chapter and appendices,
26 study results were normalized to standard PM increments, as was done in the 1996 PM AQCD.
27 In selecting PM increments for use in this review, more recent air quality data were considered,
28 resulting in no changes to the increments previously used for short-term exposure studies, but
29 smaller increments than those used in the 1996 PM AQCD for long-term exposure studies. More
30 specifically, the pollutant concentration increments used here to report relative risks (RR's) or
31 odds ratios for various health effects are as follow for short term (≤ 24 h) exposure studies:

1 50 $\mu\text{g}/\text{m}^3$ for PM_{10} ; 25 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ and $\text{PM}_{10-2.5}$; 155 nmoles/m^3 (15 $\mu\text{g}/\text{m}^3$ for SO_4^{-2} ; and
2 75 nmoles/m^3 (3.6 $\mu\text{g}/\text{m}^3$, if as H_2SO_4) for H^+ . For long-term exposure studies, the increments
3 used here are 20 $\mu\text{g}/\text{m}^3$ for PM_{10} and 10 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ and $\text{PM}_{10-2.5}$.

4 Particular emphasis is focused in the text on those studies and analyses thought to provide
5 information most directly applicable for U.S. standard setting purposes. Specifically, North
6 American studies conducted in the U.S. or Canada are generally accorded more text discussion
7 than those from other geographic regions; and analyses using gravimetric (mass) measurements
8 are generally accorded more text attention than those using non-gravimetric ambient PM
9 measures, e.g., black smoke (BS) or coefficient of haze (CoH). In addition, emphasis is placed
10 on text discussion of (a) new multi-city studies that employ standardized methodological
11 analyses for evaluating PM effects across several or numerous cities and often provide overall
12 effects estimates based on combined analyses of information pooled across multiple cities;
13 (b) other studies providing quantitative PM effect-size estimates for populations of interest; and
14 (c) studies that consider PM as a component of a complex mixture of air pollutants, including in
15 particular the gaseous criteria pollutants (O_3 , CO, NO_2 , SO_2).

16 In assessing the relative scientific quality of epidemiologic studies reviewed here and to
17 assist in interpreting their findings, the following considerations were taken into account, as was
18 done in the 1996 PM AQCD:

- 19 (1) To what extent are the aerometric data/exposure metrics used of adequate quality and
sufficiently representative to serve as credible exposure indicators, well reflecting
geographic or temporal differences in study population pollutant exposures in the range(s)
of pollutant concentrations evaluated?
- 20 (2) Were the study populations well defined and adequately selected so as to allow for
meaningful comparisons between study groups or meaningful temporal analyses of health
effects results?
- 21 (3) Were the health endpoint measurements meaningful and reliable, including clear
definition of diagnostic criteria utilized and consistency in obtaining dependent variable
measurements?
- 22 (4) Were the statistical analyses used appropriate and properly performed and interpreted,
including accurate data handling and transfer during analyses?
- 23 (5) Were likely important covariates (e.g., potential confounders or effect modifiers)
adequately controlled for or taken into account in the study design and statistical
analyses?

1 (6) Were the reported findings internally consistent, biologically plausible, and coherent in
2 terms of consistency with other known facts?

3 These guidelines provide benchmarks for judging the relative quality of various studies and
4 for focusing on the highest quality studies in assessing the body of epidemiologic evidence.
5 Detailed critical analysis of all epidemiologic studies on PM health effects, especially in relation
6 to all of the above questions, is beyond the scope of this document. Of most importance for
7 present purposes are those studies which provide useful qualitative or quantitative information
8 on exposure-effect or exposure-response relationships for health effects associated with ambient
9 air levels of PM currently likely to be encountered in the United States.

10 **8.1.2 Types of Epidemiologic Studies Reviewed**

11 Definitions of various types of epidemiologic studies assessed here were provided in the
12 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and are briefly summarized
13 here. Briefly, the epidemiologic studies are divided into *mortality* studies and *morbidity* studies.
14 *Mortality* studies evaluating PM effects on total (non-accidental) mortality and cause-specific
15 mortality provide the most unambiguous evidence related to a clearly adverse endpoint. The
16 *morbidity* studies further evaluate PM effects on a wide range of health endpoints, such as:
17 cardiovascular and respiratory-related hospital admissions, medical visits, reports of respiratory
18 symptoms, self-medication in asthmatics, changes in pulmonary function; changes in
19 cardiovascular physiology/functions, and blood coagulation; low birthweight infants, etc.

20 The epidemiologic strategies most commonly used in PM health studies are of four types:
21 (1) *ecologic studies*; (2) *time-series semi-ecologic studies*; (3) *prospective cohort studies*; and
22 (4) *case-control and crossover studies*. In addition, time-series analyses or other analytic
23 approaches have been used in so-called intervention studies or “natural experiments.” All of
24 these are observational studies rather than experimental studies. In general, the exposure of the
25 participant is not directly observed; and the concentration of airborne particles and other air
26 pollutants at one or more stationary air monitors is used as a proxy for individual exposure to
27 ambient air pollution.

28 In *ecologic studies*, the responses are at a community level (for example, annual mortality
29 rates), as are the exposure indices (for example, annual average PM concentrations) and
30 covariates (for example, the percentage of the population greater than 65 years of age).

1 No individual data are used in the analysis; therefore, the relationship between health effect and
2 exposure calculated across different communities may not reflect individual-level associations
3 between health outcome and exposure. The use of proxy measures for individual exposure and
4 covariates or effect modifiers may also bias the results, and within-city or within-unit
5 confounding may be overlooked.

6 *Time-series studies* are more informative because they allow the study of associations
7 between *changes* in a health outcome and *changes* in exposure indicators preceding or
8 simultaneous with the outcome. The temporal relationship supports a conclusion of a causal
9 relation, even when both the outcome (for example, the number of non-accidental deaths in a
10 city during a day) and the exposure (for example, daily air pollution concentration) are
11 community indices.

12 *Prospective cohort studies* use data from individuals, including health status (where
13 available), individual exposure (not usually available), and individual covariates or risk factors,
14 observed over time. The participants in a prospective cohort study are ideally recruited (using a
15 simple or stratified random sample) so as to represent a target population for which individual or
16 community exposure of the participants is known before and during the interval up to the time
17 the health endpoint occurs. The use of individual-level data is believed to give prospective
18 cohort studies greater inferential strength than other epidemiologic strategies. The use of
19 community-level or estimated exposure data, if necessary, may weaken this advantage, as it does
20 in time-series studies.

21 *Case-control studies* are retrospective studies in that exposure is determined after the
22 health endpoint occurs (as is common in occupational health studies). As Rothman and
23 Greenland (1998) describe it, “Case-control studies are best understood by defining a source
24 population, which represents a hypothetical study population in which a cohort study might have
25 been conducted . . . In a case-control study, the cases are identified and their exposure status is
26 determined just as in a cohort study . . . [and] a control group of study subjects is sampled from
27 the entire source population that gives rise to the cases . . . the cardinal requirement of control
28 selection is that the controls must be sampled independently of their exposure status.”

29 The *case-crossover design* is suited to the study of a transient effect of an intermittent
30 exposure on the subsequent risk of an acute-onset health effect thought to occur shortly after
31 exposure. In the original development of the method, effect estimates were based on within-

1 subject comparisons of exposures associated with incident disease events with exposures at
2 times before the occurrence of disease, using matched case-control methods or methods for
3 stratified follow-up studies with sparse data within each stratum. The principle of the analysis is
4 that the exposures of cases just before the event are compared with the distribution of exposure
5 estimated from some separate time period, the former being assumed to be representative of the
6 distribution of exposures for those individuals while they were at risk for the outcome of interest.

7 When measurements of exposure or potential effect modifiers are available on an
8 individual level, it is possible to incorporate this information into a case-crossover study (unlike
9 a time-series analysis). A disadvantage of the case-crossover design, however, is the potential
10 for bias due to time trends in the exposure time-series. Because case-crossover comparisons are
11 made between different points in time, the case-crossover analysis implicitly depends on an
12 assumption that the exposure distribution is stable over time (stationary). If the exposure time-
13 series is non-stationary and case exposures are compared with referent exposures systematically
14 selected from a different period in time, a bias may be introduced into estimates of the measure
15 of association for the exposure and disease. These biases are particularly important when
16 examining the small relative risks that appear to exist for PM health outcomes.

17 *Intervention studies* (often involving features of time-series or other above types of
18 analyses) provide another useful approach for evaluating possible causal relationships between
19 ambient air pollution variables (e.g., PM) and health effects in human populations. In such
20 studies, the effects of active interventions that result in reductions of one or another or several air
21 pollutants (constituting essentially a “found experiment”) are evaluated in relation to changes in
22 mortality or morbidity outcomes among population groups affected by the reduction in air
23 pollution exposure. To date, only a few epidemiological studies have evaluated the
24 consequences of interventions that allow for comparison of PM-health outcome associations
25 before and after certain relatively discrete events resulting in notable changes in concentrations
26 of ambient PM and/or one or more other copollutants. Given that the etiology of health
27 outcomes related to PM or other air pollutants are typically also affected by other risk factors, it
28 is important in intervention studies not only to measure air pollution exposure and health status
29 before and after air pollution reductions but also to identify and evaluate potential effects of
30 other risk factors before and after the air pollution reductions. The proposition that intervention
31 studies can provide strong support for causal inferences was emphasized by Hill (1965), as

1 discussed further in Section 8.1.4. In his classic monograph (The Environment and Disease:
2 Association or Causation?), Hill (1965) addressed the topic of preventive action and its
3 consequences under Aspect 8, stating:

4
5 “Experiment: Occasionally it is possible to appeal to experimental, or semi-experimental,
6 evidence. For example, because of an observed association some preventive action is taken.
7 Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed,
8 persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the
9 strongest support for the causation hypothesis may be revealed.”

11 **8.1.3 Overview of Key Methodological Issues**

12 There are a number of methodological issues that arise in analyzing and interpreting
13 epidemiologic studies that are more fully discussed in Section 8.4 below. The following brief
14 overview of two such key issues is intended to orient the reader to these issues so as to provide
15 context for the presentation and assessment of the epidemiologic studies on mortality and
16 morbidity effects in Sections 8.2 and 8.3.

18 **8.1.3.1 Issues Related to Use of General Additive Models (GAM) in PM Epidemiology**

19 In the spring of 2002, the original investigators of an important newly available multi-city
20 study (the National Mortality and Morbidity Air Pollution Study; NMMAPS) cosponsored by the
21 Health Effects Institute (HEI) reported that use of the default convergence criteria setting used in
22 the GAM routine of certain widely-used statistical software (Splus) could result in biased
23 estimates of air pollution effects when at least two non-parametric smoothers are included in the
24 model (Health Effects Institute letter, May 2002). The NMMAPS investigators also reported
25 (Dominici et al., 2002), as determined through simulation, that such bias was larger when the
26 size of risk estimate was smaller and when the correlation between the PM and the covariates
27 (i.e., smooth terms for temporal trend and weather) was higher. While the NMMAPS
28 investigators reported that reanalysis of the 90 cities air pollution-mortality data (using stringent
29 convergence criteria) did not qualitatively change their original findings (i.e., the positive
30 association between PM₁₀ and mortality; lack of confounding by gaseous pollutants; regional
31 heterogeneity of PM, etc.), the reduction in the PM₁₀ risk estimate was apparently not negligible
32 (dropping, upon reanalysis, from 2.1% to 1.4% excess deaths per 50 µg/m³ increase in PM₁₀)

1 with GAM using strict convergence criteria and a further reduction to 1.1% using a general
2 linear model (GLM).

3 Issues surrounding potential bias in PM risk estimates from time-series studies using GAM
4 analyses and default convergence criteria were raised by EPA and discussed in July 2002 at the
5 CASAC review of the Third External Review Draft of this PM AQCD. In keeping with a follow
6 up consultation with CASAC in August 2002, EPA encouraged investigators for a number of
7 important published studies to reanalyze their data by using GAM with more stringent
8 convergence criteria, as well as by using Generalized Linear Model (GLM) analyses with
9 parametric smoothers that approximated the original GAM model. EPA, working closely with
10 HEI, also arranged for (a) the resulting reanalyses first to be discussed at an EPA-sponsored
11 Workshop on GAM-Related Statistical Issues in PM Epidemiology held in November 2002;
12 (b) then for any revamping of the preliminary analyses in light of the workshop discussions;
13 before (c) submittal by the investigators of short communications describing the reanalyses
14 approaches and results to EPA and HEI for peer-review by a special panel assembled by HEI;
15 and (d) the publication of the short communications on the reanalyses, along with commentary
16 by the HEI peer-review panel, in an HEI Special Report (2003a). Some of the short
17 communications included in the HEI Special Report (2003a) included discussion of reanalyses
18 of data from more than one original publication because the same data were used to examine
19 different issues of PM-mortality associations (e.g., concentration/response function, harvesting,
20 etc.). In total, reanalyses were reported for more than 35 originally published studies.

21 22 **8.1.3.2 Confounding and Effect Modification**

23 A pervasive problem in the analysis of epidemiologic data, no matter what design or
24 strategy, is the unique attribution of a given health outcome to a nominal causal agent (e.g., to
25 airborne particles in this document). The health outcomes attributed to particles are not specific;
26 and, as such, they may also be attributable to high or low temperatures, influenza and other
27 diseases, and/or exposure to other air pollutants. Some of these co-variables may be
28 *confounders* and others *effect modifiers*. The distinctions are important.

29 *Confounding* is “. . . a confusion of effects. Specifically, the apparent effect of the
30 exposure of interest is distorted because the effect of an extraneous factor is mistaken for or

1 mixed with the actual exposure effect (which may be null)” (Rothman and Greenland, 1998,
2 p. 120).

3 Causal events occur prior to some initial bodily response. A causal association may
4 usually be defined as an association in which alteration in the frequency or quality of one
5 category (e.g., level of PM in ambient air) is followed by a change in the other (e.g, increased
6 mortality). The concept of the chain mechanism is that many variables may be related to a
7 single effect through a direct-indirect mechanism. In fact, events are not dependent on single
8 causes. A given chain of causation may represent only a fraction of a web (MacMahon and
9 Pugh, 1970). A causal pathway refers to the network of relationships among factors in one or
10 more causal chains in which the members of the population are exposed to causal agents that
11 produce the observed health effect. The primary cause may be mediated by secondary causes
12 (possibly proximal to exposure) and may have either a direct effect on exposure or an indirect
13 effect through the secondary causes, or both, as illustrated below. A non-causal pathway may
14 involve factors not actually associated or correlated with population exposure to the pollutant of
15 interest, but are coincidentally (spuriously) also associated with health outcome.

16 The determination of whether a potential confounder is an actual confounder may be
17 elucidated from biological or physical knowledge about its exposure and health effects. Patterns
18 of association in epidemiology may be helpful in suggesting where to look for this knowledge,
19 but do not replace it. In evaluating effects of ambient PM exposures, gaseous criteria pollutants
20 (CO, NO₂, SO₂, O₃) are candidates for confounders because all of these are known to cause at
21 least some types of adverse health effects that are also associated with particles (CO more often
22 being associated with cardiovascular effects and the other gases with respiratory effects,
23 including symptoms and hospital admissions). In addition, the gaseous criteria pollutants may
24 be associated with particles for several reasons, including common sources and correlated
25 changes in response to wind and weather. Lastly, SO₂ and NO₂ may be precursors to sulfate and
26 nitrate components of ambient particle mixes, while NO₂ contributes also to the formation of
27 organic aerosols during photochemical transformations.

28 The problem of disentangling the effects of other pollutants is especially difficult when
29 high correlation exists between ambient PM measurements and one or more of them.
30 For example, both CO and particles are emitted from motor vehicles. These and other fossil fuel
31 combustion sources also often emit SO₂ and/or NO, which converts to NO₂ upon emission.

1 SO₂ and NO₂, in turn, are precursors to sulfates and nitrates as two widely common contributors
2 to secondary ambient PM aerosol components. Ozone (O₃) also contributes to ambient PM via
3 (a) hydroxyl radicals which oxidize SO₂ to H₂SO₄ and NO₂ to HNO₃ and (b) participation in
4 chemical reactions underlying the formation of ultrafine particles from naturally occurring
5 terpenes, isoprene, and other hydrocarbons. A common source, such as combustion of gasoline
6 in motor vehicles emitting CO, NO₂, and primary particles (and often resulting in high
7 correlations), may play an important role in confounding among these pollutants, as do weather
8 and seasonal effects. Even though O₃ is a secondary pollutant also associated with emission of
9 NO₂, it is often more variably correlated with ambient PM concentrations, depending on
10 location, season, etc. Levels of SO₂ in the western U.S. are often quite low, so that secondary
11 formation of particle sulfates plays a much smaller role there, resulting in usually relatively little
12 confounding of SO₂ with PM mass concentration in the West. On the other hand, in the
13 industrial Midwest and northeastern states, SO₂ and sulfate levels during many of the
14 epidemiology studies were relatively high and highly correlated with fine particle mass
15 concentrations. If the correlation between PM and SO₂ is not too high, it may be possible to
16 estimate some part of their independent effects, which depend on the assumption of
17 independence under the particular model analyzed. If there is a causal pathway, then it may be
18 difficult to determine whether the observed relationship of exposure to health effect is a direct
19 effect of the exposure (to sulfate or fine PM as an example), an indirect effect mediated by the
20 potential confounder (e.g., exposure to SO₂), or a mixture of these. Consideration of additional
21 (e.g., exposure, dosimetric, toxicologic) information beyond narrow reliance on observed
22 correlations among the PM measure(s), other pollutants, and health outcome indicators is often
23 useful in helping to elucidate the plausibility of PM or other pollutants being causally related to
24 statistically-associated health effects.

25 Some variables fall into the category of *effect modifiers*. “Effect-measure modification
26 differs from confounding in several ways. The main difference is that, whereas confounding is a
27 bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure
28 modification is a property of the effect under study . . . In epidemiologic analysis one tries to
29 eliminate confounding but one tries to detect and estimate effect-measure modification”
30 (Rothman and Greenland, 1998, p. 254). Examples of effect modifiers in some of the studies
31 evaluated in this chapter include environmental variables (such as temperature or humidity),

1 individual risk factors (such as education, cigarette smoking status, age in a prospective cohort
2 study), and community factors (such as percent of population > 65 years old). It is often possible
3 to stratify the relationship between health outcome and exposure by one or more of these risk
4 factor variables. Effect modifiers may be encountered (a) within single-city time-series studies
5 or (b) across cities in a two-stage hierarchical model or meta-analysis.

6 Potential confounding is usually much more difficult to identify; and several statistical
7 methods are available, none of them being completely satisfactory. The usual methods include
8 the following:

9 *Within a city:*

- 10 (A) Fit both a single-pollutant model and then several multi-pollutant models, and
determine if including the co-pollutants greatly changes the estimated effect;
- 11 (B) If the PM index and its co-pollutants are nearly multi-collinear, carry out a factor
analysis, and determine which gaseous pollutants are most closely associated with
PM in one or more common factors;

12 *Using data from several cities:*

- 13 (C) Proceed as in Method A and pool the effect size estimates across cities for single-
and multi-pollutant models;
- 14 (D) Carry out a hierarchical regression of the PM effects versus the mean co-pollutant
concentration and determine if there is a relationship; and
- 15 (E) First carry out a regression of PM versus the co-pollutant concentration within each
city and the regression coefficient of PM versus health effect for each city. Then fit
a second-stage model regressing the PM-health effect coefficient versus the
PM-co-pollutant coefficient, concluding that the co-pollutant is a confounder if there
is an association at the second stage.

16 Each of the above methods (A through E) are subject to one or more disadvantages. The
17 multi-pollutant regression coefficients in method A, for example, may be unstable and have
18 greatly inflated standard errors, weakening their interpretation. In method B, the factors may be
19 sensitive to the choice of co-pollutants and the analysis method, and may be difficult to relate to
20 real-world entities. In method C, as with any meta-analysis, it is necessary to consider the
21 heterogeneity of the within-city effects before pooling them. Some large multi-city studies have

1 revealed unexpected heterogeneity, not fully explained at present. While method D is sometimes
2 interpreted as showing confounding if the regression coefficient is non-zero, this is an argument
3 for effect modification, not confounding. Method E is sensitive to the assumptions being made;
4 for instance, if PM is the primary cause and the co-pollutant the secondary cause, then the two-
5 stage approach may be valid. However, if the model is mis-specified and there are two or more
6 secondary causes, some of which may not be identified, then the method may give misleading
7 results.

8 Given the wide array of considerations and possibilities discussed above, it is extremely
9 important to recognize that there is no single “correct” approach to modeling ambient PM-health
10 effects associations that will thereby provide the “right” answer with regard to precise
11 quantification of PM effect sizes for different health outcomes. Rather, it is clear that emphasis
12 needs to be placed here on (a) looking for convergence of evidence derived from various
13 acceptable analyses of PM effects on a particular type of health endpoint (e.g., total mortality,
14 respiratory hospital admissions, etc.); (b) according more weight to those well-conducted
15 analyses having greater power to detect effects and yielding narrower confidence intervals; and
16 (c) evaluating the coherence of findings across pertinent health endpoints and effect sizes for
17 different health outcomes.

18 The issue of what PM effect sizes should be the main focus of presentation and discussion
19 in ensuing text – i.e., those derived from single-pollutant models including only PM or effect
20 sizes derived from multi-pollutant models that include one or more other copollutants along with
21 the PM indicator(s) – is an important one. Again, there is not necessarily any single “correct”
22 answer on this point. Implicit in arguments asserting that multi-pollutant model results must be
23 reported and accorded equal or more weight than single-pollutant model PM results is
24 a functional construct that has generally been used in epidemiologic modeling of health effects
25 of air pollution, a functional construct that considers the various air pollutants mainly
26 independently of one another in terms of their health effects, which may not necessarily be the
27 case. This may be causing either over- or under-estimation of PM health effects, depending on
28 the modeling choices made by the investigator and the study situation. For example, ozone and
29 PM_{2.5} can share some similar oxidative formation and effect pathways in exerting adverse health
30 effects on the lung, yet are often modeled as independent pollutants or are placed in models
31 simultaneously, even though they may sometimes have high correlations over space and time

1 and in their health effects on the human body. Another complication is that other pollutants can
2 be derived from like sources and may serve less as a measure of direct effects than as a marker
3 of pollution from a specific source. As an example noted earlier, SO₂ and PM_{2.5} are often
4 predominantly derived from the same sources in a locale (e.g., coal-fired power plants in the
5 mid-western U.S.), so that putting these two pollutants in a model simultaneously may cause a
6 diminution of the PM_{2.5} coefficient that may be misleading.

7 One approach that has been taken is to look at pollutant interactions (either multiplicative
8 or additive, depending on the model assumed), but until we understand (and appropriately
9 model) the biological mechanisms, such models are assumptions on the part of the researcher.
10 Present modeling practices represent the best methods now available and provide useful
11 assessments of PM health effects. However, ultimately, more biological-plausibility based
12 models are needed that more accurately model pollutant interactions and allow more
13 biologically-based interpretations of modeling results.

14 Until more is known about multiple pollutant interactions, it is important to avoid over-
15 interpreting model results regarding the relative sizes and significance of specific pollutant
16 effects, but instead to use biological plausibility in interpreting model results. For example, as
17 discussed later, Krewski et al (2000) found significant associations for both PM and SO₂ in their
18 reanalysis for the Health Effects Institute of the ACS data set published by Pope et al. (1995).
19 Regarding these pollutant associations, they concluded that: “The absence of a plausible
20 toxicological mechanism by which sulfur dioxide could lead to increased mortality further
21 suggests that it might be acting as a marker for other mortality-associated pollutants.” (Note:
22 Annual mean SO₂ averaged < 10 ppb across ca. 125 cities in the ACS data set.) Rather than
23 letting statistical significance be the sole determinant of the “most important” pollutant, the
24 authors utilized biological plausibility to conclude which association was most likely driving the
25 pollution-health effects association in question. Such biological plausibility/mechanistic
26 considerations need to be taken into account more broadly in the future in modeling and
27 assessing possible pollutant interactions in contributing to health effects attributed to PM. In the
28 meantime, the results from single-pollutant models of PM effects are emphasized here, as being
29 those most likely reflecting overall effects exerted by ambient PM either acting alone and/or in
30 combination with other ambient air pollutants.

31

1 **8.1.4 Approach to Assessing Epidemiologic Evidence**

2 The critical assessment of epidemiologic evidence presented in this chapter is conceptually
3 based upon consideration of salient aspects of the evidence of associations so as to reach
4 fundamental judgments as to the likely causal significance of the observed associations. In so
5 doing, it is appropriate to draw from those aspects initially presented in Hill's classic monograph
6 (Hill, 1965) and widely used by the scientific community in conducting such evidence-based
7 reviews. A number of these aspects are judged to be particularly salient in evaluating the body
8 of evidence available in this review, including the aspects described by Hill as strength,
9 experiment, consistency, plausibility, and coherence. Other aspects identified by Hill, including
10 temporality and biological gradient, are also relevant and considered here (e.g., in characterizing
11 lag structures and concentration-response relationships), but are more directly addressed in the
12 design and analyses of the individual epidemiologic studies included in this assessment.
13 (As noted below, Hill's remaining aspects of specificity and analogy are not considered to be
14 particularly salient in this assessment.) As discussed below, these salient aspects are inter-
15 related and considered throughout the evaluation of the epidemiologic evidence presented in this
16 chapter, and are more generally reflected in the integrative synthesis presented in Chapter 9.

17 In the following sections, the general evaluation of the strength of the epidemiological
18 evidence reflects consideration not only of the magnitude of reported PM effects estimates and
19 their statistical significance, but also of the precision of the effects estimates and the robustness
20 of the effects associations. Consideration of the robustness of the associations takes into account
21 a number of factors, including in particular the impact of alternative models and model
22 specifications and potential confounding by co-pollutants, as well issues related to the
23 consequences of measurement error. Another aspect that is related to the strength of the
24 evidence in this assessment is the availability of evidence from "found experiments", or
25 so-called intervention studies, which have the potential to provide particularly strong support for
26 making causal inferences.

27 Consideration of the consistency of the effects associations, as discussed in the following
28 sections, involves looking across the results of multi- and single-city studies conducted by
29 different investigators in different places and times. In this assessment of ambient PM-health
30 effects associations, it is important to consider the aspect of consistency in the context of
31 understanding that ambient PM in different locations and at different times originates from

1 different sources, such that its composition and physical characteristics can vary greatly across
2 studies using the same indicator for size-differentiated PM mass. Other relevant factors are also
3 known to exhibit much variation across studies, including, for example, the presence and levels
4 of co-pollutants, the relationships between central measures of PM and exposure-related factors,
5 relevant demographic factors related to sensitive subpopulations, and climatic and
6 meteorological conditions. Thus, in this case, consideration of consistency, and the related
7 heterogeneity of effects issue, is appropriately understood as an evaluation of the similarity or
8 general concordance of results, rather than an expectation of finding quantitative results within a
9 very narrow range. Particular weight is given in this assessment, consistent with Hill's views, to
10 the presence of "similar results reached in quite different ways, e.g., prospectively and
11 retrospectively" (Hill, 1965). On the other hand, in light of complexities in the chemical and
12 physical properties of the mix of ambient PM and its spatial and temporal variations, Hill's
13 specificity of effects and analogy aspects are not viewed as being particularly salient here.

14 Looking beyond the epidemiological evidence, evaluation of the biological plausibility of
15 the PM-health effect associations observed in epidemiologic studies reflects consideration of
16 both exposure-related factors and dosimetric/toxicologic evidence relevant to identification of
17 potential biological mechanisms. Similarly, consideration of the coherence of health effects
18 associations reported in the epidemiologic literature reflects broad consideration of information
19 pertaining to the nature of the various respiratory- and cardiac-related mortality and morbidity
20 effects and biological markers evaluated in toxicologic and epidemiologic studies. These
21 broader aspects of the assessment are only touched upon in this chapter but are more fully
22 integrated in the discussion presented in Chapter 9.

23 In identifying these aspects as being particularly salient in this assessment, it is also
24 important to recognize that no one aspect is either necessary or sufficient for drawing inferences
25 of causality. As Hill (1965) emphasized:

26
27 None of my nine viewpoints can bring indisputable evidence for or against the cause-and-
28 effect hypothesis and none can be required as a sine qua non. What they can do, with greater
29 or less strength, is to help us to make up our minds on the fundamental question — is there
30 any other way of explaining the set of facts before us, is there any other answer equally, or
31 more, likely than cause and effect?

1 Thus, while these aspects frame considerations weighed in assessing the epidemiologic evidence,
2 they do not lend themselves to being considered in terms of simple formulas or hard-and-fast
3 rules of evidence leading to answers about causality (Hill, 1965). One, for example, cannot
4 simply count up the numbers of studies reporting statistically significant results for the various
5 PM indicator and health endpoints evaluated in this assessment and reach credible conclusions
6 about the relative strength of the evidence and the likelihood of causality. Rather, these
7 important considerations are taken into account and discussed throughout this assessment with
8 the goal of producing an objective appraisal of the evidence, informed by peer and public
9 comment and advice, including weighing of alternative views on controversial issues, leading to
10 conclusions and inferences that reflect the best judgements of the scientists engaged in this
11 review.
12
13

8.2 MORTALITY EFFECTS ASSOCIATED WITH AIRBORNE PARTICULATE MATTER EXPOSURE

8.2.1 Introduction

The relationship of PM and other air pollutants to excess mortality has been studied extensively and represents an important issue addressed in previous PM criteria assessments (U.S. Environmental Protection Agency, 1986, 1996a). Recent findings are evaluated here mainly for the two most important epidemiology designs by which mortality is studied: time-series mortality studies (Section 8.2.2) and prospective cohort studies (Section 8.2.3). The time-series studies mostly assess acute responses to short-term PM exposure, although some recent work suggests that time-series data sets can also be useful in evaluating responses to exposures over a longer time scale. Time-series studies use community-level air pollution measurements to index exposure and community-level response (i.e., the total number of deaths each day by age and/or by cause of death). Prospective cohort studies usefully complement time-series studies; they typically evaluate human health effects of long-term PM exposures indexed by community-level measurements, using individual health records with survival lifetimes or hazard rates adjusted for individual risk factors.

8.2.2 Mortality Effects of Short-Term Particulate Matter Exposure

8.2.2.1 Summary of 1996 Particulate Matter Criteria Document Findings and Key Issues

The time-series mortality studies reviewed in the 1996 and other past PM AQCD's provided much evidence that ambient PM air pollution is associated with increases in daily mortality. The 1996 PM AQCD assessed about 35 PM-mortality time-series studies published between 1988 and 1996. Of these studies, only five studies used GAM with default convergence criteria. Recent reanalyses (Schwartz, 2003a; Klemm and Mason, 2003) using GAM with stringent convergence criteria and other non-GAM approaches for one of these five studies, i.e., the Harvard Six cities time-series analysis (the only multi-city study among the five studies), essentially confirmed the original findings. Thus, information provided in the 1996 PM AQCD can be summarized without major concern with regard to the GAM convergence issue. Information derived from those studies was generally consistent with the hypothesis that PM is a causal agent in contributing to short-term air pollution exposure effects on mortality.

1 The PM₁₀ relative risk estimates derived from short-term PM₁₀ exposure studies reviewed
2 in the 1996 PM AQCD suggested that an increase of 50 µg/m³ in the 24-h average of PM₁₀ is
3 most clearly associated with an increased risk of premature total non-accidental mortality (total
4 deaths minus those from accident/injury) on the order of relative risk (RR) = 1.025 to 1.05 in the
5 general population or, in other words, 2.5 to 5.0% excess deaths per 50 µg/m³ PM₁₀ increase.
6 Higher relative risks were indicated for the elderly and for those with pre-existing
7 cardiopulmonary conditions. Also, based on the Schwartz et al. (1996a) analysis of Harvard Six
8 City data (as later confirmed in the reanalysis by Schwartz [2003a] and Klemm and Mason
9 [2003]), the 1996 PM AQCD found the RR (combined across the six cities) for excess total
10 mortality in relation to 24-h fine particle concentrations to be about 3% excess risk per 25 µg/m³
11 PM_{2.5} increment.

12 While numerous studies reported PM-mortality associations, important issues needed to be
13 addressed in interpreting their findings. The 1996 PM AQCD evaluated in considerable detail
14 several critical issues, including: (1) seasonal confounding and effect modification;
15 (2) confounding by weather; (3) confounding by co-pollutants; (4) measurement error;
16 (5) functional form and threshold; (6) harvesting and life shortening; and (7) the role of PM
17 components. As important issues related to model specification became further clarified, more
18 studies began to address the most critical issues, some of which were at least partially resolved,
19 whereas others required still further investigation. The next several paragraphs summarize the
20 status of these issues at the time of the 1996 PM AQCD publication.

21 One of the most important components in time-series model specification is adjustment for
22 seasonal cycles and other longer-term temporal trends; not adequately adjusting for them could
23 result in biased RRs. Modern smoothing methods allow efficient fits of temporal trends and
24 reduce such statistical problems (but may also introduce some additional issues as discussed in
25 later sections). Most recent studies controlled for seasonal and other temporal trends, and it was
26 considered unlikely that inadequate control for such trends seriously biased estimated PM
27 coefficients. Effect modification by season was examined in several studies. Season-specific
28 analyses are often not feasible in small-sized studies (due to marginally significant PM effect
29 size), but some studies (e.g., Samet et al., 1996; Moolgavkar and Luebeck, 1996) suggested that
30 estimated PM coefficients varied from season to season. It was not fully resolved, however,

1 whether these results represent real seasonal effect modifications or are due to varying extent of
2 correlation between PM and co-pollutants or weather variables by season.

3 While most available studies included control for weather variables, some reported
4 sensitivity of PM coefficients to weather model specification, leading some investigators to
5 speculate that inadequate weather model specifications may still have erroneously ascribed
6 residual weather effects to PM. Two PM studies (Samet et al., 1996; Pope and Kalkstein, 1996)
7 involved collaboration with a meteorologist and utilized more elaborate weather modeling, e.g.,
8 use of synoptic weather categories. These studies found that estimated PM effects were
9 essentially unaffected by the synoptic weather variables and also indicated that the synoptic
10 weather model did not provide better model fits in predicting mortality when compared to other
11 weather model specifications used in previous PM-mortality studies. Thus, these results
12 suggested at the time that the reported PM effects were not explained by more sophisticated
13 synoptic weather models. However, some analyses in both of these studies used GAM,
14 presumably with default convergence criteria, and therefore need to be interpreted with caution,
15 especially in light of their not having been reanalyzed with more stringent GAM convergence
16 criteria and/or by GLM or other types of modeling specifications. Also, reanalyses of other
17 studies originally using GAM with default convergence criteria have contributed to reopening of
18 renewed debate on weather model specification issues, as discussed later.

19 Many earlier PM studies considered at least one co-pollutant in the mortality regression,
20 and some also examined several co-pollutants. In most cases, when PM indices were significant
21 in single pollutant models, addition of a co-pollutant diminished the PM effect size somewhat,
22 but did not eliminate the PM associations. When multiple pollutant models were performed by
23 season, the PM coefficients became less stable, again, possibly due to PM's varying correlation
24 with co-pollutants among season and/or smaller sample sizes. However, in many studies, PM
25 indices showed the highest significance (versus gaseous co-pollutants) in single and multiple
26 pollutant models. Thus, it was concluded that PM-mortality associations were not seriously
27 distorted by co-pollutants, but interpretation of the relative significance of each pollutant in
28 mortality regression as relative causal strength was difficult because of limited quantitative
29 information on relative exposure measurement/characterization errors among air pollutants.

30 Measurement error can influence the size and significance of air pollution coefficients
31 in time-series regression analyses and is also important in assessing confounding among

1 multiple pollutants, as varying the extent of such error among the pollutants could also influence
2 the corresponding relative statistical significance. The 1996 PM AQCD discussed several types
3 of such exposure measurement errors, including site-to-site variability and site-to-person
4 variability — errors thought to bias the estimated PM coefficients downward in most cases.
5 However, there was not sufficient quantitative information available to estimate such bias.

6 The 1996 PM AQCD also reviewed evidence for threshold and various other functional
7 forms of short-term PM mortality associations. Several studies appeared to suggest that
8 associations were seen monotonically below the existing PM standards. It was considered
9 difficult, however, to statistically test for a threshold from available data because of low data
10 density at lower ambient PM concentrations, potential influence of measurement error, and
11 adjustments for other covariates. Thus, the use of relative risk (rate ratio) derived from the
12 log-linear Poisson models was considered adequate and appropriate, although threshold-related
13 issues remained to be more fully resolved.

14 The extent of prematurity of death (i.e., mortality displacement or “harvesting”) in
15 observed PM-mortality associations has important public-health-policy implications. At the
16 time of the 1996 PM AQCD review, only a few studies had investigated this issue. While one of
17 the studies suggested that the extent of such prematurity might be only a few days, this may not
18 be generalizable because this estimate was obtained for identifiable PM episodes. There was not
19 sufficient evidence to suggest the extent of prematurity for non-episodic periods from which
20 most of the recent PM relative risks were derived. The 1996 PM AQCD concluded:

21
22 In summary, most available epidemiologic evidence suggests that increased mortality results
23 from both short-term and long-term ambient PM exposure. Limitations of available evidence
24 prevent quantification of years of life lost to such mortality in the population.
25 Life shortening, lag time, and latent period of PM-mediated mortality are almost certainly
26 distributed over long time periods, although these temporal distributions have not been
27 characterized. (p. 13-45)

28
29 Only a limited number of PM-mortality studies analyzed fine particles and chemically
30 specific components of PM. The Harvard Six Cities Study (Schwartz et al., 1996a) analyzed
31 size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15-2.5}$) and PM chemical components (sulfates and
32 H^+). The results suggested that, among the components of ambient PM, $PM_{2.5}$ was most

1 significantly associated with mortality. Because the original study was conducted using GAM
2 with default convergence criteria, the data were recently reanalyzed (a) by Schwartz (2003a),
3 who provided reanalyzed PM_{2.5} results for each of the six cities and a combined risk estimate
4 across the six, but only excess risk estimates for individual cities for PM_{10/15-2.5}, and
5 (b) by Klemm and Mason (2003), who analyzed PM_{2.5}, PM_{10/15}, PM_{10/15-2.5}, and sulfate. Although
6 the excess risk estimates were somewhat lower than those in the original study, both Schwartz
7 (2003) and Klemm and Mason's reanalyses confirmed the original findings with regard to the
8 relative importance of fine versus coarse particles. While H⁺ was not significantly associated
9 with mortality in the original and an earlier analysis (Dockery et al., 1992), the smaller sample
10 size for H⁺ than for other PM components made a direct comparison difficult. The 1996 PM
11 AQCD also noted that mortality associations with BS or CoH reported in earlier studies in
12 Europe and the U.S. during the 1950s to 1970s most likely reflected contributions from fine
13 particles, as those PM indices had low 50% cut-points ($\leq 4.5 \mu\text{m}$). Furthermore, certain
14 respiratory morbidity studies showed associations between hospital admissions/visits with
15 components of PM in the fine particle range. Thus, the U.S. EPA 1996 PM AQCD concluded
16 that there was adequate evidence to suggest that fine particles play especially important roles in
17 observed PM mortality effects.

18 Overall, then, the status of key issues as addressed in the 1996 PM AQCD can be
19 summarized as follows: (1) it was thought that the observed PM effects were unlikely to be
20 seriously biased by inadequate statistical modeling (e.g., control for seasonality); (2) it also
21 appeared unlikely that the observed PM effects were seriously confounded by weather (at least
22 by synoptic weather models); (3) the observed PM effects appeared to some extent to be
23 confounded or modified by co-pollutants, and such extent may vary from season to season;
24 (4) determining the extent of confounding and effect modification by co-pollutants would likely
25 require knowledge of relative exposure measurement characterization error among pollutants
26 (there was not sufficient information on this); (5) no compelling evidence substantiating a
27 threshold for PM-mortality associations was available (statistically identifying a threshold from
28 existing data was also considered difficult, if not impossible); (6) some limited evidence for
29 harvesting, a few days of life-shortening, was reported for episodic periods (no study was yet
30 conducted to evaluate possible harvesting in non-episodic U.S. data); (7) only a relatively limited
31 number of studies suggested a causal role of fine particles in PM-mortality associations, but in

1 the light of historical data, biological plausibility, and the results from morbidity studies, a
2 greater role for fine particles than coarse particles was suggested in the 1996 PM AQCD as being
3 likely. The 1996 PM AQCD concluded:

4
5 The evidence for PM-related effects from epidemiologic studies is fairly strong, with most
6 studies showing increases in mortality, hospital admissions, respiratory symptoms, and
7 pulmonary function decrements associated with several PM indices. These epidemiologic
8 findings cannot be wholly attributed to inappropriate or incorrect statistical methods,
9 mis-specification of concentration-effect models, biases in study design or implementation,
10 measurement of errors in health endpoint, pollution exposure, weather, or other variables, nor
11 confounding of PM effects with effects of other factors. While the results of the
12 epidemiologic studies should be interpreted cautiously, they nonetheless provide ample
13 reason to be concerned that there are detectable human health effects attributable to PM at
14 levels below the current NAAQS. (p. 13-92)

16 **8.2.2.2 Newly Available Information on Short-Term Mortality Effects**

17 Since the 1996 PM AQCD, numerous new studies have examined short-term associations
18 between PM indices and mortality. Of these studies (more than 80), nearly 70% used GAM
19 (presumably with default convergence criteria). In the summer of 2002, U.S. EPA asked the
20 original investigators of some of these studies to reanalyze the data using GAM with more
21 stringent convergence criteria and GLM with parametric smoothers such as natural splines.
22 Because the extent of possible bias caused by the default criteria setting in the GAM models is
23 difficult to estimate for individual studies, the discussion here will focus only on those studies
24 that did not use GAM Poisson models and those studies that have reanalyzed data using more
25 stringent convergence criteria and/or alternative approaches. Newly available U.S. and Canadian
26 studies on relationships between short-term PM exposure and daily mortality that meet these
27 criteria are summarized in Table 8-1. More detailed summaries of all the short-term exposure
28 PM-mortality studies, including other geographic areas (e.g., Europe, Asia, etc) are described in
29 Appendix Table 8A-1. These include the studies that apparently used GAM with default
30 convergence criteria, and those studies are noted as such. Information on study location and
31 period, levels of PM, health outcomes, methods, results, and reported risk estimates and lags is
32 provided in Table 8A-1. In addition to these summary tables, discussion in the text below

**TABLE 8-1. RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF
PM-RELATED DAILY MORTALITY***

Reference	Type**	Location(s)/period	Pollutants	Comments
<i>Multi- City Mortality Studies in the U.S. and Canada</i>				
<i>PM₁₀ studies using NMMAPS data</i>				
Samet et al. (2000a, b, c); Dominici et al. (2000a, b); Dominici et al. (2003a)	A	88 cities in the 48 contiguous U.S. states plus AK and HI, 1987-1994; mainly 20 largest.	PM ₁₀ , O ₃ , CO, NO ₂ , SO ₂	Numerous models; range of PM ₁₀ values depending on city, region, co- pollutants. Pooled estimates for 88 cities, individual estimates for 20 largest with co- pollutant models.
Daniels et al. (2000); Dominici et al. (2003a)	A	20 cities in the 48 contiguous U.S. states, 1987-1994	PM ₁₀ only	Smooth non- parametric spline model for concentration- response functions. Average response curve nearly linear.
Dominici et al. (2002) Dominici et al. (2003a)	A	88 cities in the 48 contiguous U.S. states, 1987-1994.	PM ₁₀ only	Smooth non-parametric spline models for PM ₁₀ concentration-response functions. Average response curves are nearly linear in the industrial Midwest, Northeast regions, and overall, but non- linear (usually concave) in the other regions. Possible thresholds in Southeast.
<i>Studies using every day PM₁₀ data</i>				
Schwartz (2000a); Schwartz (2003b)	A	Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Detroit, MI; Birmingham, AL; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993.	PM ₁₀ , O ₃ , CO, NO ₂ , SO ₂	Pooled PM ₁₀ (0 and 1 day lag average) mortality estimates for the ten cities were presented. Confounding and/or effect modification was examined for season, co-pollutants, in- versus out-of-hospital deaths.
Schwartz (2000b); Schwartz (2003b).	A	Same ten U.S. cities as in (Schwartz, 2000a)	PM ₁₀ only.	Several pooled estimates across 10 cities for single day, moving average, and distributed lags.
Braga et al. (2001a); Schwartz (2003b)	A	Same ten U.S. cities as in (Schwartz, 2000a)	PM ₁₀ only.	Pooled estimates across cities evaluated for deaths due to pneumonia, COPD, CVD, and MI using distributed lags models.

**TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES
OF PM-RELATED DAILY MORTALITY***

Reference	Type**	Location(s)/period	Pollutants	Comments
<i>Multi-City Mortality Studies in the U.S. and Canada (cont'd)</i>				
<i>Other multi-city studies</i>				
Schwartz (1996a) Schwartz (2003a)		Six cities in Harvard Six City Study, with Harvard air monitors and community daily mortality time-series: Boston (Watertown), MA, Harriman- Kingston, TN; Portage-Madison, WI; St. Louis, MO; Steubenville, OH; Topeka, KS.	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , sulfates	City-specific associations and combined effect estimates recalculated for mortality due to all causes (total), ischemic heart disease, COPD, and pneumonia. Associations with PM _{2.5} recalculated by several techniques, including natural splines, penalized splines, etc. Associations with PM _{10-2.5} only recalculated by use of penalized splines for individual cities.
Klemm et al., (2000); Klemm and Mason (2003)	A	Same six cities as Harvard Six City Study (Schwartz et al., 1996a), 1979-1988.	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , sulfates	Replicated Schwartz et al. (1996a) and did additional sensitivity analyses.
Laden et al.. (2000); Schwartz (2003a)	A	Same six cities as Harvard Six City Study (Schwartz et al., 1996a), 1979-1988.	Chemically speciated PM _{2.5} and factors aligned with putative sources for each city identified by specific chemical elements as tracers.	Different coefficients in different cities, depending on source type, chemical indicators, and principal factor method. The motor vehicle combustion component was significant, other factors occasionally, but not the crustal element component.
Tsai et al. (1999, 2000)	B	Camden, Elizabeth, and Newark, NJ, 1981-1983.	PM _{2.5} , PM ₁₅ , sulfates, trace elements.	Significant effects of PM _{2.5} , PM ₁₀ , and sulfates in Newark, Camden at most lags, but not Elizabeth. Source-specific factors (oil burning, automobiles) were also associated with mortality.
Burnett et al. (2000); Burnett and Goldberg (2003)	A	Eight Canadian cities: Montreal, Ottawa, Toronto, Windsor, Calgary, Edmonton, Winnipeg, Vancouver, 1986-1996.	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , sulfates, O ₃ , CO, NO ₂ , SO ₂ .	The results of reanalysis indicate no clear difference between PM _{2.5} and PM _{10-2.5} in associations with mortality.

**TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES
OF PM-RELATED DAILY MORTALITY***

Reference	Type**	Location(s)/period	Pollutants	Comments
<i>Single-City Mortality Studies in the U.S. and Canada</i>				
Moolgavkar (2000a); Moolgavkar (2003).	A	Three large U.S. counties (cities): Cook Co., IL; Los Angeles Co., CA; Maricopa Co., (Phoenix), AZ, 1987-1995 in the original analysis. In the reanalysis, Maricopa Co. was not analyzed.	PM ₁₀ in all three; PM _{2.5} in Los Angeles. O ₃ , CO, NO ₂ , and SO ₂ in some models. In the GAM reanalysis, O ₃ was not analyzed.	Gaseous pollutants were at least as significantly associated as PM indices. In particular, CO was the best single index of air pollution association with mortality in Los Angeles.
Ostro et al. (1999a, 2000); Ostro et al. (2003)	A	Coachella Valley (Palm Springs), CA, 1989-1998.	PM ₁₀ in earlier study, PM _{2.5} and PM _{10-2.5} in later study; O ₃ , CO, NO ₂ . Reanalysis reported PM risk estimates only.	PM ₁₀ (~65% of which was coarse particles) and PM _{10-2.5} (missing values predicted from PM ₁₀) were associated with cardiovascular mortality. PM _{2.5} was available for shorter period.
Fairley (1999); Fairley (2003)	A	Santa Clara County (San Jose), CA, 1989-1996.	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , sulfates, nitrates, O ₃ , CO, NO ₂ .	All significant in one- pollutant models, nitrates significant in all multi- pollutant models, PM _{2.5} significant except with particle nitrates.
Schwartz et al. (1999)	B	Spokane, WA, 1989-1995.	PM ₁₀ only.	No association between mortality and high PM ₁₀ concentrations on dust storm days with high concentrations of crustal particles.
Lippmann et al. (2000); Ito (2003)	A	Detroit, MI, 1985-1990; 1992-1994 (separate analysis for two periods).	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , sulfates, acidity, TSP, O ₃ , CO, NO ₂ , SO ₂	PM mass indices were more strongly associated with mortality than sulfate or acidity. The extent of association with health outcomes was similar for PM _{2.5} and PM _{10-2.5} .
Chock et al. (2000)	B	Pittsburgh, PA, 1989-1991.	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , O ₃ , CO, NO ₂ , SO ₂	Fine and coarse particle data on about ½ of days with PM ₁₀ . Data split into ages < 75 and 75+, and seasons. Significant effects for PM ₁₀ but not for other size fractions, likely because of smaller sample size.

**TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES
OF PM-RELATED DAILY MORTALITY***

Reference	Type**	Location(s)/period	Pollutants	Comments
<i>Single-City Mortality Studies in the U.S. and Canada (cont'd)</i>				
Klemm and Mason (2000)	B	Atlanta, GA, 1998-1999 (one year).	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , oxygenated hydrocarbons (HC), elemental carbon (EC), organic carbon (OC), sulfates, acidity	No significant effects likely due to short time-series (ca. one year).
Schwartz (2000c); Schwartz (2003a)	A	Boston, MA, 1979-1986.	PM _{2.5}	Larger effects with longer-term PM _{2.5} and mortality moving averages (span 15 to 60 days) for total and cause-specific mortality.
Lipfert et al. (2000a)	B	Philadelphia, PA- Camden, NJ seven- county area, 1995-1997.	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , sulfates, acidity, metals, O ₃ , CO, NO ₂ , SO ₂	Exploration of mortality in different areas relative to air monitor location. Peak O ₃ very significant, greatly reduced PM coefficients.
Mar et al. (2000); Mar et a. (2003)	A	Phoenix, AZ, near the EPA platform monitor, 1995-1997.	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , PM _{2.5} metals, EC, OC, O ₃ , CO, NO ₂ , SO ₂ , and source- apportioned factor scores.	Only cardiovascular mortality was reanalyzed; it was significantly associated with PM ₁₀ , PM _{2.5} , PM _{10-2.5} , EC, OC, factors associated with motor vehicle, vegetative-burning, and regional sulfate.
Clyde et al. (2000)	B	Phoenix, AZ, 1995-1997.	PM _{2.5} and PM _{10-2.5}	Effect on elderly mortality consistently higher for PM _{10-2.5} among 25 "best" models. Estimates combined using Bayesian model averaging.
Smith et al. (2000)	B	Phoenix, AZ (within city and within county), 1995-1997.	PM _{2.5} and PM _{10-2.5}	Significant linear relationship with PM _{10-2.5} , not PM _{2.5} Piecewise linear models with possible PM _{2.5} threshold for elderly mortality at 20-25 µg/m ³ .

**TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES
OF PM-RELATED DAILY MORTALITY***

Reference	Type**	Location(s)/period	Pollutants	Comments
<i>Single-City Mortality Studies in the U.S. and Canada (cont'd)</i>				
Ostro (1995)	B	San Bernardino and Riverside Counties, CA, 1980- 1986.	PM _{2.5} estimated from visual range, O ₃	Positive, significant PM _{2.5} association only in summer.
Murray and Nelson (2000)	B	Philadelphia, PA, 1973- 1990	TSP only	Kalman filtering used to estimate hazard function in a state space model. Both TSP and the product of TSP and average temperature are significant, but not together. Includes estimate of risk population.
Goldberg et al. (2000, 2001a,b,c,d; 2003); Goldberg and Burnett (2003)	A	Montreal, PQ, Canada, 1984- 1995	CoH and extinction were available daily. PM _{2.5} and PM ₁₀ every sixth day until 1992, daily through 1993.	Reanalysis indicated attenuation of PM risk estimates, especially sensitive to weather model specification. Congestive heart failure, as classified based on medical records from insurance plan, was associated with CoH, SO ₂ , and NO ₂ .

*Brief summary of new time-series studies on daily mortality since the 1996 Air Quality Criteria Document for Particulate Matter (U.S. Environmental Protection Agency, 1996a). More complete descriptive summaries are provided in Appendix Table 8A-1. The endpoint is total daily non- trauma mortality, unless noted otherwise. Due to the large number of models reported for sensitivity analyses for some of these papers, some evaluating various lags and co-pollutant models, some for individual cities, and others for estimates pooled across cities, quantitative risk estimates are not presented in this table.

**Type: Type of studies: (A) Original study used GAM model including non-parametric smoothing terms with default or other lax convergence criteria, but was reanalyzed using stringent convergence criteria and/or using parametric smoothers; (B) Original study used GLM with parametric smoothers or other approaches, or used GAM but with only one non-parametric smoother.

1 highlights findings from several multi-city studies (Section 8.2.2.3) and single-city studies
2 (Section 8.2.2.4). Discussion of implications of new study results for types of issues identified
3 in foregoing text is mainly deferred to Section 8.4.

4 The summary of studies in Table 8-1 and 8A-1 (and in other tables) is not meant to imply
5 that all listed studies should be accorded equal weight in the overall interpretive assessment of
6 evidence regarding PM-associated health effects. In general, for those studies not clearly flawed
7 and having adequate control for confounding, increasing scientific weight should be accorded to
8 in proportion to the precision of their estimate of a health effect. Small studies and studies with
9 an inadequate exposure gradient generally produce less precise estimates than large studies with
10 an adequate exposure gradient. Therefore, the range of exposures (e.g., as indicated by the IQR),
11 the size of the study as indexed by the total number of observations (e.g., days) and total number
12 of events (i.e., total deaths), and the inverse variance for the principal effect estimate are all
13 important indices useful in determining the likely precision of health effects estimates and in
14 according relative scientific weight to the findings of a given study.

15 As can be seen in Tables 8-1 and 8A-1, many of the newly reported analyses continue to
16 show statistically significant associations between short-term (24 h) PM exposures indexed by a
17 variety of ambient PM measurements and increases in daily mortality in numerous U.S. and
18 Canadian cities, as well as elsewhere around the world. Several newly available PM
19 epidemiologic studies that conducted time-series analyses in multiple cities, as discussed first
20 below, are of particular interest.

21 22 **8.2.2.3 New Multi-City Studies**

23 The new multi-city studies are of interest here due to their evaluation of a wide range of
24 PM exposures and large numbers of observations, thus holding promise of possibly providing
25 more precise effects estimates than most smaller scale independent studies of single cities.
26 Another potential advantage of the multi-city studies, over meta-analyses for multiple
27 “independent” studies, is consistency in data handling and model specifications that eliminates
28 variation due to study design. Also, unlike regular meta-analysis, they clearly do not suffer from
29 potential omission of negative analyses due to “publication bias.” Furthermore, geographic
30 patterns of air pollution effects can be systematically evaluated in multiple-city analyses. Thus,
31 results from multi-city studies have the potential to provide especially valuable evidence

1 regarding relative homogeneity and/or heterogeneity of PM-health effects relationships across
2 geographic locations. Also, many of the cities included in these multi-city studies were ones for
3 which no time-series analyses had been previously reported. Most of these new multi-city
4 studies used GAM Poisson models, but the data sets have recently been reanalyzed using GAM
5 models with more stringent convergence criteria, as well as by using GLM with parametric
6 smoothers.

7 8 **8.2.2.3.1 U.S. Multi-City Studies**

9 **U.S. PM₁₀ 90-Cities NMMAPS Analyses**

10 The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) focused on time-
11 series analyses of PM₁₀ effects on mortality during 1987-1994 in the 90 largest U.S. cities
12 (Samet et al., 2000a,b,c), in the 20 largest U.S. cities in more detail (Dominici et al., 2000a,b),
13 and PM₁₀ effects on emergency hospital admissions in 14 U.S. cities (Samet et al., 2000a,b).
14 These NMMAPS analyses employed sophisticated statistical approaches addressing issues of
15 measurement error biases, co-pollutant evaluations, regional spatial correlation, and synthesis of
16 results from multiple cities by hierarchical Bayesian meta-regressions and meta-analyses. These
17 analyses provide extensive new information of much relevance to the setting of U.S. PM
18 standards, because no other study has examined so many U.S. cities in such a consistent manner.
19 That is, NMMAPS used only one consistent PM index (PM₁₀) across all cities (based on PM₁₀
20 samples collected only every 6 days in most of the 90 cities); death records were collected in a
21 uniform manner; and demographic variables were uniformly addressed. The 90-cities analyses
22 studies employ multi-stage models (see Table 8-1) in which heterogeneity in individual city's
23 coefficients in the first stage Poisson models were evaluated in the second stage models with
24 city- or region-specific explanatory variables.

25 As noted earlier, the original investigators of the NMMAPS study reported in 2002 a
26 potential problem with using the GAM Poisson models with default convergence criteria
27 available in widely-used statistical software in estimating air pollution risks (Dominici et al.,
28 2002). The default convergence criteria were too lax to attain convergence in the setting of air
29 pollution, weather, and mortality/morbidity parameters where “small” PM regression
30 coefficients were estimated and at least two covariates were modeled with non-parametric
31 smoothers. The NMMAS investigators simulation analysis also suggested that the extent of bias

1 could be more serious when the magnitude of risk coefficient was smaller and when PM
2 correlations with covariates were stronger. The investigators have since reanalyzed the 90 cities
3 data, using more stringent convergence criteria as well as using fully parametric smoothers, and
4 reported revised results. The following description of the NMMAPS mortality study therefore
5 focuses on the results of the reanalysis of the 90 cities study.

6 In both the original and reanalyzed NMMAPS 90 cities studies, the combined estimates of
7 PM_{10} coefficients were positively associated with mortality at all the lags examined (0, 1, and
8 2 day lags), although the 1-day lag PM_{10} gave the largest overall combined estimate. Figure 8-1
9 shows the reanalyzed results for the estimated percent excess total deaths per $10 \mu\text{g}/\text{m}^3$ PM_{10} at
10 lag 1 day in the 88 (90 minus Honolulu and Anchorage) largest cities, as well as (weighted
11 average) combined estimates for U.S. geographic regions depicted in Figure 8-2. The majority
12 of the coefficients were positive for the various cities listed along the left axis of Figure 8-1. The
13 estimates for the individual cities were first made separately. The cities were then grouped into
14 the 7 regions seen in Figure 8-2 (based on characteristics of the ambient PM mix typical of each
15 region, as delineated in the 1996 PM AQCD). The bolded segments represent the posterior
16 means and 95% posterior intervals of the pooled regional effects without borrowing information
17 from other regions. The triangle and bolded segment at the bottom of Figure 8-1 display the
18 combined estimate of overall nationwide effects of PM_{10} for all the cities.

19 Note that there appears to be some regional-specific variation in the overall combined
20 estimates for all the cities in a given region. This can be discerned most readily in Figure 8-3,
21 which depicts overall region-specific excess risk estimates for 0, 1, and 2 day lags. For example,
22 the coefficients for the Northeast for any given lag are generally higher than for other regions.
23 The NMMAPS investigators noted that the extent of the regional heterogeneity seen with the
24 reanalysis was reduced slightly compared to the original finding (between-city standard
25 deviation changed from 0.112 to 0.088 in the unit of percent excess deaths per $10 \mu\text{g}/\text{m}^3$ PM_{10}),
26 but the pattern of heterogeneity remained the same. The overall national combined estimate
27 (i.e., at lag 1 day, 1.4% excess total deaths per $50 \mu\text{g}/\text{m}^3$ increase in PM_{10} using GAM with
28 stringent convergence criteria) for the 90 cities is somewhat lower than the range of available
29 estimates reported in the 1996 PM AQCD (i.e. 2.5 to 5.0%) for the general U.S. population.

30 In the original 90 cities study, the weighted second-stage regression included five types of
31 county- specific variables: (1) mean weather and pollution variables; (2) mortality rate (crude

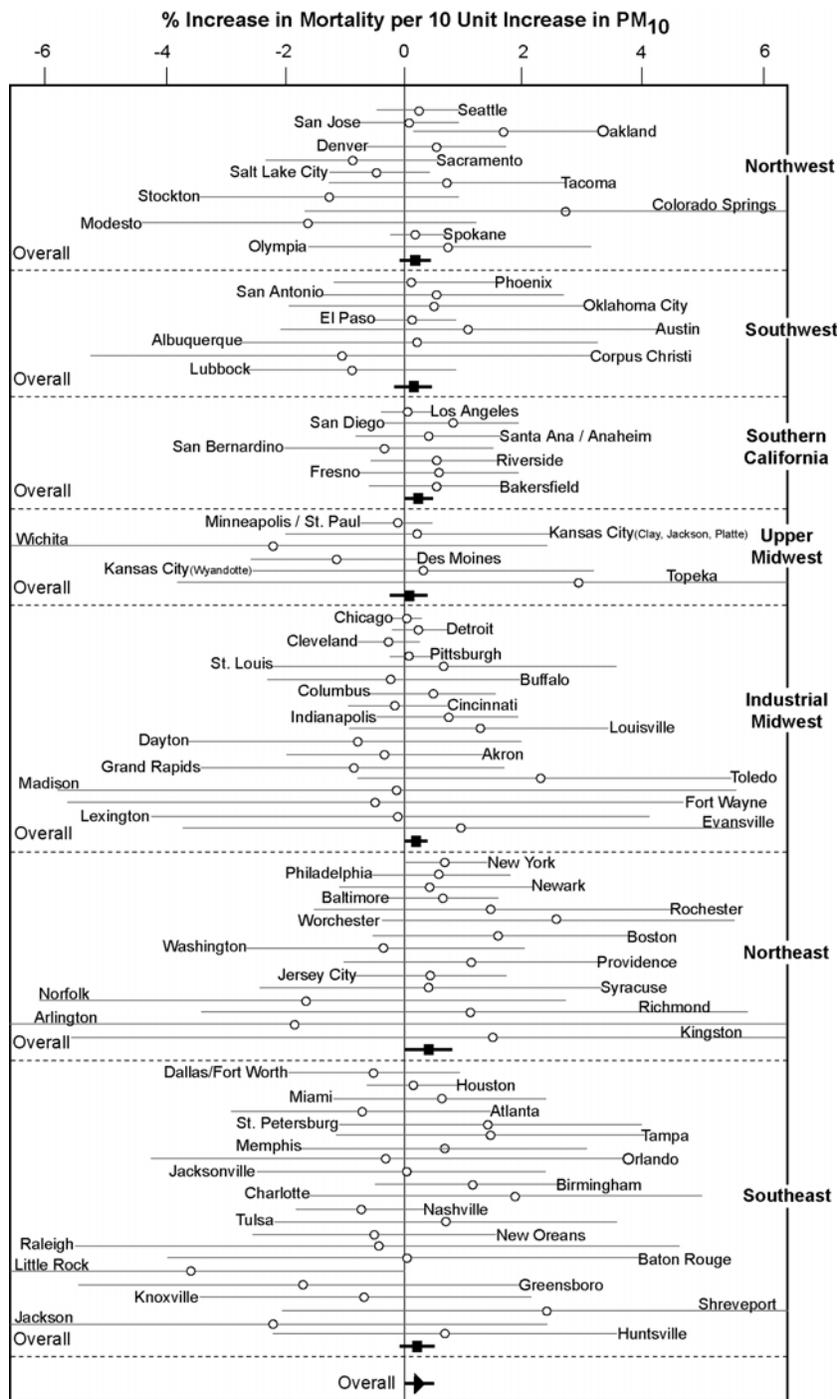


Figure 8-1. Estimated excess risks for PM mortality (1 day lag) for the 88 largest U.S. cities as shown in the revised NMMAPS analysis.

Source: Dominici et al. (2002; 2003).

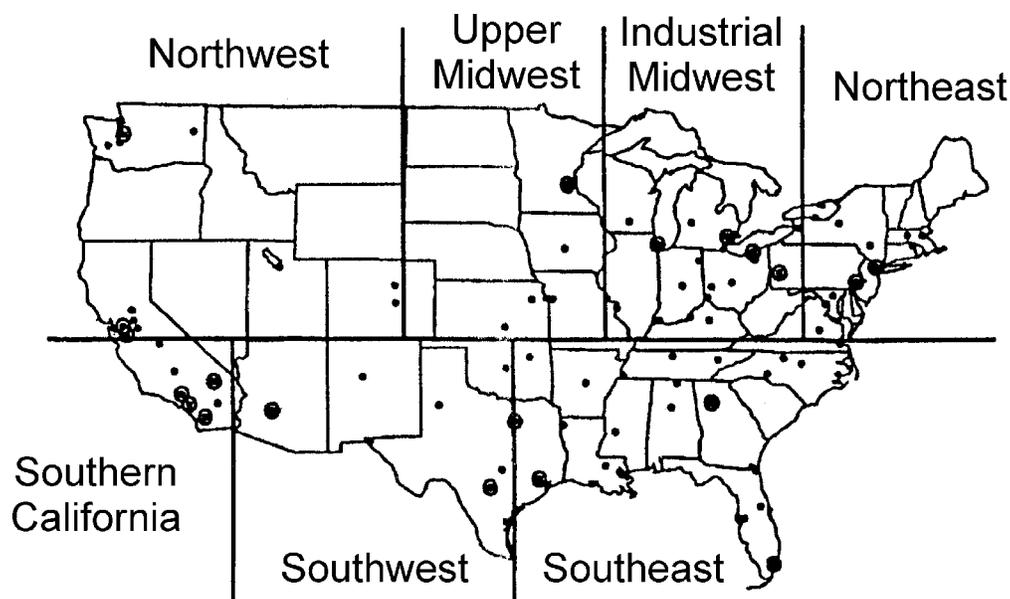


Figure 8-2. Map of the United States showing the 88 cities (the 20 cities are circled) and the seven U.S. regions considered in the NMMAPS geographic analyses.

1 mortality rate); (3) sociodemographic variables (% not graduating from high school and median
 2 household income);(4) urbanization (public transportation); and (5) variables related to
 3 measurement error (median of all pair-wise correlations between monitors). Some of these
 4 variables were apparently correlated (e.g., mean PM_{10} and NO_2 , household income and
 5 education) so that the sign of coefficients in the regression changed when correlated variables
 6 were included in the model. Thus, while some of the county-specific variables were statistically
 7 significant (e.g., mean NO_2 levels), interpreting the role of these county-specific variables may
 8 require caution. Regarding the heterogeneity of PM_{10} coefficients, the investigators concluded
 9 that they “did not identify any factor or factors that might explain these differences.”

10 Another important finding from Samet and coworkers’ analyses was the weak influence of
 11 gaseous co-pollutants on the PM_{10} effect size estimates (see Figure 8-4). In the reanalysis of
 12 90 cities data, PM_{10} coefficients slightly increased when O_3 was added to regression models.
 13 Additions of a third pollutant (i.e., $PM_{10} + O_3 +$ another gaseous pollutant) hardly changed the
 14 posterior means of PM_{10} effect size estimates, but widened the distribution. However, the
 15 posterior probabilities that the overall PM_{10} effects are greater than zero remained at or above

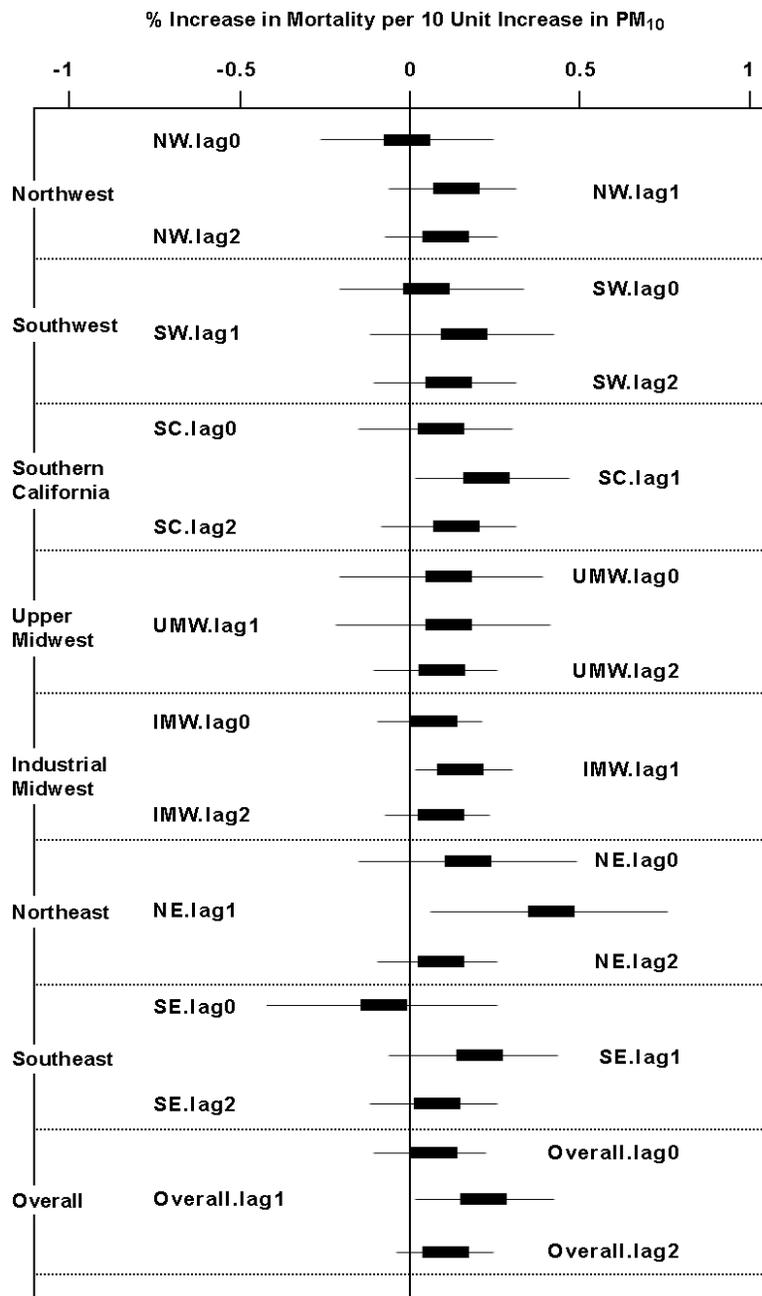


Figure 8-3. Percent excess mortality risk (lagged 0, 1, or 2 days) estimated in the NMMAPS 90-City Study to be associated with 10- $\mu\text{g}/\text{m}^3$ increases in PM₁₀ concentrations in cities aggregated within U.S. regions shown in Figure 8-4.

Source: Dominici et al. (2002; 2003).

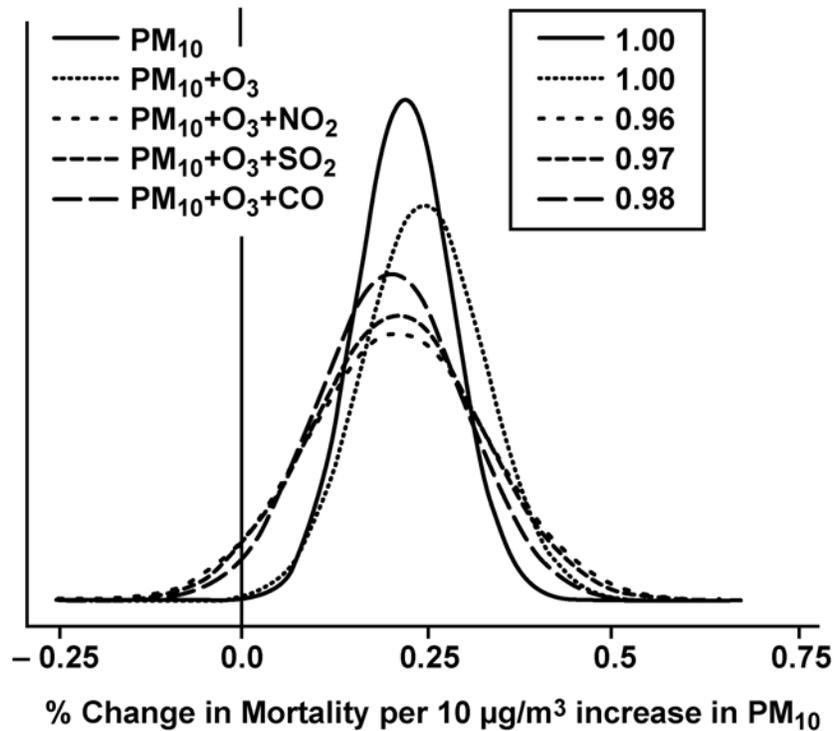


Figure 8-4. Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1 with and without control for other pollutants, for the 90 cities. The numbers in the upper right legend are the posterior probabilities that the overall effects are greater than 0.

Source: Dominici et al. (2003).

1 0.96. The gaseous pollutants themselves in single-, two-, and three-pollutant models were less
 2 consistently associated with mortality than PM_{10} . Ozone was not associated with mortality using
 3 year-round data; but, in season-specific analyses, it was associated with mortality negatively in
 4 winter and positively in summer. SO_2 , NO_2 , and CO were weakly associated with mortality, but
 5 additions of PM_{10} and other gaseous pollutants did not always reduce their coefficients, possibly
 6 indicative of their independent effects. As noted in Section 8.1, CO and NO_2 from motor
 7 vehicles are likely confounders of $PM_{2.5}$ and, thus, of PM_{10} when it is not dominated by the
 8 coarse particle fraction. The investigators stated that the PM_{10} effect on mortality “was
 9 essentially unchanged with the inclusion of either O_3 alone or O_3 with additional pollutants.”

1 The reanalyses of the 90 cities data by the original NMMAPS investigators also included a
2 sensitivity analysis of lag 1 day PM_{10} GLM results to the alternative degrees of freedom for
3 adjustment of the confounding factors: season, temperature, and dewpoint. The degrees of
4 freedom for each of these three smoothing terms were either doubled or halved, resulting in nine
5 scenarios in addition to the degrees of freedom in the original GLM model. The PM_{10} effect
6 posterior means were generally higher when the degrees of freedom were halved for season, and
7 lower when they were doubled, ranging between 1.6% to 0.9% (the main GLM result was 1.1%)
8 excess total mortality per $50 \mu\text{g}/\text{m}^3$ PM_{10} increase. These results underscore the fact that the
9 magnitude of sensitivity of the results due to model specification (in this case, degrees of
10 freedom alone) can be as great as the potential bias caused by the GAM convergence problem.

11 HEI (2003a) states that the revised NMMAPS 90 individual-city mortality results show
12 that, in general, the estimates of PM effect are shifted downward and the confidence intervals are
13 widened. In the revised analyses, a second stage meta-analysis was used to combine results on
14 effects of PM and other pollutants on health outcomes across cities. Tightening the convergence
15 criteria in GAM obtained a substantially lower estimate of effect of PM_{10} combined over all
16 cities, and use of GLM with natural splines decreased the estimate further. The revised analyses
17 yielded a small, but statistically significant, effect of PM_{10} at lag 1 on total mortality, now
18 estimated to be 0.21% per $10 \mu\text{g}/\text{m}^3$, with a posterior standard error of 0.06%. HEI (2003a)
19 agrees with the investigators' conclusions that the qualitative conclusions of NMMAPS II have
20 not changed, although the evidence for an effect of PM_{10} at lag 0 and lag 2 is less convincing
21 under the new models. The NMMAPS II report found that the PM_{10} effect remained when
22 copollutants were introduced into the model (Samet et al., 2000a); and this conclusion has not
23 changed.

24 The extent of reduction in PM_{10} excess risk estimate due to the change in the convergence
25 criteria (2.3% per $50 \mu\text{g}/\text{m}^3$ PM_{10} using default versus 1.4% using stringent) using GAM models
26 in the 90 cities study appears to be greater than those reported for most of the other reanalysis
27 studies. This may be partly due to the smaller risk estimate (2.3%) in the original study
28 compared to other studies ($> 3\%$), as the smaller coefficient is likely more strongly affected as a
29 relative reduction. This may also be in part due to the more "aggressive" adjustment for possible
30 weather effects (discussed later) used in this study, which may have increased the concavity
31 between PM and the covariates (which included four smoothing terms for weather adjustment).

1 Dominici et al. (2002) reported that the higher the concurvity, the larger the potential bias that a
2 GAM model with default convergence criteria could produce.

3 In summary, the 90-cities NMMAPS study provides useful information regarding: (1) the
4 magnitude of the combined PM_{10} risk estimate; (2) lack of sensitivity of PM_{10} risk estimates to
5 gaseous co-pollutants; (3) indications of regional heterogeneity in PM_{10} risk estimates across the
6 U.S.; (4) the shape of concentration-response relationship (discussed in a later section); and
7 (5) the range of sensitivity of PM_{10} risk estimates to the extent of smoothing of covariates in
8 original weather model specification. A major uncertainty not extensively examined in this
9 study is the sensitivity of the PM_{10} risk estimates to different weather model specifications.

10 11 *U.S. 10-Cities Studies*

12 In another set of multi-city analyses, Schwartz (2000a,b), Schwartz and Zanobetti (2000),
13 Zanobetti and Schwartz (2000), Braga et al. (2000), and Braga et al. (2001a) analyzed 1987-1995
14 air pollution and mortality data from ten U.S. cities (New Haven, CT; Birmingham, AL;
15 Pittsburgh, PA; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado
16 Springs, CO; Spokane, WA; and Seattle, WA.) or subsets (4 or 5 cities) thereof. The selection of
17 these cities was based on the availability of daily (or near daily) PM_{10} data. All of these original
18 studies utilized GAM Poisson models with default convergence criteria. Of these studies,
19 Schwartz (2003) reanalyzed the data from Schwartz (2000a), Schwartz (2000b), and Braga et al.
20 (2001a) using GAM with stringent convergence criteria as well as alternative models such as
21 GLM with natural cubic splines or penalized splines, both of which are expected to give correct
22 standard errors. The main original results of the study were presented in the Schwartz (2000a)
23 paper; and the other studies noted above focused on each of several specific issues, including
24 potential confounding, effect modification, distributed lag, and threshold. In this section, the
25 results for the three reanalysis studies noted above are discussed.

26 In the reanalysis (Schwartz, 2003b) of the main results (Schwartz, 2000a), daily total (non-
27 accidental) mortality in each of the 10 cities was fitted using a GAM Poisson model (with
28 stringent convergence criteria) or a GLM Poisson model with natural splines, adjusting for
29 temperature, dewpoint, barometric pressure, day-of-week, season, and time. The data were also
30 analyzed by season (November through April as heating season). The inverse-variance weighted
31 averages of the ten cities' estimates were used to combine results. PM_{10} (average of lag 0 and 1

1 days) was significantly associated with total deaths, and the effect size estimates were
2 comparable in summer and winter. Adjusting for other pollutants did not substantially change
3 the PM₁₀ effect size estimates. The combined percent-excess-death estimate for total mortality
4 was 3.4% (CI: 2.6, 4.1)¹ per 50 µg/m³ increase in the average of lag 0 and 1 days PM₁₀
5 (essentially unchanged from the original study) using GAM with stringent convergence criteria.
6 The PM₁₀ risk estimate using GLM with natural splines was 2.8% (CI: 2.0, 3.6).

7 In the reanalysis (Schwartz, 2003b) of the study of multi-day effects of air pollution
8 (Schwartz, 2000b), constrained (quadratic model over 0 through 5 day lags) and unconstrained
9 (0 through 5 day lags) distributed lag models were fitted in each city. The overall estimate was
10 computed using the inverse-variance weighted average of individual city estimates. Among the
11 results obtained using GAM with stringent convergence criteria, the PM₁₀ effect size estimate
12 was 6.3% (CI: 4.9, 7.8) per 50 µg/m³ increase for the quadratic distributed lag model, and
13 5.8% (CI: 4.4, 7.3) for the unconstrained distributed lag model. Corresponding values using the
14 penalized splines were somewhat smaller (~5.3%). These values are about twice the effect-size
15 estimate for single-day PM₁₀ in the original report or the two-day mean PM₁₀ reported in the
16 reanalysis above (this reanalysis did not report results for single-day or 2-day mean PM₁₀).

17 Schwartz (2003b) also reanalyzed the data from Braga et al.'s (2001a) study to examine the
18 lag structure of PM₁₀ association with specific cause of mortality in the 10 cities. Unconstrained
19 distributed lags for 0 through 5 days as well as two-day mean were fitted in each city for COPD,
20 pneumonia, all cardiovascular, and myocardial infarction deaths using GAM with stringent
21 convergence criteria and penalized spline models. Combined estimates by lag were obtained
22 across the 10 cities. The distributed lag estimates were generally larger than the two-day mean
23 estimates for COPD and pneumonia mortality, but they were comparable for all cardiovascular
24 and myocardial infarction mortality. For example, in the results using GAM with stringent
25 convergence criteria, the PM₁₀ effect size estimate for COPD mortality was 11.0% (CI: 7.2, 14.8)
26 per 50 µg/m³ increase for two-day mean model and 16.8% (CI: 8.3, 25.9) for the unconstrained
27 distributed lag model. Note that these values are substantially larger than those reported for total
28 non-accidental deaths.

¹ 95% Confidence Intervals for a given percent risk estimate are standardly provided in parenthesis following the risk estimate in this chapter. For example, 95% CI = 2.6 to 4.1% is expressed as (CI: 2.6,4.1).

1 The PM₁₀ risk estimates from these 10 cities analyses are larger than those from the
2 NMMAPS 90 cities study and these results suggest a possibility that PM effects may be
3 underestimated when only single-day PM indices are used. That is, if ambient PM effects on
4 mortality occur only very immediately, e.g., the same day, then the full risk would be reflected
5 by single day lag analyses. However, if PM-associated deaths occurred over a more extended
6 time, e.g., the next several days, then the fuller PM-related mortality risk would presumably be
7 more closely reflected by distributed lag models and, overall, would logically be higher than for
8 any single lag day. Differences in the number of cities analyzed, in weather model specification,
9 and/or in the extent of smoothing for temporal trends may also have contributed to the
10 differences in the size of PM₁₀ risk estimates found by the NMMAPS 90 cities versus the
11 Schwartz 10 cities studies. These issues are further discussed in Section 8.2.2.3.5.

12 13 *Reanalyses of Harvard Six Cities Study*

14 Both the original Harvard Six Cities Study time-series analysis (Schwartz et al., 1996a) and
15 the replication analysis by Klemm et al. (2000), which essentially replicated Schwartz et al.'s
16 original findings, used GAM Poisson models with default convergence criteria. Schwartz
17 (2003a) and Klemm and Mason (2003) conducted reanalyses of the Harvard Six Cities data to
18 address the GAM statistical issues.

19 Schwartz (2003a) not only reported risk estimates for PM_{2.5} and PM_{10-2.5}, but also provided
20 results using several other spline smoothing methods (natural splines, B-splines, penalized
21 splines, and thin plate splines) in addition to GAM with stringent convergence criteria. The risk
22 estimate combined across the six cities per 25 µg/m³ in PM_{2.5} (average of lag 0 and 1 day) using
23 GAM with stringent convergence criteria was 3.5% (CI: 2.5, 4.5), as compared to the original
24 value of 3.7% (CI: 2.7, 4.7). The corresponding value from a GLM model with natural splines
25 was 3.3% (CI: 2.2, 4.3); and the values using B-splines, penalized splines, and thin plate splines
26 were somewhat lower (3.0%, 2.9%, and 2.6%, respectively). However, when the Harvard Six
27 Cities were examined individually in the reanalysis of Schwartz using GLM and penalized
28 splines, Boston and St. Louis gave significant associations with PM_{2.5} and Steubenville gave a
29 significant association with “thoracic” coarse PM (i.e. PM_{10-2.5}).

30 Klemm and Mason’s reanalysis (2003) reported risk estimates for PM_{2.5}, PM_{10-2.5}, PM₁₀
31 (PM₁₅ or PM₁₀), and SO₄⁻². They also conducted sensitivity analyses using GLM with natural

1 splines that approximated the degrees of freedom used in the LOESS smoothers in the GAM
2 models, as well as 12 knots per year and 4 knots per year for smoothing of temporal trends. The
3 $PM_{2.5}$ and $PM_{10-2.5}$ total non-accidental mortality risk estimates combined across the six cities per
4 $25 \mu\text{g}/\text{m}^3$ (average of lag 0 and 1 day) using GAM with stringent convergence criteria were
5 3.0% (CI: 2.1, 4.0) and 0.8% (CI: -0.5, 2.0), respectively. The corresponding PM_{10} mortality
6 excess risk estimate per $50 \mu\text{g}/\text{m}^3$ (average of lag 0 and 1 day) was 3.6% (CI: 2.1, 5.0). In their
7 sensitivity analysis, increasing the degrees of freedom for temporal trends for natural splines in
8 GLM models from 4 knots/year to 12 knots/year markedly reduced PM risk estimates. For
9 example, the $PM_{2.5}$ risk estimate per $25 \mu\text{g}/\text{m}^3$ was reduced from 2% in the 4 knots/year model to
10 1% in the 12 knots/year model. The results showing the smaller PM risk estimates for larger
11 degrees of freedom for smoothing of temporal trends are consistent with similar findings
12 reported for the reanalysis of the NMMAPS 90 cities study. It also should be noted that Klemm
13 and Mason (2003) reported positive (but not significant at $p < .05$) associations between total
14 mortality and $PM_{10-2.5}$ in Steubenville, which parallels the Schwartz (2003a) finding of a positive
15 (and statistically significant at $p < .05$) total mortality association with $PM_{10-2.5}$ for Steubenville.

16 Although PM effect estimates from the Klemm and Mason (2003) reanalysis are somewhat
17 smaller than those from Schwartz (2003a); e.g., 3.5% by Schwartz versus 3.0% by Klemm and
18 Mason for $PM_{2.5}$ using strict convergence criteria, the results are very similar. Both studies also
19 showed that the comparable GLM models produced smaller risk estimates than GAM models.

21 **8.2.2.3.2 Canadian Multicity Studies**

22 Burnett et al. (2000) analyzed various PM indices (PM_{10} , $PM_{2.5}$, $PM_{10-2.5}$, sulfate, CoH, and
23 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants
24 (NO_2 , O_3 , SO_2 , and CO) for association with total mortality in the 8 largest Canadian cities:
25 Montreal, Ottawa-Hull, Toronto, Windsor, Winnipeg, Calgary, Edmonton, and Vancouver. This
26 study differs from Burnett et al. (1998a) in that it included fewer cities but more recent years of
27 data (1986-1996 versus 1980-1991) and detailed analyses of particle mass components by size
28 and elemental composition. Each city's mortality, pollution, and weather variables were
29 separately filtered for seasonal trends and day-of-week patterns. The residual series from all
30 cities were then combined and analyzed in a GAM Poisson model.

1 In Burnett and Goldberg's reanalysis (2003) of the eight Canadian cities data, they only
2 evaluated the PM indices ($PM_{2.5}$, $PM_{10-2.5}$, and PM_{10}), using GAM models with more stringent
3 convergence criteria. The reanalysis used co-adjustment regression (i.e., simultaneous
4 regression), rather than the regression with pre-filtered data that was the main approach of the
5 original analysis. The reanalysis also considered several sensitivity analyses, including models
6 with and without day-of-week adjustment and several alternative approaches (fitting criteria and
7 extent of smoothing) to adjust for temporal trends using natural splines. Adjusting for temporal
8 trends, smoothing of same-day temperature, pressure, and day-of-week effects, the pooled PM
9 effect estimates across the eight Canadian cities were: 2.2% (CI: 0.1, 4.2) per $25 \mu\text{g}/\text{m}^3$ increase
10 in $PM_{2.5}$; 1.8% (CI: -0.6, 4.4) per $25 \mu\text{g}/\text{m}^3$ increase $PM_{10-2.5}$; and 2.7% (CI: -0.1, 5.5) per
11 $50 \mu\text{g}/\text{m}^3$ increase PM_{10} . These effect size estimates are fairly close to the estimates reported in
12 the original study, despite the differences in the regression approach (pre-filtering and GAM
13 with default convergence criteria in the original study versus use of co-adjustment and GAM
14 with stringent convergence criteria in the reanalyses).

15 The temporal adjustment of the above model used LOESS smoothing with a span of
16 ~ 0.022 (= 90 days/4012 study days). Sensitivity analysis included several choices of degrees of
17 freedom for natural splines of temporal trend, with two fitting criteria (i.e., Bartlett's test for
18 white noise and AIC) and either using the same degrees of freedom for all eight cities or varying
19 degrees of freedom for each city. The PM risk estimates based on natural splines were generally
20 smaller than those based on LOESS smoothers. The PM risk estimates also varied inversely
21 with the number of knots for temporal trend. That is, the more details of the temporal trend were
22 described by natural splines, the smaller the PM risk estimates became. The reported $PM_{2.5}$ risk
23 estimates per $25 \mu\text{g}/\text{m}^3$ increase were 3.0% ($t=3.12$), 2.8% ($t=2.28$), 2.2% ($t=2.14$), 2.1%
24 ($t=2.07$), and 1.9% ($t=1.72$) for knot/year, knot/6 months, knot/3 months, knot/2 months, and
25 knot/1 month, respectively. The corresponding values for $25 \mu\text{g}/\text{m}^3$ increase in $PM_{10-2.5}$ were
26 3.9% ($t=3.42$), 2.9% ($t=2.52$), 2.1% ($t=1.69$), 1.8% ($t=1.46$), and 1.2% ($t=0.91$), suggesting
27 greater sensitivity of $PM_{10-2.5}$ risk estimates to the extent of temporal smoothing. The authors
28 suggested that this was likely due to the stronger correlation between (and temporal trends in)
29 mortality and mass concentrations for $PM_{10-2.5}$ (average correlation among cities of -0.45) than
30 for $PM_{2.5}$ (-0.36). Because the relative size and significance of $PM_{2.5}$ and $PM_{10-2.5}$ risk estimates
31 varied depending on the model and extent of smoothing for temporal trend, it is difficult to

1 compare the relative importance of the two size-fractionated PM indices in this study; but,
2 overall, they do not appear to be markedly different.

3 4 **8.2.2.3.3 European Multi-City APHEA Study Analyses**

5 The Air Pollution and Health: A European Approach (APHEA) project is a multi-center
6 study of short-term effects of air pollution on mortality and hospital admissions within and
7 across a number of European cities having a wide range of geographic, climatic, air quality, and
8 sociodemographic patterns. The obvious strength of this approach is its ability to evaluate
9 potential confounders or effect modifiers in a consistent manner. However, it should be noted
10 that PM indices measured in those cities varied. In APHEA1, the PM indices measured were
11 mostly black smoke (BS), except for: Paris and Lyon (PM₁₃); Bratislava, Cologne, and Milan
12 (TSP); and Barcelona (BS and TSP). In APHEA2, 10 out of the 29 cities used direct PM₁₀
13 measurements; and, in 11 additional cities, PM₁₀ levels were estimated based on regression
14 models relating collocated PM₁₀ measurements to BS or TSP. In the remaining 8 cities, only BS
15 measurements were available (14 cities had BS measurements). As discussed below, there have
16 been several papers published that present either a meta-analysis or pooled summary estimates of
17 these multi-city mortality results: (1) Katsouyanni et al. (1997) — SO₂ and PM results from
18 12 cities; (2) Touloumi et al. (1997) — ambient oxidants (O₃ and NO₂) results from six cities;
19 (3) Zmirou et al. (1998) — cause-specific mortality results from 10 cities (see Section 8.2.2.5);
20 (4) Samoli et al. (2001) — a reanalysis of APHEA1 using a different model specification (GAM)
21 to control for long-term trends and seasonality; and (5) Katsouyanni et al. (2001) — APHEA2,
22 with emphasis on the examination of confounding and effect modification. The original APHEA
23 protocol used sinusoidal terms for seasonal adjustment and polynomial terms for weather
24 variables in Poisson regression models. Therefore, publications 1 through 3 above are not
25 subject to the GAM default convergence issue. Publications 4 and 5 did use GAM Poisson
26 model with default convergence criteria, but the investigators have reanalyzed the data using
27 GAM with more stringent convergence criteria, as well as GLM with natural splines (Katsouyanni
28 et al., 2003; Samoli et al., 2003). The discussions presented below on publications 4 and 5 are
29 focused on the results from the reanalyses.

1 ***APHEA1 Sulfur Dioxide and Particulate Matter Results for 12 Cities***

2 The Katsouyanni et al. (1997) analyses evaluated data from the following cities: Athens,
3 Barcelona, Bratislava, Cracow, Cologne, Lodz, London, Lyon, Milan, Paris, Poznan, and
4 Wroclaw. In the western European cities, an increase of 50 $\mu\text{g}/\text{m}^3$ in BS or SO_2 was associated
5 with a 3% (CI: 2.0, 4.0) increase in daily mortality; and 2% (CI: 1.0, 3.0) for per 50 $\mu\text{g}/\text{m}^3$
6 increase in estimated PM_{10} based on ($\text{PM}_{10} = \text{TSP} \cdot 0.55$ conversion). In the 31 central/eastern
7 European cities, the increase in mortality associated with a 50 $\mu\text{g}/\text{m}^3$ change was
8 0.6% (CI: 0.1, 1.1) per 50 $\mu\text{g}/\text{m}^3$ change in BS and 0.8% (CI: 0.1, 2.4) for SO_2 . Estimates of
9 cumulative effects of prolonged (two to four days) exposure to air pollutants were comparable to
10 those for one day effects. The effects of both pollutants (BS, SO_2) were stronger during the
11 summer and were mutually independent. Regarding the contrast between the western and
12 central/eastern Europe results, the authors speculated that this could be due to differences in
13 exposure representativeness; differences in pollution toxicity or mix; differences in proportion of
14 sensitive subpopulation; and differences in model fit for seasonal control. Bobak and Roberts
15 (1997) commented that the heterogeneity between central/eastern and western Europe could be
16 due to the difference in mean temperature. However, Katsouyanni and Touloumi (1998) noted
17 that, having examined the source of heterogeneity, other factors could apparently explain the
18 difference in estimates as well as or better than temperature.

19
20 ***APHEA1 Ambient Oxidants (Ozone and Nitrogen Dioxide) Results for Six Cities***

21 Touloumi et al. (1997) reported on additional APHEA data analyses, which evaluated
22 (a) short-term effects of ambient oxidants on daily deaths from all causes (excluding accidents),
23 and (b) impacts on effect estimates for NO_2 and O_3 of including a PM measure (BS) in
24 multi-pollutant models. Six cities in central and western Europe provided data on daily deaths
25 and NO_2 and/or O_3 levels. Poisson autoregressive models allowing for overdispersion were
26 fitted. Significant positive associations were found between daily deaths and both NO_2 and O_3 .
27 Increases of 50 $\mu\text{g}/\text{m}^3$ in NO_2 (1-hour maximum) or O_3 (1-hour maximum) were associated with
28 a 1.3% (CI: 0.9, 1.8) and 2.9% (CI: 1.0, 4.9) increase in the daily mortality, respectively. There
29 was a tendency for larger effects of NO_2 in cities with higher levels of BS; that is, when BS was
30 included in the model, the coefficient for NO_2 was reduced by half (but remained significant)
31 whereas the pooled estimate for the O_3 effect was only slightly reduced. The authors speculated

1 that the short-term effects of NO₂ on mortality might be confounded by other vehicle-derived
2 pollutants (e.g., airborne ambient PM indexed by BS measurements). Thus, while this study
3 reports only relative risk levels for NO₂ and O₃ (but not for BS), it illustrates the potential
4 importance of confounding between NO₂ and PM effects and relative limited confounding
5 between O₃ and PM effects.

7 ***APHEA1: A Sensitivity Analysis for Controlling Long-Term Trends and Seasonality***

8 The original study (Samoli et al., 2001) examined the sensitivity of APHEA1 results to
9 how the temporal trends were modeled (i.e., sine/cosine in the APHEA1 versus LOESS
10 smoother using GAM with default convergence criteria). Samoli et al. (2003) reanalyzed the
11 data using GAM with more stringent convergence criteria, as well as GLM with natural splines.
12 Thus, the reanalysis allowed a comparison of results across a fixed functional model
13 (sine/cosine), a non-parametric smoother (GAM with LOESS), and a parametric smoother (GLM
14 with natural splines). The combined estimate across cities for percent excess in total non-
15 accidental mortality per 50 µg/m³ increase in BS using GAM with stringent convergence criteria
16 (2.3%; CI: 1.9, 2.7) was bigger than that using sine/cosine (1.3%; CI: 0.9, 1.7). The GAM with
17 stringent convergence criteria reduced the combined estimate by less than 10% versus that from
18 GAM with default convergence criteria. The corresponding estimate using GLM with natural
19 splines (1.2%; CI: 0.7, 1.7) was comparable to that from the sine/cosine model but smaller than
20 that using GAM. The contrast between western and eastern Europe in the original APHEA1
21 study (2.9% for west versus 0.6% for east) was less clear in results using GAM with stringent
22 convergence criteria (2.7% versus 2.1%) or GLM with natural splines (1.6% versus 1.0%). This
23 suggests that the apparent regional heterogeneity found in the original APHEA1 study could be
24 sensitive to model specification. Because the number of cities used in the APHEA1 study was
25 relatively small (eight western and five central-eastern cities), the apparent regional
26 heterogeneity found in the earlier publications could also be due to chance. These reanalysis
27 findings also suggest that the results are somewhat sensitive to model specification for temporal
28 trends.

1 *APHEA2: Confounding and Effect Modification Using Extended Data*

2 The APHEA2 original study (Katsouyanni et al. 2001) included more cities (29 cities) and
3 a more recent study period (variable years in 1990-1997, compared to 1975-1992 in APHEA1).
4 Also, the APHEA2 original study used a GAM (with default convergence criteria) Poisson
5 model with LOESS smoothers to control for season and trends. Katsouyanni et al. (2003)
6 reanalyzed the data using GAM with more stringent convergence criteria and two parametric
7 approaches: natural splines and penalized splines. Because the reanalysis GAM results changed
8 the PM₁₀ risk estimates only slightly from the original estimates and the investigators mention
9 that the patterns of effect modification were preserved in their reanalyses regardless of model
10 specification, the qualitative description below of the effect modification relies on the original
11 study, but PM₁₀ estimates for various models are from the reanalysis.

12 The analyses put emphasis on effect modification by city-specific factors. Thus, the city-
13 specific coefficients from the first stage of Poisson regressions were modeled in the second stage
14 regression using city-specific characteristics as explanatory variables. Inverse-variance
15 weighted pooled estimates (fixed-effects model) were obtained as part of this model. When
16 substantial heterogeneity was observed, the pooled estimates were obtained using random-effects
17 models. These city-specific variables included (1) air pollution level and mix, such as average
18 air pollution levels and PM/NO₂ ratio (as an indicator of traffic-generated PM); (2) climatic
19 variables, such as mean temperature and relative humidity; (3) health status of the population,
20 such as the age-adjusted mortality rates, the percentage of persons over 65 years of age, and
21 smoking prevalence; and (4) geographic area (three regions: Central-Eastern, Southern, and
22 North-Western). The study also addressed the issue of confounding by simultaneous inclusion
23 of gaseous co-pollutants in city-specific regressions and obtained pooled PM estimates for each
24 co-pollutant included. Unlike APHEA1, in which the region (larger PM estimates in western
25 Europe than in Central-Eastern Europe) was highlighted as the important factor, APHEA2 found
26 several effect modifiers. NO₂ (i.e., index of high pollution from traffic) was an important one.
27 Cities with higher NO₂ levels showed larger PM effects, as did cities with a warmer climate.
28 The investigators noted that this might be due to better indexing of population exposures by
29 outdoor community monitors (because of more open windows). Also, cities with low
30 standardized mortality rate showed larger PM effects. The investigators speculated that this may
31 be because a smaller proportion of susceptible people (to air pollution) are available in a

1 population with a large age-standardized mortality rate. Interestingly, in the pooled PM risk
2 estimates from models with gaseous pollutants, it was also NO₂ that affected (reduced) PM risk
3 estimates most. For example, in the fixed-effects models, ~50% reductions in both PM₁₀ and BS
4 coefficients were observed when NO₂ was included in the model. SO₂ only minimally reduced
5 PM coefficients; whereas O₃ actually increased PM coefficients. Thus, in this analysis, NO₂ was
6 implicated as a confounder, an effect modifier, and/or as an indicator of PM source. The overall
7 random-effects model combined estimates for total mortality for 50 µg/m³ increase in PM₁₀ were
8 3.0% (CI: 2.0, 4.1), 2.1% (CI: 1.2, 3.0), and 2.8% (CI: 1.8, 3.8), for GAM (stringent convergence
9 criteria), natural splines, and penalized splines models, respectively. The original excess
10 mortality risk estimate (3.1%) using GAM with default convergence criteria was thusly reduced
11 by 3 to 33% in the different reanalyses models. While the effect estimates varied somewhat
12 depending on the choice of GAM with LOESS, natural splines, or penalized splines, the
13 investigators reported that the patterns of effect modification (by NO₂, etc.) were preserved.

15 ***8.2.2.3.4 Comparison of Effect Size Estimates from Multi-City Studies***

16 Based on different pooled analyses of data combined across multiple cities, the percent
17 excess total (non-accidental) deaths estimated per 50 µg/m³ increase in PM₁₀ in the above multi-
18 city studies were (a) 1.4% using GAM (1.1% using GLM) at lag 1-day in the 90 largest U.S.
19 cities (the Northeast region results being about twice as high); (b) 3.4% using GAM (2.8% using
20 GLM) for average of 0 and 1 day lags in 10 U.S. cities; (c) 3.6% using GAM (2.7% using GLM)
21 for 1 day lag PM₁₀ in the 8 largest Canadian cities; and (d) 3.0% using GAM (2.1% using GLM)
22 in APHEA2 for average of 0 and 1 day lags for 29 European cities during 1990-1997.

23 The estimate for NMMAPS 90 cities study is somewhat smaller than those for the other
24 multi-city studies and the range reported in the previous PM AQCD (2.5 to 5%). There are
25 several possible explanations for this, including differences in (a) model specifications for
26 weather, (b) extent of smoothing to adjust for temporal trends, (c) use of different specific
27 smoothing approaches, and (d) consequent effects of each of these differences on ranges of
28 degrees of freedom assigned for different aspects of the analyses.

29 Model specification for weather appears to be one of the more crucial factors. The
30 NMMAPS 90 cities study used much more “aggressive” adjustment for possible weather effects
31 than did most other studies. The 90 cities analysis included four separate weather terms:

1 (1) smoothing splines (natural splines when GLM was used) of same-day temperature with
2 6 degrees of freedom; (2) smoothing splines of the average of lag 1 through 3 day temperature
3 with 6 degrees of freedom; (3) smoothing splines of same-day dewpoint with 3 degrees of
4 freedom; and (4) smoothing splines of the average of lag 1 through 3 day dewpoint with
5 3 degrees of freedom. In contrast, most of the other studies used only one or two terms for
6 weather variables. For example, the Harvard Six Cities Study used a LOESS smoother (or
7 natural splines or other smoothers in reanalysis) of same-day temperature with a span of 0.5 and
8 a LOESS smoother of same-day dewpoint with a span of 0.5. Note, too, that the NMMAPS
9 90 cities study not only used more terms for weather effects, but it also used more degrees of
10 freedom for temperature than Schwartz et al.'s analysis (according to Klemm and Mason's
11 reanalysis, the span of 0.5 in LOESS corresponds to ~3.5 degrees of freedom). It should be
12 noted that the purpose for inclusion of dewpoint in these models is often explained as "to adjust
13 for possible effects of humidity"; but there are differing perspectives related to the need for
14 inclusion of dewpoint along with temperature, given that dewpoint and temperature tend to be
15 highly correlated ($r > 0.9$) in most cities. Thus, although the inclusion of these terms may
16 statistically (i.e., by AIC, etc.) provide a better fit, the epidemiologic implications of the use of
17 these terms are not yet fully clear. On the one hand, extreme temperatures, hot or cold, are
18 known to cause excess mortality and the combined effects of high temperature and high
19 humidity occurring together can cause especially high excess mortality. Thus, it is clear that
20 these models need somehow to control for high "heat index" effects when notable increases in
21 weather-related mortality occur (hence the need for heat index forecasts) and/or for cold-induced
22 deaths when sufficiently low temperatures occur in a given locale. On the other hand, it is also
23 not clear at this time as to whether these models may be overcorrecting for weather effects in the
24 more moderate range that is typical of much of the data. These issues are further discussed later
25 in Section 8.4.3.

26 Another factor that may contribute to the difference in PM risk estimates is the extent of
27 smoothing to adjust for temporal trends. Several of the reanalysis studies (Dominici et al., 2002;
28 Burnett and Goldberg, 2003; Ito, 2003; Klemm and Mason, 2003) consistently reported, though
29 to varying extents, that using more degrees of freedom for temporal trends tended to reduce PM
30 coefficients. That is, when more details in the short-term fluctuations of mortality were ascribed
31 to temporal trends, PM risk estimates were reduced. For example, in Dominici et al.'s (2002)

1 sensitivity analysis, the PM₁₀ risk estimate was larger (1.6% per 50 µg/m³ increase in PM₁₀) for
2 the GLM model with 3 degrees of freedom per year that the estimate using 7 degrees of freedom
3 (1.1%). Note that, in general, the presumed objective of including temporal trends in the
4 mortality regression is to adjust for potential confounding (measured or unmeasured) by time-
5 varying factors that change seasonally or in shorter time spans (e.g., influenza epidemics).
6 However, ascribing “too short” temporal fluctuations to these “confounding temporal trends”
7 may inadvertently take away PM effects. Because the “right” extent of smoothing is not known,
8 these sensitivity analyses are useful. In the reanalyses mentioned above, the PM risk estimates
9 changed, at times, by a factor of two when a range of degrees of freedom was applied even for a
10 model specification in which all the other terms were kept unchanged.

11 Based on the results from the reanalysis studies, it has become apparent that different
12 smoothing approaches can also affect PM risk estimates. For example, the models with natural
13 splines (parametric smoothing) appear, in general but not always, to result in smaller PM risk
14 estimates than GAM models with LOESS or smoothing splines. GAM models may possibly
15 suffer from biased standard error of risk estimates, but they also seem to fit the data better (i.e.,
16 based on AIC) than GLM models with natural splines. In any case, the choice of these
17 smoothers does not seem to affect PM risk estimates (~ 10 to 30%) as much as the range of
18 weather model specifications or the range of the degrees of freedom for temporal trends
19 adjustment do (as large as a factor of two).

20 A less explored issue is the effect of multi-day effects of PM. The PM₁₀ risk estimates
21 summarized above are either for a single-day lag (U.S. NMMAPS 90 cities study, Canadian 8
22 cities study, and APHEA1), or an average of two days (U.S. 10 cities study and APHEA2).
23 However, the reanalysis of U.S. 10 cities study data suggests that the multi-day PM effect,
24 accounting for 0 through 5 day lag, could be twice as large as the effect sizes estimated from
25 single or two-day average models and even bigger (~ 3 to 4 fold) when more specific cause of
26 death categories are examined. This issue warrants further investigation.

27 In summary, considering the wide variability in possible reasonable model specification
28 choices that can affect the PM risk estimates, the reported combined PM₁₀ total non-accidental
29 mortality risk estimates from multi-city studies are in reasonably good agreement. That is, they
30 fall mainly in the range of ~1.0 to 3.5% per 50 µg/m³ increase in single or two-day average
31 PM₁₀. Combinations of choices in model specifications (the number of weather terms and

1 degrees of freedom for smoothing of mortality temporal trends) alone may explain the extent of
2 the difference in PM₁₀ risk estimates across studies. The range for these newly available
3 combined estimates from multi-cities studies overlap with the range of PM₁₀ estimates (2.5 to
4 5%, obtained from single cities studies) previously reported in the 1996 PM AQCD, but extends
5 to somewhat lower values.

6 7 **8.2.2.4 U.S. Single-City Studies**

8 In addition to the new multi-city studies assessed above, many studies newly available
9 since the 1996 PM AQCD evaluated relationships between mortality and short-term exposure to
10 PM using data from individual cities. The results of such studies are summarized in tabular form
11 in Appendix 8A-1. The ensuing discussion focuses on the results of recent U.S. single-city
12 studies, especially those including PM₁₀, PM_{2.5} and PM_{10-2.5} data. Results of analyses using PM_{2.5}
13 and PM_{10-2.5} measurements are also discussed further in Section 8.2.2.5.

14 Moolgavkar (2000a) evaluated (using GAM with default convergence criteria) associations
15 between short-term measures of major air pollutants and daily deaths in three large U.S. urban
16 areas (Cook Co., IL, encompassing Chicago; Los Angeles Co., CA; and Maricopa Co., AZ,
17 encompassing Phoenix) during a 9-year period (1987-1995). Moolgavkar (2003) reanalyzed the
18 data for Cook Co. and Los Angeles Co. (but not Maricopa Co.), using GAM with stringent
19 convergence criteria as well as GLM with natural splines. Ozone was analyzed in the original
20 analysis but not in the reanalyses (it was only positive and significant in Cook county in the
21 original analysis). This section describes the results from the reanalyses. Total non-accidental
22 deaths, deaths from cardiovascular disease (CVD) and chronic obstructive lung disease (COPD)
23 were analyzed in relation to 24-h readings for PM, CO, NO₂, and SO₂ averaged over all monitors
24 in a given county. Cerebrovascular mortality was analyzed in the original analysis but not in the
25 reanalyses (its association with air pollution was weak in the original analysis). The results of
26 cause-specific mortality analyses are described in a later section. Daily readings were available
27 for each of the gaseous pollutants in both Cook Co. and Los Angeles Co., as were PM₁₀ values
28 for Cook Co. However, PM₁₀ and PM_{2.5} values were only available every sixth day in Los
29 Angeles Co. PM values were highest in summer in Cook Co. and in the winter and fall in Los
30 Angeles Co.; whereas the gases (except for O₃) were highest in winter in both counties. The PM
31 indices were moderately correlated ($r = 0.30$ to 0.73) with CO, NO₂, and SO₂ in Cook Co. and

1 Los Angeles Co. Total non-accidental, CVD, and COPD deaths were all highest during winter
2 in both counties. Adjusting for temperature and relative humidity effects in separate analyses for
3 each mortality endpoint for these two counties, varying patterns of results were found, as noted
4 in Appendix A, Table 8A-1. Moolgavkar (2003) also reported sensitivity of results to different
5 degrees of freedom (df) for smoothing of temporal trends (30 df and 100 df).

6 As for Cook Co., PM_{10} was significantly associated with total non-accidental mortality at
7 lag 0 (most significant) and 1 day in GAM models with both 30 df and 100 df for smoothing of
8 temporal trends, as well as in a GLM model with 100 df for smoothing of temporal trends. The
9 gaseous pollutants were also significantly associated with total non-accidental mortality at
10 various lags (wider lags than PM_{10}), but were most significant at lag 1 day. These associations
11 did not appear to be sensitive to the extent of smoothing for temporal trends, at least at their most
12 significant lags. In two pollutant models (results were not shown in tables but described in text),
13 the PM_{10} association remained “robust and statistically significant” at lag 0 day; whereas the
14 coefficients for the gases became non-significant. However, at lag 1 day, the PM_{10} association
15 became non-significant and the gases remained significant. Thus, some extent of “sharing” of
16 the association is apparent, and whichever pollutant is more strongly associated than the other at
17 that lag tended to prevail in the two pollutant models in this data set.

18 For Los Angeles Co., CO was more significantly associated (positive and significant at lag
19 0 through 3 days) with mortality than PM_{10} (positive and significant at lag 2) or $PM_{2.5}$ (positive
20 and significant at lag 1). In two pollutant models in which CO and PM indices were included
21 simultaneously at PM indices = “best” lags, CO remained significant, whereas PM coefficients
22 became non-significant (and negative for cases with 30 df for temporal smoothing). For Los
23 Angeles data, the PM coefficients appeared to be more sensitive to the choice of the degrees of
24 freedom than to the default versus stringent convergence criteria. GLM models tended to
25 produce smaller risk estimates than GAM models. Moolgavkar also reported that these
26 associations were robust to varying the extent of smoothing for weather covariates.

27 The results for these two cities do not reflect a common pattern. In Cook Co., all the
28 pollutants were associated with mortality, and their relative importance varied depending on the
29 lag day, whereas CO appeared to show the strongest mortality associations in Los Angeles.
30 Moolgavkar concluded that, considering the substantial differences that can result from different

1 analytic strategies, no particular numeric estimates were too meaningful, although the patterns of
2 associations appeared to be robust.

3 Ostro et al. (2000; reanalyzed Ostro et al., 2003) conducted a study in Coachella Valley,
4 CA, using (a) PM₁₀ data collected from 1989-1998 and (b) PM_{2.5} and PM_{10-2.5} data collected
5 during the last 2.5 years of the study period. Both PM_{2.5} and PM_{10-2.5} were also estimated for the
6 earlier remaining years to increase the power of the analyses, but only PM_{10-2.5} could be reliably
7 estimated; so, predicted PM_{2.5} data were not used. Original analyses used GAMs, with smoothing
8 functions for time and indicators for day of week. Different lags for temperature, humidity and
9 dewpoint were tested for use in the models; and then pollutants were added individually and next
10 in combination. In the reanalyses, more stringent convergence criteria and natural splines were
11 used, but the reanalyses were only done for cardiovascular mortality. For such cause-specific
12 mortality, significant associations were found for PM_{10-2.5} and PM₁₀, but not for PM_{2.5} (possibly
13 due to the low range of PM_{2.5} concentrations and reduced sample size for PM_{2.5} data) and PM
14 risk estimates were higher for multi-day averages. The PM risk estimates were slightly reduced
15 in the reanalyses using GAM with stringent convergence criteria or using GLM; but sensitivity
16 analyses showed that results were not sensitive to alternative degrees of freedom for temporal
17 trends and temperature.

18 In another study, total, cardiovascular, and respiratory deaths in Santa Clara Co., CA were
19 regressed on PM₁₀, PM_{2.5}, PM_{10-2.5}, CoH, nitrate, sulfate, O₃, CO, NO₂, adjusting for time trend,
20 season, and minimum and maximum temperature, using a Poisson GAM model (Fairley, 1999;
21 reanalyzed Fairley, 2003). Reanalyses included use of GAM with stringent convergence criteria,
22 as well as natural splines and an additional indicator for O₃ (daily number of hours exceeding 60
23 ppb). In the reanalyses, the PM coefficients were either unchanged or only slightly decreased or
24 increased; and the original findings, including the pattern in two-pollutant models, were
25 unchanged. PM_{2.5} and nitrate were most significantly associated with mortality, but significant
26 associations were reported for all pollutants except PM_{10-2.5} in single-pollutant models. In two-
27 and four- pollutant models, PM_{2.5} or nitrate remained significant for total mortality, but the other
28 pollutants did not. The PM_{2.5} risk estimates for respiratory deaths were larger than those for total
29 or cardiovascular deaths but the associations were only significant for total mortality.

30 Lippmann et al. (2000; reanalyzed Ito, 2003) used aerometric data from Detroit which
31 included measurements of PM₁₀, PM_{2.5}, PM_{10-2.5}, sulfate, H⁺, O₃, SO₂, NO₂, and CO for a

1 1992-1994 study period. Associations with total (non-accidental), cardiovascular, respiratory,
2 and other deaths were analyzed using GAM Poisson models, adjusting for season, temperature,
3 and relative humidity. Analyses were also done for an earlier 1985-1990 study period that
4 included measurements of PM₁₀ and TSP along with the gaseous co-pollutants. Reanalyses were
5 done using stringent convergence criteria as well as natural splines, as well as additional
6 sensitivity analyses to examine the influence of alternative weather models and selection of
7 degrees of freedom on model results. In the reanalyses, PM coefficients were often reduced (but
8 sometimes unchanged or increased somewhat) when GAM with stringent convergence criteria or
9 GLM/natural splines were used. The reductions in coefficients were not different across PM
10 components; the original conclusion regarding the relative importance of PM components
11 remained the same. PM₁₀, PM_{2.5}, and PM_{10-2.5} were more significantly associated with mortality
12 outcomes than sulfate or H⁺. PM coefficients were generally not sensitive to inclusion of
13 gaseous pollutants. PM₁₀, PM_{2.5}, and PM_{10-2.5} effect size estimates were comparable in terms of
14 the same distributional increment (5th to 95th percentile). Both PM₁₀ (lag 1 and 2 day) and TSP
15 (lag 1 day), but not TSP-PM₁₀ or TSP- SO₄⁻, were significantly associated with respiratory
16 mortality for the 1985-1990 period. The simultaneous inclusions of gaseous pollutants with
17 PM₁₀ or TSP reduced the PM effect size by 0 to 34%. Effect size estimates for total, circulatory,
18 and “other” categories were smaller than for respiratory mortality.

19 Chock et al. (2000) evaluated associations between daily mortality and several air pollution
20 variables (PM₁₀, PM_{2.5}, PM_{10-2.5}, CO, O₃, NO₂, SO₂) in two age groups (< 75 yr., > 75 yr.) in
21 Pittsburgh, PA, during 1989-1991 (data on PM_{2.5} and PM_{10-2.5} were only available for half of the
22 3-year study period). Poisson GLM regression was used, including filtering of data based on
23 cubic B-spline functions to adjust for seasonal trends; models included indicators for day of
24 week, and temperature was modeled as a V-shape function. Single- and multi-pollutant models
25 were run for 0, 1, 2, and 3 day lags. Single- and multi-pollutant non-seasonal models showed
26 significant positive associations between PM₁₀ and daily mortality, but seasonal models showed
27 much multi-collinearity, masking association of any pollutant with mortality. PM_{2.5} and PM_{10-2.5}
28 were both positively associated with mortality, but the coefficients were unstable in this small
29 data set when stratified by age group and season and no conclusions were drawn on the relative
30 roles of PM_{2.5} and PM_{10-2.5}. In their conclusions, the authors emphasized issues of seasonal

1 dependence of correlation among pollutants, multi-collinearity among pollutants, and instability
2 of coefficients for $PM_{2.5}$ and $PM_{10-2.5}$.

3 Lipfert et al. (2000a), using data for Philadelphia and the seven-county Philadelphia
4 metropolitan area from 1992-1995, regressed twelve mortality variables (as categorized by area,
5 age, and cause) on 29 pollution variables (PM components, O_3 , SO_2 , NO_2 , CO, and by
6 sub-areas), yielding 348 regression results. Both dependent and explanatory variables were
7 pre-filtered using the 19-day-weighted average filter prior to OLS regression. Covariates were
8 selected from filtered temperature (several lagged and averaged values), indicator variables for
9 hot and cold days and day-of-week using stepwise procedure, and the average of current and
10 previous days' pollution levels were used. Significant associations were reported for a wide
11 variety of particulate and gaseous pollutants, especially for peak O_3 . No systematic differences
12 were seen according to particle size or chemistry. Mortality for one part of the metropolitan area
13 could be associated with air quality from another, not necessarily neighboring part.

14 Mar et al. (2000; reanalyzed Mar et al., 2003) evaluated associations between air pollutants
15 and total (non-accidental) and cardiovascular deaths in Phoenix for only those who resided in the
16 zip codes located near the air pollution monitor. GAM Poisson models were used, adjusting for
17 season, temperature, and relative humidity, and a variety of air pollution variables were used,
18 including O_3 , SO_2 , NO_2 , CO, TEOM PM_{10} , TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn,
19 Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were evaluated.
20 Factor analysis was also conducted on chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe,
21 Zn, Mn, Pb, Br, KS, OC, and EC); and factor scores were included in the mortality analyses.
22 Reanalyses were done using stringent convergence criteria as well as natural splines only for
23 cardiovascular mortality. In the reanalyses, small reductions were seen in risk estimates for PM
24 mass concentration indices using GAM/stringent convergence criteria or GLM/natural splines.
25 For source factors, there were moderate reductions in risk estimates for the motor vehicle factor
26 and slight increases for the regional sulfate factor and slight reductions in the coefficients for EC
27 and OC; but the estimates remained unchanged for the vegetative burning factor. Cardiovascular
28 mortality was significantly associated with CO, NO_2 , SO_2 , $PM_{2.5}$, PM_{10} , $PM_{10-2.5}$, OC and EC.
29 Vehicular traffic factors and regional sulfate factors were also associated with cardiovascular
30 mortality. Soil-related factors, as well as individual variables that are associated with soil were
31 negatively associated with total mortality. However, soil in $PM_{2.5}$ was positively and

1 significantly associated with total mortality during the third year of the study when a WINS
2 impactor (with sharper cut) was used instead of a cyclone sampler.

3 In all of the studies discussed above, some statistically significant associations between
4 mortality and PM indicators, especially PM_{10} and $PM_{2.5}$ were found. In multi-pollutant models,
5 PM coefficients were often robust to inclusion of gaseous pollutants, but sometimes reduced for
6 specific co-pollutants (see also the co-pollutant model discussion in Section 8.4).

7 8 **8.2.2.5 The Role of Particulate Matter Components**

9 Delineation of the roles of specific ambient PM components in contributing to associations
10 between short-term PM exposures and mortality requires evaluation of several factors, e.g., size,
11 chemical composition, surface characteristics, and the presence of gaseous co-pollutants. While
12 possible combinations of these factors can in theory be limitless, the actual data tend to cover
13 definable ranges of aerosol characteristics and co-pollutant environments due to typical source
14 characteristics (e.g., fine particles tend to be combustion products in most cities). Newly
15 available studies conducted in the last few years have begun to provide more extensive
16 information on the roles of PM components; and their results are discussed below in relation to
17 three topics: (1) PM particle size (e.g., $PM_{2.5}$ versus $PM_{10-2.5}$); (2) chemical components; and
18 (3) source oriented evaluations.

19 The ability to compare the relative roles of different PM size fractions and various PM
20 constituents is restricted by the limitations of the available studies. Comparisons nevertheless
21 can be attempted, using such information as the relative level of significance and/or the strength
22 of correlation between component estimate and health outcome. The relative significance across
23 cities/studies is influenced by the sample size and the level of the pollutants. The width of the
24 confidence band also needs to be taken into account, according more weight for studies with
25 narrower confidence bands. Caution in interpretation of such information, however, is warranted
26 because of potential measurement error and possible high correlations between indices being
27 compared. Additionally, limitations of single-city studies must be recognized.

8.2.2.5.1 *Particulate Matter Particle Size Evaluations*

With regard to the relative importance of the fine and coarse fractions of inhalable PM_{10} particles capable of reaching thoracic regions of the respiratory tract, at the time of the 1996 PM AQCD only one acute mortality study (Schwartz et al., 1996a) had examined this issue. That study (which used GAM with default convergence criteria in analyzing Harvard Six-City study data) suggested that fine particles ($PM_{2.5}$), distinctly more so than thoracic coarse-fraction ($PM_{10-2.5}$) particles, were associated with daily mortality. Recent reanalyses using GAM with more stringent convergence criteria have yielded only slightly smaller $PM_{2.5}$ effect-size estimates (Schwartz, 2003a). It should also be noted that (a) the Klemm et al. (2000) reanalysis reconstructed the data and replicated the original analyses (using GAM with default convergence criteria) and (b) the Klemm and Mason (2003) reanalysis, using GAM with stringent convergence criteria and GLM with parametric smoothers, also essentially reproduced the original investigators' results.

Since the 1996 PM AQCD, several new studies have used size-fractionated PM data to investigate the relative importance of fine ($PM_{2.5}$) versus coarse ($PM_{10-2.5}$) fraction particles. Table 8-2 provides synopses of those studies with regard to the relative importance of the two size fractions, as well as some characteristics of the data. The average levels of $PM_{2.5}$ ranged from about 13 to 30 $\mu\text{g}/\text{m}^3$ in the U.S. cities, but much higher average levels were measured in Santiago, Chile (64.0 $\mu\text{g}/\text{m}^3$). As can be seen in Table 8-2, in the northeastern U.S. cities (Philadelphia, PA and Detroit, MI), there was more $PM_{2.5}$ mass than $PM_{10-2.5}$ mass on the average; whereas in the western U.S. (Phoenix, AZ; Coachella Valley, CA; Santa Clara County, CA) the average $PM_{10-2.5}$ levels were higher than $PM_{2.5}$ levels. It should be noted that the three Phoenix studies in Table 8-2 used much the same data set; all used fine and coarse particle data from EPA's 1995-1997 platform study. Seasonal differences in PM component levels should also be noted. For example, in Santa Clara County and in Santiago, Chile, winter $PM_{2.5}$ levels averaged twice those during summer. The temporal correlation between $PM_{2.5}$ and $PM_{10-2.5}$ ranged between 0.30 and 0.65. Such differences in ambient PM mix features from season to season or from location to location complicates assessment of the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$.

TABLE 8-2. SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF PM_{2.5} AND PM_{10-2.5}

Author, City	Means ($\mu\text{g}/\text{m}^3$); ratio of PM _{2.5} to PM ₁₀ ; and correlation between PM _{2.5} and PM _{10-2.5}	Results regarding relative importance of PM _{2.5} versus PM _{10-2.5} and comments.
Fairley (1999 & 2003)* Santa Clara County, CA	PM _{2.5} mean = 13; PM _{2.5} /PM ₁₀ = 0.38; r = 0.51.	Of the various pollutants (including PM ₁₀ , PM _{2.5} , PM _{10-2.5} , sulfates, nitrates, CoH, CO, NO ₂ , and O ₃), the strongest associations were found for ammonium nitrate and PM _{2.5} . PM _{2.5} was significantly associated with mortality, but PM _{10-2.5} was not, separately and together in the model. Winter PM _{2.5} level is more than twice that in summer. The daily number of O ₃ ppb-hours above 60 ppb was also significantly associated with mortality.
Ostro et al. (2000 & 2003)* Coachella Valley, CA	PM _{2.5} (Palm Springs and Indio, respectively) mean = 12.7, 16.8; PM _{2.5} /PM ₁₀ = 0.43, 0.35; r = 0.46, 0.28.	Coarse particles dominate PM ₁₀ in this locale. PM _{2.5} was available only for the last 2.5 years, and a predictive model could not be developed; so that a direct comparison of PM _{2.5} and PM _{10-2.5} results is difficult. Cardiovascular mortality was significantly associated with PM ₁₀ (and predicted PM _{10-2.5}), whereas PM _{2.5} was mostly negatively associated (and not significant) at the lags examined.
Mar et al. (2000 & 2003)* Phoenix, AZ 1995-1997	PM _{2.5} (TEOM) mean = 13.0; PM _{2.5} /PM ₁₀ = 0.28; r = 0.42.	Cardiovascular mortality was significantly associated with both PM _{2.5} (lags 1, 3, and 4) and PM _{10-2.5} (lag 0). Of all the pollutants (SO ₂ , NO ₂ , and elemental carbon were also associated), CO was most significantly associated with cardiovascular mortality.
Smith et al. (2000) Phoenix, AZ	Not reported, but likely same as Clyde's or Mar's data from the same location.	In linear PM effect model, a statistically significant mortality association with PM _{10-2.5} was found, but not with PM _{2.5} . In models allowing for a threshold, indications of a threshold for PM _{2.5} (in the range of 20-25) were found, but not for PM _{10-2.5} . A seasonal interaction in the PM _{10-2.5} effect was also reported: the effect being highest in spring and summer when the contributions of Fe, Cu, Zn, and Pb to PM _{10-2.5} were lowest.
Clyde et al. (2000) Phoenix, AZ	PM _{2.5} mean = 13.8; PM _{2.5} /PM ₁₀ = 0.30; r = 0.65.	Using Bayesian Model Averaging that incorporates model selection uncertainty with 29 covariates (lags 0- to 3-day), the effect of coarse particle (most consistent at lag 1 day) was stronger than that for fine particles. The association was for mortality defined for central Phoenix area where fine particles (PM _{2.5}) are expected to be uniform.
Lippmann et al. (2000); Ito, (2003)* Detroit, MI 1992-1994	PM _{2.5} mean=18; PM _{2.5} /PM ₁₀ =0.58; r = 0.42.	Both PM _{2.5} and PM _{10-2.5} were positively (but not significantly) associated with mortality outcomes to a similar extent. Simultaneous inclusion of PM _{2.5} and PM _{10-2.5} also resulted in comparable effect sizes. Similar patterns were seen in hospital admission outcomes.
Lipfert et al. (2000a) Philadelphia, PA 1992-1995.	PM _{2.5} mean=17.3; PM _{2.5} /PM ₁₀ =0.72.	The authors conclude that no systematic differences were seen according to particle size or chemistry. However, when PM _{2.5} and PM _{10-2.5} were compared, PM _{2.5} (at lag 1 or average of lag 0 and 1) was more significantly and precisely associated with cardiovascular mortality than PM _{10-2.5} .

TABLE 8-2 (cont'd). SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF PM_{2.5} AND PM_{10-2.5}

Author, City	Means (µg/m ³); ratio of PM _{2.5} to PM ₁₀ ; and correlation between PM _{2.5} and PM _{10-2.5}	Results regarding relative importance of PM _{2.5} versus PM _{10-2.5} and comments
Klemm and Mason (2000) Atlanta, GA	PM _{2.5} mean = 19.9; PM _{2.5} /PM ₁₀ = 0.65	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for PM _{2.5} than for PM _{10-2.5} .
Schwartz (2003a) 6 U.S. cities	Not specified in Schwartz (2003a) paper; but see values below for same 6 cities.	Schwartz (2003a) reanalysis of Schwartz et al. (1996a) Harvard Six City time-series analyses confirmed original study findings of significant associations between total mortality and PM _{2.5} across the six U.S. cities, but not with PM _{10-2.5} (except in one city, Steubenville).
Klemm et al. (2000); Klemm and Mason (2003)* 6 U.S. cities	Mean ranged from 11.3 to 29.6; Mean PM _{10-2.5} ranged from 6.6 to 16.1; Mean PM _{2.5} /PM ₁₀ ranged from 0.50 to 0.66 in the six cities.	This reanalysis of the Harvard Six-Cities time-series analysis by Schwartz et al. (1996a) found significant associations between total mortality and PM _{2.5} in 3 cities and in pooled effect, but no significant association with PM _{10-2.5} in the reanalysis of the replication study for any city. These results essentially confirmed the findings of the original study by Schwartz et al. (1996a).
Chock et al. (2000) Pittsburgh, PA	Data distribution not reported. PM _{2.5} /PM ₁₀ = 0.67	Seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients were all emphasized in discussion and conclusion. These considerations and the small size of the data set (stratified by age group and season) limit confidence in finding of no consistently significant associations for any size fractions.
Burnett et al. (2000); Burnett and Goldberg (2003)* 8 Canadian cities	PM _{2.5} mean=13.3; PM _{2.5} /PM ₁₀ =0.51; r = 0.37.	Both PM _{2.5} and PM _{10-2.5} were significantly associated with total non-accidental mortality. Results using varying extent of smoothing of mortality temporal trends show that there is no consistent pattern of either PM mass index being more important. The authors note that PM _{10-2.5} was more sensitive to the type of smoother and amount of smoothing.
Cifuentes et al. (2000) Santiago, Chile 1988-1996	PM _{2.5} mean=64.0; PM _{2.5} /PM ₁₀ =0.58; r = 0.52.	In GLM results for the whole years, PM _{2.5} and NO ₂ were more consistently significantly associated with total non-accidental mortality than PM _{10-2.5} .

Note: * next to author name indicates that the study was originally analyzed using GAM models only with default convergence criteria using at least two non-parametric smoothing terms.

1 To facilitate a quantitative overview of the effect size estimates and their corresponding
2 uncertainties from these studies, the percent excess risks are plotted in Figure 8-5. These
3 excluded the Smith et al. study (which did not present linear term RRs for PM_{2.5} and PM_{10-2.5})
4 and the Clyde et al. study (for which the model specification did not obtain RRs for PM_{2.5} and

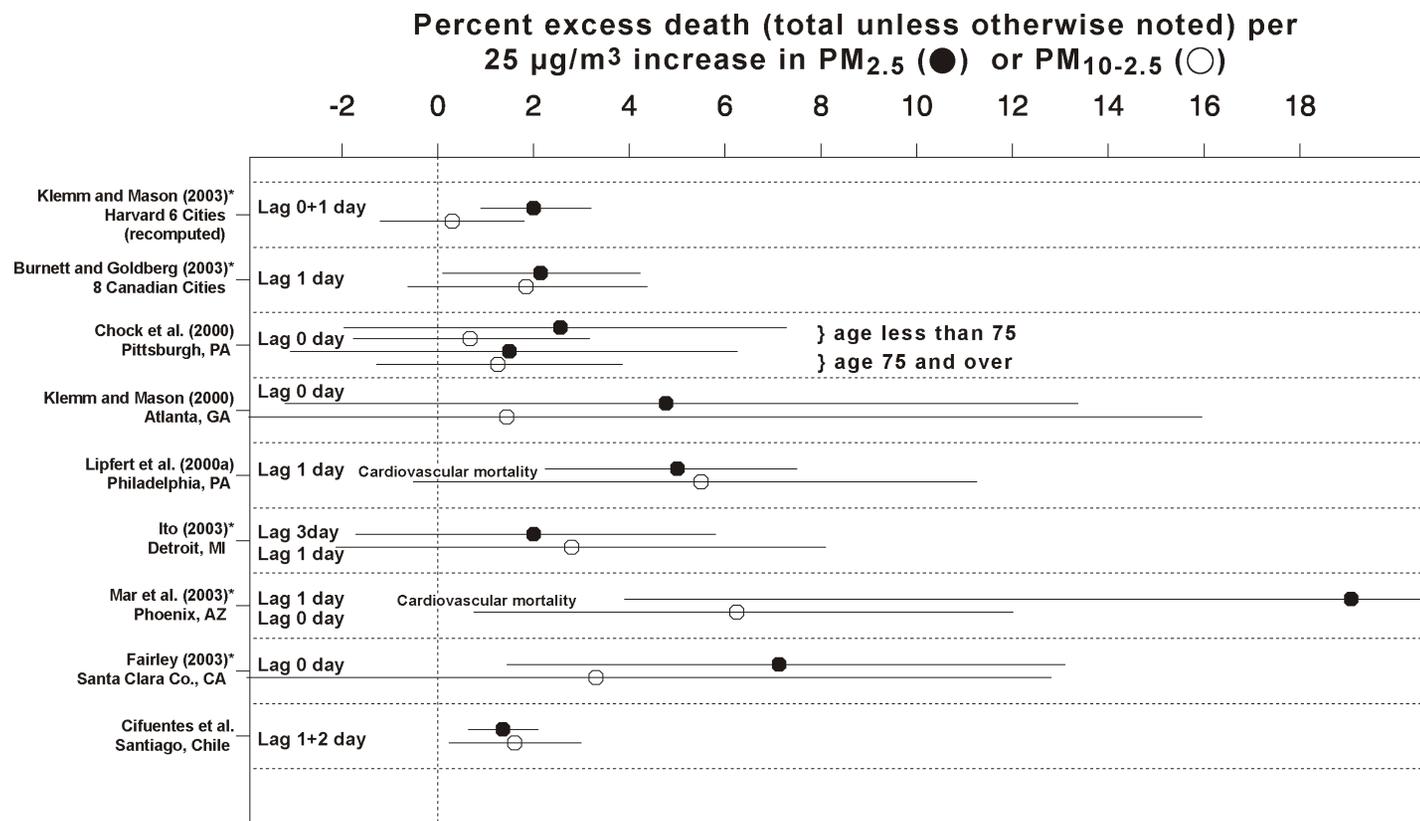


Figure 8-5. Percent excess risks estimated per 25 µg/m³ increase in PM_{2.5} or PM_{10-2.5} from new studies that evaluated both PM_{2.5} and PM_{10-2.5}, based on single pollutant (PM only) models. The asterisk next to reference indicates reanalysis of data using GLM with natural splines. Other studies used GLM or OLS.

1 PM_{10-2.5} separately). Note that, in most of the original studies, the RRs were computed for
2 comparable distributional features (e.g., interquartile range, mean, 5th -to-95th percentile, etc.).
3 However, the increments derived and their absolute values varied across studies; therefore, the
4 RRs used in deriving the excess risk estimates delineated in Figure 8-5 were re-computed for
5 consistent increments of 25 µg/m³ for both PM_{2.5} and PM_{10-2.5}. Note also that re-computing the
6 RRs per 25 µg/m³ in some cases changed the relative effect size between PM_{2.5} and PM_{10-2.5}, but
7 it did not affect the relative significance.

8 All of the studies found positive associations between both the fine and coarse PM indices
9 and increased mortality risk, however, most of the studies did not have large enough sample
10 sizes to separate out what often appear to be relatively small differences in effect size estimates.
11 However, three studies do show distinctly larger mortality associations with PM_{2.5} than for non-
12 significant PM_{10-2.5} effects. For example, the Klemm et al. (2000) and Klemm and Mason's
13 (2003) re-computations of the Harvard Six Cities time-series study data reconfirmed the original
14 Schwartz et al. (1996a) finding that PM_{2.5} was significantly associated with excess total
15 mortality, but PM_{10-2.5} across all cities was not (although the Schwartz [2003a] reanalyses also
16 reconfirmed their original findings of a statistically significant PM_{10-2.5}-mortality relationship in
17 one city, i.e., Steubenville, OH). Similar findings of PM_{2.5} being significantly associated with
18 total mortality were obtained in Santa Clara County (Fairley, 1999; Fairley 2003), and Mar et al.
19 (2000, 2003) reported much larger PM_{2.5} associations with cardiovascular mortality than for
20 PM_{10-2.5} (although both were statistically significant at p<0.05). There were several other studies
21 in which the importance of PM_{2.5} and PM_{10-2.5} were considered to be similar or, at least, not
22 distinguishable: Philadelphia, PA (Lipfert et al., 2000a); Detroit, MI (Lippmann et al., 2000;
23 reanalysis by Ito 2003); Eight Canadian cities (Burnett et al., 2000; reanalysis by Burnett and
24 Goldberg, 2003); and Santiago, Chile (Cifuentes et al., 2000). Some other studies suggested that
25 PM_{10-2.5} was more important than PM_{2.5}: Coachella Valley, CA (Ostro et al., 2000 & 2003) and
26 Phoenix, AZ (Smith et al., 2000, and Clyde et al., 2000).

27 In the reanalysis (Burnett and Goldberg, 2003) of the Canadian 8-city study (Burnett et al.,
28 2000), the relative importance of PM_{2.5} and PM_{10-2.5} was not clear, with both PM indices being
29 significant in single pollutant models. In GAM models (stringent convergence criteria) with
30 LOESS smoothers, PM_{2.5} was more significant and showed larger risk estimates than PM_{10-2.5}.
31 However, in sensitivity analysis in which varying degrees of freedom for mortality temporal

1 trends were applied in GLM models, the effect size and significance for these PM indices were
2 often comparable. The authors commented that $PM_{10-2.5}$ coefficient was more sensitive to the
3 extent of temporal smoothing than $PM_{2.5}$.

4 The Lippmann et al. (2000) results and reanalyses (Ito, 2003) for Detroit are also
5 noteworthy in that additional PM indices were evaluated besides those depicted in Figure 8-5,
6 and the overall results obtained may be helpful in comparing fine- versus coarse-mode PM
7 effects. In analyses of 1985 to 1990 data, PM-mortality relative risks and their statistical
8 significance were generally in descending order: PM_{10} , $TSP-SO_4^{-2}$, and $TSP-PM_{10}$. For the
9 1992-1994 period, relative risks for equivalent distributional increment (e.g., IQR) were
10 comparable among PM_{10} , $PM_{2.5}$, and $PM_{10-2.5}$ for both mortality and hospital admissions
11 categories; and SO_4^{-2} was more strongly associated with most outcomes than H^+ . Consideration
12 of the overall pattern of results led the authors to state that the mass of the smaller size index
13 could explain a substantial portion of the variation in the larger size indices. In these data, on
14 average, $PM_{2.5}$ accounted for 60% of PM_{10} (up to 80% on some days) and PM_{10} for 66% of TSP
15 mass. The temporal correlation between TSP and $PM_{2.5}$ was $r = 0.63$, and that for $PM_{2.5}$ and
16 PM_{10} was $r = 0.90$, suggesting that much of the apparent larger particle effects may well be
17 mainly driven by temporally covarying smaller $PM_{2.5}$ particles. The stronger associations for
18 sulfates than H^+ , suggestive of non-acid fine particle effects, must be caveated by noting the very
19 low H^+ levels present (often at or near the detection limit).

20 Three research groups, using different methods, have utilized the same U.S. EPA research
21 platform aerometric data to evaluate ambient PM-mortality associations in the Phoenix, AZ area.
22 While these groups used somewhat different approaches, there is some consistency among their
23 results in that $PM_{10-2.5}$ appeared in all three to emerge as a likely important predictor of mortality.
24 The Mar et al. (2000, 2003) analyses evaluated total and cardiovascular mortality among people
25 residing in zip code areas proximal to the one containing the EPA monitoring platform yielding
26 PM_{10} , $PM_{2.5}$, $PM_{10-2.5}$ and compositional data. In the Mar et al. (2000 & 2003) analyses, PM_{10}
27 was significantly associated with total mortality, whereas $PM_{2.5}$ and $PM_{10-2.5}$ were positively (but
28 not quite significantly) associated. However, cardiovascular mortality (CVM) was significantly
29 associated with both $PM_{2.5}$ and $PM_{10-2.5}$, as well as being significantly associated with several
30 source categories (as shown by factor analyses discussed later). The Smith et al. (2000) analyses
31 related mortality in Phoenix to the EPA $PM_{2.5}$ data, but used mortality data from surrounding

1 areas (Tempe, Scottsdale, etc.) within 50 miles of Phoenix in analyses of $PM_{10-2.5}$ effects. Based
2 on a linear PM effect, Smith et al. found $PM_{10-2.5}$ to be significantly associated with total
3 mortality, but $PM_{2.5}$ was not. However, Smith et al.'s additional finding that $PM_{2.5}$ may have a
4 threshold effect further complicates a simple comparison of the two size-fractionated mass
5 concentration indices. In the Clyde et al. (2000) analysis, PM-mortality associations were found
6 only for the geographic area where $PM_{2.5}$ was considered uniformly distributed, but the
7 association was stronger for $PM_{10-2.5}$ than for $PM_{2.5}$. That is, whereas the posterior probability for
8 $PM_{2.5}$ effect was ~ 0.91 , the highly ranked models (based on the Bayes Information Criterion)
9 consistently included 1-day lagged $PM_{10-2.5}$. The $PM_{2.5}$ in Phoenix is mostly generated from
10 motor vehicles, whereas $PM_{10-2.5}$ consists mainly of two types of particles: (a) crustal particles
11 from natural (wind blown dust) and anthropogenic (construction and road dust) processes, and
12 (b) organic particles from natural biogenic processes (endotoxin and molds) and anthropogenic
13 (sewage aeration) processes. The crustal particles, however, are also likely contaminated with
14 metals secondarily deposited over many years as the result of emissions from smelters operating
15 until recently in the Phoenix area.

16 In summary, issues regarding the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$ have not yet
17 been fully resolved. Caution in interpreting size-fraction PM studies is warranted due to
18 (a) problems with measurement and exposure error (likely higher for $PM_{10-2.5}$) and (b) the
19 correlation between the two size fractions. Limitations of single-city studies have also been
20 noted. While limited sample sizes typically prevented clear statistical distinction between
21 relative roles played by $PM_{2.5}$ and $PM_{10-2.5}$, recent studies show mixed results, with some studies
22 suggesting coarse particle effects. The relative importance may also vary depending on the
23 chemical constituents in each size fraction, which may vary from city to city. Nevertheless, a
24 number of studies published since the 1996 PM AQCD do appear to substantiate associations
25 between $PM_{2.5}$ and increased total and/or CVD mortality. Consistent with the 1996 PM AQCD
26 findings, effect-size estimates from the new studies generally fall within the range of ~ 1.5 to
27 6.5% excess total mortality per $25 \mu\text{g}/\text{m}^3$ $PM_{2.5}$. The coarse particle ($PM_{10-2.5}$) effect-size
28 estimates also tend to fall in about the same range, mainly from ~ 0.5 to 6.0% .

1 *Crustal Particle Effects*

2 Since the 1996 PM AQCD, several studies have yielded interesting new information
3 concerning possible roles of crustal wind-blown particles or crustal particles within the fine
4 particle fraction (i.e., PM_{2.5}) in contributing to observed PM-mortality effects.

5 Schwartz et al. (1999), for example, investigated the association of coarse particle
6 concentrations with non-accidental deaths in Spokane, WA, where dust storms elevate coarse
7 PM concentrations. During the 1990-1997 period, 17 dust-storm days were identified. The
8 PM₁₀ levels during those storms averaged 263 µg/m³, compared to 39 µg/m³ for the entire period.
9 The coarse particle domination of PM₁₀ data on those dust-storm days was confirmed by a
10 separate measurement of PM₁₀ and PM_{1.0} during a dust storm in August, 1996: the PM₁₀ level
11 was 187 µg/m³, while PM_{1.0} was only 9.5 µg/m³. The deaths on the day of a dust storm were
12 contrasted with deaths on control days (n = 95 days in the main analysis and 171 days in the
13 sensitivity analysis), which are defined as the same day of the year in other years when dust
14 storms did not occur. The relative risk for dust-storm exposure was estimated using Poisson
15 regressions, adjusting for temperature, dewpoint, and day of the week. Various sensitivity
16 analyses considering different seasonal adjustment, year effects, and lags were conducted. The
17 expected relative risk for these storm days with an increment of 221 µg/m³ would be about 1.04,
18 based on PM₁₀ relative risk from past studies, but the estimated RR for high PM₁₀ days was
19 found to be only 1.00 (CI: 0.95, 1.05) per 50 µg/m³ PM₁₀ change in this study. Schwartz et al.
20 concluded that there was no evidence to suggest that coarse (presumably crustal) particles were
21 associated with daily mortality.

22 Ostro et al. (2000 & 2003) also analyzed Coachella Valley, CA data for 1989-1998. This
23 desert valley, where coarse particles of geologic origin comprise circa 50-60% of annual-average
24 PM₁₀ (> 90% during wind episodes throughout the year), includes the cities of Palm Springs and
25 Indio, CA. Cardiovascular deaths were analyzed using GAM (with stringent convergence
26 criteria) and GLM Poisson models adjusting for temperature, humidity, day-of-week, season,
27 and time. Actual PM_{2.5} and PM_{10-2.5} data were only available for the last 2.5 years of the 10 yr
28 study period. So, predictive models were developed for estimating PM_{2.5} and PM_{10-2.5}
29 concentrations for earlier years, but the model for PM_{2.5} was not considered successful and,
30 therefore, was not used. Thus, a strict comparison of relative strength of risk estimates for PM_{2.5}
31 and PM_{10-2.5} in this data set is difficult. Cardiovascular mortality was reported to be positively

1 associated with both PM_{10} and $PM_{10-2.5}$ at multiple lags between 0 and 2 day lags; whereas the
2 $PM_{2.5}$ coefficient was positive only at lag 4 day, based on analyses involving far fewer
3 observations for $PM_{2.5}$ (only over a 2 yr period is 10 years for PM_{10} and $PM_{10-2.5}$). These results
4 hint at crustal particle effects possibly being important in this desert situation, but use of
5 estimated values for $PM_{10-2.5}$ lessens the credibility of the reported $PM_{10-2.5}$ findings. Also, the
6 ability to discern more clearly the role of fine particles would likely be improved by analyses of
7 more years of actual data for $PM_{2.5}$.

8 In two other studies, Laden et al. (2000) and Schwartz (2003b) analyzed Harvard Six-
9 Cities Study data and Mar et al. (2000) analyzed the Phoenix data to investigate the influence of
10 crustal particles in $PM_{2.5}$ samples on daily mortality. These studies are discussed in more detail
11 in Section 8.2.2.4.3 on the source-oriented evaluation of PM; and only the basic results regarding
12 crustal particles are mentioned here. The elemental abundance data (from X-ray fluorescence
13 spectroscopy analysis of daily filters) were analyzed to estimate the concentration of crustal
14 particles in $PM_{2.5}$ using factor analysis. Then the association of mortality with fine crustal mass
15 was estimated using Poisson regression (regressing mortality on factor scores for “crustal
16 factor”), adjusting for time trends and weather. No positive association was found between the
17 fine crustal mass factor and mortality. However, the soil component of $PM_{2.5}$ was positively and
18 significantly associated with total mortality when only the third year of data (when a WINS
19 impactor was used instead of a cyclone) was analyzed.

20 The above results, overall, mostly suggest that crustal particles (coarse or fine) per se are
21 not likely associated with daily mortality. However, as noted in the previous section, three
22 analyses of Phoenix, AZ data do suggest that $PM_{10-2.5}$ was associated with mortality. The results
23 from one of the three studies (Smith et al., 2000) indicate that coarse particle-mortality
24 associations are stronger in spring and summer, when the anthropogenic metal (Fe, Cu, Zn, and
25 Pb) contribution to $PM_{10-2.5}$ is lowest as determined by factor analysis. However, during spring
26 and summer, biogenic processes (e.g., wind-blown pollen fragments, fungal materials,
27 endotoxins, and glucans) may contribute more to the $PM_{10-2.5}$ fraction in the Phoenix area,
28 clouding any attribution of observed $PM_{10-2.5}$ effects there to crustal particles alone, per se.
29 (See the discussion of bioaerosols in Chapter 7 and, also in Section 8.4.3 of this chapter).

1 *Ultrafine Particle Effects*

2 Wichmann et al. (2000) evaluated the attribution of PM effects to specific size fractions,
3 including both the number concentration (NC) and mass concentration (MC) of particles in a
4 given size range. To respond to the GAM convergence issues, Stolzel et al. (2003) reanalyzed
5 the data, using GAM with stringent convergence criteria and GLM with natural splines. The
6 study was carried out in the former German Democratic Republic city of Erfurt (pop. 200,000)
7 German. Erfurt was heavily polluted by particles and SO₂ in the 1980s, and excess mortality
8 was attributed to high levels of TSP by Spix et al. (1993). Ambient PM and SO₂ concentrations
9 have markedly dropped since then. The present study provides a more detailed look at potential
10 health effect associations with ultrafine particles (diameter < 0.1 μm) than earlier studies,
11 including examination of effects in relation to number counts for fine and ultrafine particles as
12 well as for their mass. This was made possible by use of the Mobile Aerosol Spectrometer
13 (MAS), developed by Gessellschaft für Strahlenforschung (GSF), which measures number and
14 mass concentrations in three ultrafine size classes (0.01 to 0.1 μm) and three size classes of
15 larger fine particles (0.1 μm to 2.5 μm). The mass concentration MC_{0.01-2.5} is well correlated with
16 gravimetric PM_{2.5}, and the number concentration NC_{0.01-2.5} is well correlated with total particle
17 counts from a condensation particle counter (CPC). Mortality data were coded by cause of
18 death, with some discrimination between underlying causes and prevalent conditions of the
19 deceased.

20 In the reanalysis by Stolzel et al. (2003), daily mortality data were fitted using a Poisson
21 GAM (with stringent convergence criteria) and GLM, with adjustments for weather variables,
22 time trends, day of week, and particle indices. Weekly data for all of Germany on influenza
23 and similar diseases were also included in the model. In the original study, two types of models
24 were fitted; one used the best single-day lag for air pollution and a second used the
25 best polynomial distributed lag (PDL) model for air pollution. Both linear (i.e., raw) and
26 log-transformed pollution indices were examined. PDL models in the original analysis generally
27 had larger and more significant PM effects than single-day lag models, but the reanalysis by
28 Stolzel et al. (2003) focused on single-day lag results only. Therefore, the numerical results in
29 the following discussion only include the single day lag results from the reanalysis. It should be
30 noted that, unlike most of the recent reanalyses that have been conducted to address the GAM

1 conversion issue, the reanalysis results from this study were virtually unchanged from the
2 original results.

3 Both mass and number concentrations at the size ranges examined were mostly positively
4 (and nearly significantly) associated with total non-accidental mortality. The best single-day
5 lags reported were mostly 0 or 1 day lag for mass concentrations and the 4 day lag for number
6 concentrations. For example, the estimated excess risk for $MC_{0.01-2.5}$ at lag 1 day was about 3.9%
7 (CI: 0, 7.7) per $25 \mu\text{g}/\text{m}^3$. The corresponding number for smaller fine particles, $MC_{0.01-1.0}$, was
8 3.5% (CI: -0.4, 7.7). For number concentration, the estimated excess risk for $NC_{0.01-2.5}$ at lag 4
9 day was about 4.1% (CI: -0.9, 9.3) per IQR (13,269 particles/ cm^3). The corresponding number
10 for smaller fine particles, $NC_{0.01-1.0}$, was 4.6% (CI: -0.3, 9.7) per IQR (12,690 particles/ cm^3).
11 An examination of all the results for $MC_{0.01-2.5}$ and $NC_{0.01-0.1}$ shown for lags 0 through 5 days
12 indicates that the associations were mostly positive for these mass and number concentrations,
13 except for the “dip” around 2 or 3 day lags.

14 The estimated excess risks are reduced, sometimes drastically, when co-pollutants
15 (especially SO_2 and NO_2) are included in a two-pollutant model. This is not surprising, as the
16 number and mass concentrations of various ultrafine and fine particles in all size ranges are
17 rather well correlated with gaseous co-pollutants, except for the intermodal size range $MC_{1.0-2.5}$.
18 The number correlations range from 0.44 to 0.62 with SO_2 , from 0.58 to 0.66 with NO_2 , and
19 from 0.53 to 0.70 with CO. The mass correlations range from 0.53 to 0.62 with SO_2 , from 0.48
20 to 0.60 with NO_2 , and from 0.56 to 0.62 with CO. The authors found that ultrafine particles, CO
21 and NO_2 form a group of pollutants strongly identified with motor vehicle traffic. Immediate
22 and delayed effects seemed to be independent in two-pollutant models, with single-day lags of 0
23 to 1 days and 4 to 5 days giving ‘best fits’ to data. The delayed effect of ultrafine particles was
24 stronger than that for NO_2 or CO. The large decreases in excess risk for number concentration,
25 particularly when NO_2 is a co-pollutant with $NC_{0.01-0.1}$, clearly involves a more complex structure
26 than simple correlation. The large decrease in excess risk when SO_2 is a co-pollutant with
27 $MC_{0.01-2.5}$ is not readily explained and is discussed in some detail in Wichmann et al. (2000).

28 SO_2 is a strong predictor of excess mortality in this study; and its estimated effect is little
29 changed when different particle indicators are included in a two-pollutant model. The authors
30 noted “. . .the [LOESS] smoothed dose response curve showed most of the association at the left
31 end, below $15 \mu\text{g}/\text{m}^3$, a level at which effects were considered biologically implausible. . .”

1 Replacement of sulfur-rich surface coal has reduced mean SO₂ levels in Erfurt from 456 µg/m³
2 in 1988 to 16.8 µg/m³ during 1995 to 1998 and to 6 µg/m³ in 1998. The estimated
3 concentration-response functions for SO₂ are very different for these time periods, comparing
4 Spix et al. (1993) versus Wichmann et al. (2000) results. Wichmann et al. concluded “These
5 inconsistent results for SO₂ strongly suggested that SO₂ was not the causal agent but an indicator
6 for something else.” The authors offered no specific suggestions as to what the “something else”
7 might be, but they did finally conclude that their studies from Germany strongly supported PM
8 air pollution as being more relevant than SO₂ to observed mortality outcomes. However, the
9 HEI committee also did not agree with the investigators’ interpretation that the association of
10 SO₂ with mortality was an artifact, given the similar magnitude of effect sizes between
11 particulate matter and SO₂ and the persistence of an SO₂ effect in the two-pollutant analyses.
12

13 **8.2.2.5.2 Chemical Components**

14 Several new studies from the U.S., Canada, and The Netherlands examined mortality
15 associations with specific chemical components of ambient PM. Table 8-3 shows the chemical
16 components examined in these studies; the mean concentrations for Coefficient of Haze (CoH),
17 sulfate, and H⁺; and indications of those components found to be associated with increased
18 mortality.
19

20 ***Coefficient of Haze, Elemental Carbon, and Organic Carbon***

21 CoH is highly correlated with elemental carbon (EC) and is often considered as a good PM
22 index for motor vehicle sources, although other combustion processes such as space heating
23 likely also contribute to CoH levels. Several studies (Table 8-3) examined CoH; and, in most
24 cases, positive and significant associations with mortality outcomes were reported. In terms of
25 relative significance of CoH in comparison to other PM components, CoH was not the clearly
26 most significant PM component in most of these studies. The average level of CoH in these
27 studies ranged from 0.24 (Montreal, Quebec) to 0.5 (Santa Clara County, CA) 1000 linear feet.
28 The correlations between CoH and NO₂ or CO in these studies (8 largest Canadian cities; Santa
29 Clara County, CA) were moderately high (r .0.7 to 0.8) and suggested a likely motor vehicle
30 contribution. Both EC and OC were significant predictors of cardiovascular mortality in the
31 Phoenix study; their effect sizes per IQR were comparable to those for PM₁₀, PM_{2.5}, and PM_{10-2.5}.

**TABLE 8-3. NEWLY AVAILABLE STUDIES OF MORTALITY
RELATIONSHIPS TO PM CHEMICAL COMPONENTS**

Author, City	Mean CoH (1000ft)	Mean SO₄⁼ (ug/m³)	Mean H⁺ (nmol/m³)	Other PM components analyzed	Specific PM components found to be associated with mortality (comments).
Burnett et al. (2000); Burnett and Goldberg (2003)* 8 largest Canadian cities, 1986- 1996.	0.26	2.6		PM ₁₀ , PM _{2.5} , PM _{10-2.5} , and 47 trace elements	PM ₁₀ , PM _{2.5} , CoH, sulfate, Zn, Ni, and Fe were significantly associated with total mortality in the original analysis. The reanalysis only analyzed mass concentration indices.
Fairley (1999 & 2003)*; Santa Clara County, CA.	0.5	1.8		PM ₁₀ , PM _{2.5} , PM _{10-2.5} , and nitrate	CoH, sulfate, nitrate, PM ₁₀ , and PM _{2.5} were associated with mortality. PM _{2.5} and nitrate most significant.
Goldberg et al. (2000); Goldberg and Burnett (2003); Goldberg et al. (2003)* Montreal, Quebec, Canada. 1984-1993.	0.24	3.3		Predicted PM _{2.5} , and extinction coefficient (visual- range derived).	CoH and extinction coefficient were associated with the deaths that were classified as having congestive heart failure before death based on medical records. Associations were stronger in warm season.
Lipfert et al., (2000a) Philadelphia, PA. 1992-1995.	0.28	5.1	8.0	Nephelometry, NH ₄ ⁺ , TSP, PM ₁₀ , PM _{2.5} , and PM _{10-2.5}	Essentially all PM components were associated with mortality.
Lippmann et al. (2000); Ito (2003)* Detroit, MI. 1992-1994.		5.2	8.8	PM ₁₀ , PM _{2.5} , and PM _{10-2.5}	PM ₁₀ , PM _{2.5} , and PM _{10-2.5} were more significantly associated with mortality outcomes than sulfate or H ⁺ .
Klemm and Mason (2000) Atlanta, GA 1998-1999		5.2	8.8	Nitrate, EC, OC, oxygenated HC, PM ₁₀ , PM _{2.5} , and PM _{10-2.5}	“Interim” results based on one year of data. No statistically significant associations for any pollutants. Those with t-ratio of at least 1.0 were H ⁺ , PM ₁₀ , and PM _{2.5} .
Mar et al. (2000 & 2003)* Phoenix, AZ. 1995-1997.				EC, OC, TC, PM ₁₀ , PM _{2.5} , and PM _{10-2.5}	EC, OC, TC, PM ₁₀ , PM _{2.5} , and PM _{10-2.5} were associated with cardiovascular mortality.
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.		12.7		PM ₁₅ , PM _{2.5} , cyclohexane-solubles (CX), dichloromethane- solubles (DCM), and acetone-solubles (ACE).	PM ₁₅ , PM _{2.5} , sulfate, CX, and ACE were significantly associated with total and/or cardiovascular mortality in Newark and/or Camden.
Hoek (2003)* The Netherlands. 1986-1994.		3.8 (median)		PM ₁₀ , BS, and nitrate	Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM ₁₀ .

*Note: The study was originally analyzed by GAM models only using default convergence criteria and at least two non-parametric smoothing terms and was recently reanalyzed by GAM using stringent convergence criteria and/or other non-GAM analyses.

1 Also, both EC and OC represented major mass fractions of PM_{2.5} (11% and 38%, respectively)
2 and were correlated highly with PM_{2.5} (r = 0.84 and 0.89, respectively). They were also highly
3 correlated with CO and NO₂ (r = 0.8 to 0.9), indicating their associations with an “automobile”
4 factor. Thus, the CoH and EC/OC results from the Mar et al. (2000 and 2003) study suggest that
5 PM components from motor vehicle sources are likely associated with mortality. In a recent
6 study in Montreal, Quebec, by Goldberg et al. (2000 and 2003), CoH appeared to be correlated
7 with the congestive heart failure mortality (as classified based on medical records) more strongly
8 than other PM indices such as the visual-range derived extinction coefficient (considered to be
9 a good indicator of sulfate). However, the main focus of the study was the role of
10 cardiorespiratory risk factors for air pollution, and the investigators warned against comparing
11 the relative strength of associations among PM indices, pointing out complications such as likely
12 error involved in the visual range measurements. Additionally, the estimated PM_{2.5} values were
13 predicted from other PM indices, including CoH and extinction coefficient, making it difficult to
14 compare straightforwardly the relative importance of PM indices.

16 *Sulfate and Hydrogen Ion*

17 Sulfate and H⁺, markers of acidic components of PM, have been hypothesized to be
18 especially harmful components of PM (Lippmann et al., 1983; Lippmann and Thurston, 1996).
19 The newly available studies that examined sulfate are shown in Table 8-3; two of them also
20 analyzed H⁺ data. The sulfate concentrations ranged from 1.8 µg/m³ (Santa Clara County, CA)
21 to 12.7 µg/m³ (three NJ cities). Aside from the west versus east coast contrast, the higher levels
22 observed in the three NJ cities are likely due to their study period coverage of the early 1980’s,
23 when sulfate levels were higher. Sulfate explained 25 to 30% of PM_{2.5} mass in eastern U.S. and
24 Canadian cities, but it was only 14% of PM_{2.5} mass in Santa Clara County, CA. The H⁺ levels
25 measured in Detroit and Philadelphia were low. The mean H⁺ concentration for Detroit, MI (the
26 H⁺ was actually measured in Windsor, a Canadian city a few miles from downtown Detroit), 8.8
27 nmol/m³, was low as compared to the reported detection limit of 15.1 nmol/m³ (Brook et al.,
28 1997) for the measurement system used in the study. Note that the corresponding detection limit
29 for sulfate was 3.6 nmol/m³ (or 0.34 µg/m³); and the mean sulfate level for Detroit was 54
30 nmol/m³ (or 5.2 µg/m³), so that the signal-to-noise ratio is expected to be higher for sulfate than

1 for H⁺. Thus, the ambient levels and possible relative measurement errors for these data should
2 be considered in interpreting the relative strength of mortality associations in these data.

3 Sulfate was a statistically significant predictor of mortality, at least in single pollutant
4 models, in: Santa Clara County, CA; Philadelphia, PA; Newark, NJ; and Camden, NJ, but not in
5 Elizabeth, NJ; Detroit, MI; or Montreal, CN. However, it should be noted that the relative
6 significance across the cities is influenced by the sample size (both the daily mean death counts
7 and number of days available), as well as the range of sulfate levels and should be interpreted
8 with caution. Figure 8-6 shows the excess risks (\pm 95% CI) estimated per 5 $\mu\text{g}/\text{m}^3$ increase in
9 24-h sulfate reported in these studies compared to the reanalysis results of the earlier Six Cities
10 Study by Klemm and Mason (2003). The largest estimate was seen for Santa Clara County, CA;
11 but the wide confidence band (possibly due to the small variance of the sulfate, because its levels
12 were low) should be taken into account. In addition, the sulfate effect in the Santa Clara County
13 analysis was eliminated once PM_{2.5} was included in the model, perhaps being indicative of
14 sulfate mainly serving as a surrogate for fine particles in general there. In any case, more weight
15 should be accorded to estimates from other studies with narrower confidence bands. In the other
16 studies, the effect size estimates mostly ranged from about 1 to 4% per 5 $\mu\text{g}/\text{m}^3$ increase in 24-h
17 sulfate.

18 The relative significance of sulfate and H⁺ compared to other PM components is not
19 clear in the existing small number of publications. Because each study included different
20 combinations of co-pollutants that had different extents of correlation with sulfate and because
21 multiple mortality outcomes were analyzed, it is difficult to assess the overall importance of
22 sulfate across the available studies. The fact that the Lippmann et al. (2000) study and the
23 reanalysis by Ito (2003) found that Detroit, MI data on H⁺ and sulfate were less significantly
24 associated with mortality than the size-fractionated PM mass indices may be due to acidic
25 aerosols levels being mostly below the detection limit in that data. In this case, it appears that
26 the Detroit PM components show mortality effects even without much acidic input.

27 In summary, assessment of new study results for individual chemical components of PM
28 suggest that an array of PM components (mainly fine particle constituents) are associated with
29 mortality outcomes, including CoH, EC, OC, sulfate, and nitrate. The variations seen with
30 regard to the relative significance of these PM components across studies may be in part due to

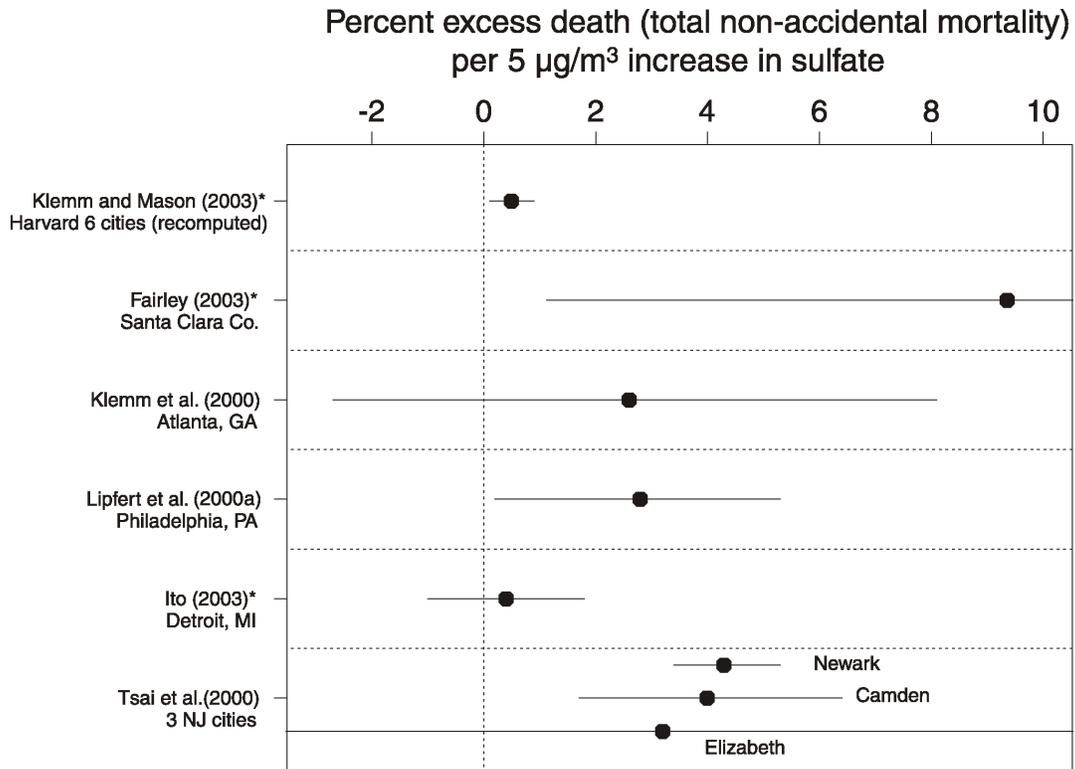


Figure 8-6. Excess risks estimated per 5 µg/m³ increase in sulfate, based on the studies in which both PM_{2.5} and PM_{10-2.5} data were available.

1 differences in their concentrations from locale to locale. This issue is further discussed below as
 2 part of the assessment of new studies involving source-oriented evaluation of PM components.

3
 4 **8.2.2.5.3 Source-Oriented Evaluations**

5 Several new studies have conducted source-oriented evaluation of PM components.
 6 In these studies, daily concentrations of PM components (i.e., trace elements) and gaseous
 7 co-pollutants were analyzed using factor analysis to estimate daily concentrations due to
 8 underlying source types (e.g., motor vehicle emissions, soil, etc.), which are weighted linear
 9 combinations of associated individual variables. The mortality outcomes were then regressed on
 10 those factors (factor scores) to estimate the effect of source types rather than just individual
 11 variables. These studies differ in terms of specific objectives/focus, the size fractions from

1 which trace elements were extracted, and the way factor analysis was used (e.g., rotation). The
 2 main findings from these studies regarding the source-types identified (or suggested) and their
 3 associations with mortality outcomes are summarized in Table 8-4.
 4
 5

TABLE 8-4. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PM COMPONENTS IN RECENT STUDIES

Author, City	Source types identified (or suggested) and associated variables	Source types associated with mortality (Comments)
Laden et al., (2000); Schwartz (2003a)* Harvard Six Cities. 1979-1988.	<i>Soil and crustal material:</i> Si <i>Motor vehicle emissions:</i> Pb <i>Coal combustion:</i> Se <i>Fuel oil combustion:</i> V <i>Salt:</i> Cl Note: the trace elements are from PM _{2.5} samples	Strongest increase in daily mortality was associated with the mobile source factor. Coal combustion factor was also positively associated with mortality. Crustal factor from fine particles not associated (negative but not significant) with mortality. Coal and mobile sources account for the majority of fine particles in each city.
Mar et al. (2000 & 2003)* Phoenix, AZ. 1995-1997.	PM_{2.5} (from DFPSS) trace elements: <i>Motor vehicle emissions and re-suspended road dust:</i> Mn, Fe, Zn, Pb, OC, EC, CO, and NO ₂ <i>Soil:</i> Al, Si, and Fe <i>Vegetative burning:</i> OC, and K _s (soil-corrected potassium) <i>Local SO₂ sources:</i> SO ₂ <i>Regional sulfate:</i> S	PM_{2.5} factors results: Motor vehicle factor (1 day lag), vegetative burning factor (3 day lag), and regional sulfate factor (0 day lag) were significantly positively associated with cardiovascular mortality.
	PM_{10-2.5} (from dichot) trace elements: <i>Soil:</i> Al, Si, K, Ca, Mn, Fe, Sr, and Rb <i>A source of coarse fraction metals:</i> Zn, Pb, and Cu <i>A marine influence:</i> Cl	Factors from dichot PM _{10-2.5} trace elements not analyzed for their associations with mortality because of the small sample size (every 3 rd -day samples from June 1996).
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	<i>Motor vehicle emissions:</i> Pb, CO <i>Geological (Soil):</i> Mn, Fe <i>Oil burning:</i> V, Ni <i>Industrial:</i> Zn, Cu, Cd (separately) <i>Sulfate/secondary aerosol:</i> sulfate Note: the trace elements are from PM ₁₅ samples	Oil burning, industry, secondary aerosol, and motor vehicle factors were associated with mortality.

*Note: The study was originally analyzed using GAM models only with default convergence criteria using at least two non-parametric smoothing terms, but was later reanalyzed using more stringent convergence criteria and/or other approaches.

1 The Laden et al. (2000) analysis of Harvard Six Cities data for 1979-1988 (reanalyzed by
2 Schwartz, 2003a) aimed to identify distinct source-related fractions of $PM_{2.5}$ and to examine each
3 fraction's association with mortality. Fifteen elements in the fine fraction samples routinely
4 found above their detection limits were included in the data analysis. For each of the six cities,
5 up to 5 common factors were identified from among the 15 elements, using specific rotation
6 factor analysis. Using the Procrustes rotation (a type of oblique rotation), the projection of the
7 single tracer for each factor was maximized. This specification of the tracer element was based
8 on (a) knowledge from previous source apportionment research; (b) the condition that the
9 regression of total fine mass on that element must result in a positive coefficient; and (c) the
10 identifications of additional local source factors that positively contributed to total fine mass
11 regression. Three source factors were identified in all six cities: (1) a soil and crustal material
12 factor with Si as a tracer; (2) a motor vehicle exhaust factor with Pb as a tracer; and (3) a coal
13 combustion factor with Se as a tracer. City-specific analyses also identified a fuel combustion
14 factor (V), a salt factor (Cl), and selected metal factors (Ni, Zn, or Mn). In the original analysis
15 by Laden et al., a GAM Poisson regression model (with default convergence criteria), adjusting
16 for trend/season, day-of-week, and smooth function of temperature/dewpoint, was used to
17 estimate impacts of each source type (using absolute factor scores) simultaneously for each city.
18 In the reanalysis reported by Schwartz (2003a), GAM models with LOESS smoothers were
19 replaced with penalized splines. Summary estimates across cities were obtained by combining
20 the city-specific estimates, using inverse-variance weights. The identified factors and their
21 tracers are listed in Table 8-4. The reanalysis using penalized splines changed somewhat the risk
22 estimates for source-apportioned mass concentrations in each city compared to those in the
23 original GAM results (increasing estimates in some cities and reducing them in others), but the
24 combined estimates across the six cities did not change substantially. The combined estimates
25 indicated that the largest increase in daily mortality was associated with the mobile source
26 associated fine mass concentrations, with an excess risk increase of 9.3% (CI: 4.0, 14.9) per
27 $25 \mu\text{g}/\text{m}^3$ source-apportioned $PM_{2.5}$ (average of 0 and 1 day lags). The corresponding value for
28 the $PM_{2.5}$ mass apportioned for the coal combustion factor was 2.0% (CI: -0.3, 4.4). The crustal
29 factor was not associated with mortality (-5.1%; CI: -13.9, 4.6).

30 Mar et al. (2000) analyzed PM_{10} , $PM_{10-2.5}$, $PM_{2.5}$ measured by two methods, and various
31 sub-components of $PM_{2.5}$ for their associations with total (non-accidental) and cardiovascular

1 deaths in Phoenix, AZ during 1995-1997, using both individual PM components and factor
2 analysis-derived factor scores. In the original analysis, GAM Poisson models (with default
3 convergence criteria) were used and adjusted for season, temperature, and relative humidity.
4 In the reanalysis (Mar et al., 2003), GAM models with stringent convergence criteria and GLM
5 models with natural splines were used. Only cardiovascular mortality was analyzed in the
6 reanalysis; and the results for that category are summarized here. The evaluated air pollution
7 variables included O₃, SO₂, NO₂, CO, TEOM PM₁₀, TEOM PM_{2.5}, TEOM PM_{10-2.5}, DFPSS PM_{2.5},
8 S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were
9 evaluated. A factor analysis conducted on the chemical components of DFPSS PM_{2.5} (Al, Si, S,
10 Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC) identified factors for motor vehicle emissions/re-
11 suspended road dust; soil; vegetative burning; local SO₂ sources; and regional sulfate (see
12 Table 8-4). The results of mortality regression with these factors suggested that the motor
13 vehicle factor (lag 1 day), vegetative burning factor (3 day lag), and regional sulfate factor
14 (0 day lag) each had significant positive associations with cardiovascular mortality. The PM_{2.5}
15 mass was not apportioned to these factors in this study; so information on the excess-deaths
16 estimate per source-apportioned PM_{2.5} concentrations was not available. The authors also
17 analyzed elements from dichot PM_{10-2.5} samples and identified soil, coarse fraction metals, and
18 marine influence factors. However, these factors were not analyzed for their associations with
19 mortality outcomes due to the short measurement period (starting in June 1996 with every 3rd-
20 day sampling).

21 It should be noted here that the Smith et al. (2000) analysis of Phoenix data also included
22 factor analysis on the elements from the coarse fraction and identified essentially the same
23 factors (the “coarse fraction metals” factor in Mar et al.’s study was called “the anthropogenic
24 elements” in Smith et al.’s study). While Smith et al. did not relate these factors to mortality
25 (due to a small sample size), they did show that the anthropogenic elements were low in summer
26 and spring, when the PM_{10-2.5} effect was largest. These results suggest that the PM_{10-2.5} effects
27 may not necessarily be due to anthropogenic components of the coarse particles, biogenically-
28 contaminated coarse particles perhaps being key during the warmer months (as noted in
29 Chapter 7 discussions of bioaerosols).

30 Tsai et al. (2000) conducted an exploratory analysis of mortality in relation to specific PM
31 source types for three New Jersey cities (Camden, Newark, and Elizabeth) using factor analysis -

1 Poisson regression techniques. During the three-year study period (1981-1983), extensive
2 chemical speciation data were available, including nine trace elements, sulfate, and particulate
3 organic matter. Total (excluding accidents and homicides), cardiovascular, and respiratory
4 mortality were analyzed. A factor analysis of trace elements and sulfate was first conducted and
5 identified several major source types: motor vehicle (Pb, CO); geological (Mn, Fe); oil burning
6 (V, Ni); industrial (Zn, Cu); and sulfate/secondary aerosols (sulfate). In addition to Poisson
7 regression of mortality on these factors, an alternative approach was also used, in which the
8 inhalable particle mass (IPM, $D_{50} < 15 \mu\text{m}$) was first regressed on the factor scores of each of the
9 source types to apportion the PM mass and then the estimated daily PM mass for each source
10 type was included in Poisson regression, so that RR could be calculated per mass concentration
11 basis for each PM source type. Oil burning (V, Ni), various industrial sources (Zn, Cd), motor
12 vehicle (Pb, CO), and secondary aerosols, as well as the individual PM indices IPM, FPM
13 ($D_{50} < 3.5 \mu\text{m}$), and sulfates, were all associated with total and/or cardiorespiratory mortality in
14 Newark and Camden, but not in Elizabeth. In Camden, the RRs for the source-oriented PM were
15 higher (1.10) than those for individual PM indices (1.02).

16 In summary, these source-oriented factor analyses studies suggest that a number of source
17 types are associated with mortality, including motor vehicle emissions, coal combustion, oil
18 burning, and vegetative burning. The crustal factor from fine particles was not associated with
19 mortality in the Harvard Six Cities data. In Phoenix, where coarse particles were reported to be
20 associated with mortality, the associations between the factors related to coarse particles (soil,
21 marine influence, and anthropogenic elements) and mortality could not be evaluated due to the
22 small sample size. Thus, although unresolved issues do remain (mainly due to the lack of
23 sufficient data), the limited results from the source-oriented evaluation approach (using factor
24 analysis) thus far seem to implicate ambient fine particles of anthropogenic origin from several
25 sources as likely being important in contributing to increased mortality risks.

26 27 **8.2.2.6 New Assessments of Cause-Specific Mortality**

28 Consistent with similar findings described in the 1996 PM AQCD, most of the newly
29 available studies summarized in Tables 8-1 and 8A-1 that examined non-accidental total,
30 circulatory, and respiratory mortality categories (e.g., the NMMAPS analyses reported by
31 Samet) have continued to find significant PM associations with both cardiovascular and/or

1 respiratory-cause mortality. Several studies (e.g., Fairley, 1999; his reanalysis, 2003; Wordley
2 et al., 1997; Prescott et al., 1998) reported estimated PM effects that were generally higher for
3 respiratory deaths than for circulatory or total deaths.

4 The NMMAPS 90-cities analyses not only examined all-cause mortality (excluding
5 accidents), but also evaluated cardiorespiratory and other remaining causes of deaths (Samet
6 et al., 2000a,b; reanalysis by Dominici et al., 2002 and 2003). Results were presented for all-
7 cause, cardiorespiratory, and “other” mortality for lag 0, 1, and 2 days. The investigators
8 commented that, compared to the result for cardiorespiratory deaths showing 1.6% (CI: 0.8, 2.4)
9 increase per 50 $\mu\text{g}/\text{m}^3\text{PM}_{10}$ in a GLM model (versus 1.1% for total non-accidental mortality
10 using GLM), there was less evidence for non-cardiorespiratory deaths. However, the estimates
11 for “other” mortality, although less than half the size of those for cardiorespiratory mortality,
12 were nevertheless positive, with a fairly high posterior probability (e.g., 0.92 at lag 1 day) that
13 the overall effects were greater than zero. It should be noted that the “other” (other than
14 cardiorespiratory) category for underlying cause of mortality may at times include some deaths
15 influenced by cardiovascular or respiratory causes. For example, Lippmann et al. (2000) noted
16 that the “other” (non-circulatory and non-respiratory) mortality in their study showed seasonal
17 cycles and apparent influenza peaks, suggesting that this series may have also been influenced
18 by respiratory contributing causes. Thus, interpretation of the observed associations between
19 PM and broad “specific” categories (e.g., other) of underlying causes of death may not be
20 straightforward.

21 As also mentioned earlier in the multi-cities results section, Schwartz (2003b) reanalyzed
22 data from Braga et al. (2001a) to examine the lag structure of PM_{10} associations with specific
23 causes of mortality in ten U.S. cities. The pattern of larger PM_{10} excess risk estimates for
24 respiratory categories than for cardiovascular categories found in this study was similar to that in
25 the Hoek et al. analyses noted above. For example, the combined risk estimates across 10 cities
26 per 50 $\mu\text{g}/\text{m}^3$ increase in PM_{10} (2-day mean) were 4.1% (CI: 2.5, 5.6), 7.7% (CI: 4.1, 11.5), and
27 11.0% (CI: 7, 15.1) for cardiovascular, COPD, and pneumonia, respectively, using GAM with
28 stringent convergence criteria. These values were even larger for unconstrained distributed lag
29 models.

30 Another U.S. study, that of Moolgavkar (2000a), evaluated possible PM effects on cause-
31 specific mortality across a broad range of lag times (0-5 days) in Cook Co., IL; Los Angeles Co.,

1 CA; and Maricopa Co., AZ. In addition to total non-accidental mortality, deaths related to all
2 cardiovascular disease (CVD), cerebrovascular disease (CRV), and chronic obstructive lung
3 disease (COPD) were analyzed in the original study. The data for Cook Co. and Maricopa Co.
4 were reanalyzed using GAM model with stringent convergence criteria and GLM model with
5 natural splines (Moolgavkar, 2003). Cerebrovascular disease mortality was not reanalyzed
6 because there was little evidence of association for PM with this category at any lag in any of the
7 three counties analyzed. Moolgavkar reported varying patterns of results for PM indices in
8 evaluations of daily deaths related to CVD and COPD in the two counties. In the Cook Co.
9 (Chicago) area, the association of PM₁₀ with CVD mortality was statistically significant at a lag
10 of 3 days based on a single-pollutant analysis and continued to be significantly associated with
11 CVD deaths with a 3-day lag in two pollutant models including one or another of CO, NO₂, SO₂,
12 or O₃. In Los Angeles single-pollutant analyses, CVD mortality was significantly associated
13 with PM₁₀ (2 day lag) and PM_{2.5} (0 and 1 day lag). Their percent excess risk estimates were up
14 to twice those for total non-accidental mortality. In a two-pollutant model with CO (most
15 strongly positively associated with mortality in Los Angeles Co. among the pollutants), PM₁₀
16 risk estimates were reduced. However, PM_{2.5} excess risk estimates in the two-pollutant model
17 with CO nearly doubled (2.5% per 25 µg/m³ increase in PM_{2.5} to 4.8% using GLM); whereas that
18 for CO became significantly negative. Obviously, given that CO and PM_{2.5} were fairly well
19 correlated ($r \approx 0.58$), the estimated associations were most likely confounded between these two
20 pollutants in this locale. With regard to COPD deaths, PM₁₀ was significantly associated with
21 COPD mortality (lag 2 days) in Cook Co., but in Los Angeles Co., both PM₁₀ and (especially)
22 PM_{2.5} showed erratic associations with COPD mortality at varying lags, alternating positive and
23 negative (significantly, at lag 3 day) coefficients. The combination of the every 6th-day PM data
24 in Los Angeles (versus daily PM₁₀ in Cook Co.) and relatively small daily counts for COPD
25 (median = 6/day versus 57/day for CVD) in Los Angeles makes the effective sample size of
26 COPD mortality analysis small and the results unstable for that county.

27 The Goldberg et al. (2000; 2001a,b,c,d) study, and its reanalyses (Goldberg et al., 2003;
28 Goldberg and Burnett, 2003) in Montreal, CN, investigated the role of co-morbidity prior to
29 deaths in PM-mortality associations for various subcategories, including cancer, acute lower
30 respiratory disease, chronic coronary artery disease, and congestive heart failure (CHF). They
31 could classify deaths into these subcategories using medical records from the universal Quebec

1 Health Insurance Plan (QHIP). This way of classifying deaths would presumably take into
2 account more detailed information on the disease condition prior to death than the “underlying
3 cause” in the death records. Thus, the PM-mortality associations could be compared by using
4 subcategories defined by underlying cause of health (from death records versus those deaths for
5 which patient records from QHIP could be used to identify the co-morbidity conditions). The
6 Goldberg and Burnett (2003) reanalysis found that total non-accidental mortality (which was
7 significantly associated with PM indices in the original report using GAM with default
8 convergence criteria) was not associated with PM indices in GLM models. They reported that
9 the associations between PM and non-accidental mortality were rather sensitive to weather
10 model specification and did not find significant PM associations with most of the subcategories
11 as defined from either QHIP or underlying cause. However, they did find significant
12 associations between CoH, NO₂, and SO₂ and the CHF deaths as defined from QHIP, but not
13 the CHF deaths as defined from underlying cause. The association was even stronger in
14 warm seasons. It should be noted, however, that while the period for this study was relatively
15 long (~10 years) and the counts for the total non-accidental deaths were not small
16 (median = 36 deaths per day), the counts for various subcategories were quite small (e.g., CHF
17 underlying cause mortality mean = 0.75 per day).

18 Zmirou et al. (1998) presented cause-specific mortality analyses results for 10 of the
19 12 APHEA European cities (APHEA1). Using Poisson autoregressive models parametrically
20 adjusting for trend, season, influenza epidemics, and weather, each pollutant’s relative risk was
21 estimated for each city and “meta-analyses” of city-specific estimates were conducted. The
22 pooled excess risk estimates for cardiovascular mortality were 1.0% (CI: 0.3, 1.7) per
23 25 µg/m³ increase in BS and 2.0% (CI: 0.5, 3.0) per 50 µg/m³ increase in SO₂ in western
24 European cities. The pooled risk estimates for respiratory mortality in the same cities were
25 2.0% (CI: 0.8, 3.2) and 2.5% (CI: 1.5, 3.4) for BS and SO₂, respectively.

26 Seeking unique cause-specificity of effects associated with various pollutants has been
27 difficult because the “cause specific” categories examined are typically rather broad (usually
28 cardiovascular and respiratory) and overlap and because cardiovascular and respiratory
29 conditions tend to occur together. Examinations of more specific cardiovascular and respiratory
30 subcategories may be necessary to test hypotheses about any specific mechanisms, but smaller
31 sample sizes for more specific sub-categories may make a meaningful analysis difficult. The

1 Hoek et al. (2000 and 2001) study and its reanalysis by Hoek (2003) took advantage of a larger
2 sample size to examine cause-specific mortality. The large sample size, including the whole
3 population of the Netherlands (mean daily total deaths ~330, or more than twice that of Los
4 Angeles County), allowed examination of specific cardiovascular causes of deaths. The
5 reanalysis using GAM with stringent convergence criteria as well as GLM with natural splines
6 either did not change or even increased the effect estimates. Deaths due to heart failure,
7 arrhythmia, and cerebrovascular causes were more strongly (~2 to 4 times larger excess risks)
8 associated with air pollution than the overall cardiovascular deaths. The investigators concluded
9 that specific cardiovascular causes (such as heart failure) were more strongly associated with air
10 pollution than total cardiovascular mortality, but noted that the largest contribution to the
11 association between air pollution and cardiovascular mortality was from ischemic heart disease
12 (about half of all CVD deaths). The analyses of specific respiratory causes, COPD, and
13 pneumonia yielded even larger risk estimates (e.g., ~ 6 to 10 times, respectively, larger than that
14 for overall cardiovascular deaths). Estimated PM₁₀ excess risks per 50 µg/m³ PM₁₀ (average of
15 0 through 6 day lags) were 1.2% (CI: 0.2, 2.3), 0.9% (CI: -0.8, 2.7), 2.7% (CI: -4.2, 10.1),
16 2.4% (CI: -2.3, 7.4), 6.1% (CI: 1, 11.4), and 10.3% (CI: 3.7, 17.2), respectively, for total non-
17 accidental, cardiovascular, arrhythmia, heart failure, COPD, and pneumonia, using GAM models
18 with stringent convergence criteria. Thus, the results from this study with a large effective
19 sample size also confirm past observations that PM risk estimates for specific causes of
20 cardiovascular or respiratory mortality can be larger than those estimated for total non-accidental
21 mortality.

22 Another study (Gouveia and Fletcher, 2000), using data from Sao Paulo, Brazil for
23 1991-1993, evaluated respiratory mortality in children (age ≤ 5 years). The Poisson auto-
24 regressive model included parametric terms (e.g., quadratic, two-piece linear temperature etc.) to
25 adjust for weather and temporal trends. Although Gouveia and Fletcher found significant
26 associations between air pollution and elderly mortality, they did not find statistically significant
27 associations between air pollution and child respiratory mortality (the PM₁₀ coefficient was
28 negative and not significant). However, it should be noted that the average daily respiratory
29 mortality counts for this study were relatively small (~2.4/day) and the modest period of
30 observations (3 years) short. Thus, the statistical power of the data was likely less than

1 desirable, and there may not have been sufficient power to elucidate the range of short-term PM
2 effects on child respiratory mortality.

3 Overall, then, the above assessment of newly available studies provides interesting
4 additional new information with regard to cause-specific mortality related to ambient PM. That
5 is, a growing number of studies continue to report increased cardiovascular- and respiratory-
6 related mortality risks as being significantly associated with ambient PM measures at one or
7 another varying lag times. When specific subcategories of cardiovascular disease were
8 examined in a large population (e.g. in the Netherlands study by Hoek et al.), some of the
9 subcategories such as heart failure were more strongly associated with PM and other pollutants
10 than total cardiovascular mortality. Largest PM effect size estimates are most usually reported
11 for 0-1 day lags (with some studies also now noting a second peak at 3-4 day lags). A few of the
12 newer studies also report associations of PM metrics with “other” (i.e., non-cardiorespiratory)
13 causes, as well. However, at least some of these “other” associations may also be due to
14 seasonal cycles that include relationships to peaks in influenza epidemics that may imply
15 respiratory complications as a contributing cause to the “other” deaths. Alternately, the “other”
16 category may include sufficient numbers of deaths due to diabetes or other diseases which may
17 also involve cardiovascular complications as contributing causes. Varying degrees of robustness
18 of PM effects are seen in the newer studies, as typified by PM estimates in multiple pollutant
19 models containing gaseous co-pollutants. That is, some studies show little effect of gaseous
20 pollutant inclusion on estimated PM effect sizes, some show larger reductions in PM effects to
21 non-significant levels upon such inclusion, and a number also report significant associations of
22 cardiovascular and respiratory effects with one or more gaseous co-pollutants. Thus, the newer
23 studies both further substantiate PM effects on cardiovascular- and respiratory-related mortality,
24 while also pointing toward possible significant contributions of gaseous pollutants to such cause-
25 specific mortality. The magnitudes of the PM effect size estimates are consistent with the range
26 of estimates derived from the few earlier available studies assessed in the 1996 PM AQCD.

8.2.2.7 Salient Points Derived from Assessment of Studies of Short-Term Particulate Matter Exposure Effects on Mortality

The most salient key points to be extracted from the above discussion of newly available information on short-term PM exposures relationships to mortality can be summarized as follow:

PM₁₀ effects estimates. Since the 1996 PM AQCD, there have been more than 80 new time-series PM-mortality analyses published. Estimated mortality relative risks in these studies are generally positive, statistically significant, and consistent with the previously reported PM-mortality associations. However, due to the concerns regarding the GAM convergence issue, quantitative evaluations were made here based only on the studies that either did not use GAM Poisson model with default convergence criteria or on those studies that have reanalyzed the data using more stringent convergence criteria and/or used fully parametric approaches.

Of interest are several studies that evaluated multiple cities using consistent data analytical approaches. The NMMAPS analyses for the largest 90 U.S. cities (Samet et al., 2000a,b; Dominici et al., 2002 and 2003) derived a combined nationwide excess risk estimate of about 1.4% (1.1% using GLM) increase in total (non-accidental) mortality per 50 $\mu\text{g}/\text{m}^3$ increase in PM₁₀. Other well-conducted multi-city analyses, as well as various single city analyses, obtained larger PM₁₀-effect size estimates for total non-accidental mortality, generally falling in the range of 2 to 3.5% per 50 $\mu\text{g}/\text{m}^3$ increase in PM₁₀. These estimates are consistent with and overlap the lower end of the range of PM₁₀ risk estimates given in the 1996 PM AQCD. However, somewhat more geographic heterogeneity is evident among the newer multi-city study results than was the case among the few studies assessed in the 1996 PM AQCD. In the NMMAPS analysis of the 90 largest U.S. cities data, for example, the risk estimates varied by U.S. geographic region, with the estimate for the Northeast being the largest (approximately twice the nation-wide estimate). The observed heterogeneity in the estimated PM risks across cities/regions could not be explained by city-specific explanatory variables, such as mean levels of pollution and weather, mortality rate, sociodemographic variables (e.g., median household income), urbanization, or variables related to measurement error. Notable apparent heterogeneity was also seen among effects estimates for PM (and SO₂) indices in the multi-city APHEA studies conducted in European cities. In APHEA2, they found that several city-specific characteristics, such as NO₂ levels and warm climate, were important effect modifiers. The issue of heterogeneity of effect estimates is discussed further in Section 8.4.

1 *Model specification Issue:* The investigations of the GAM convergence issue also led to
2 examination of the sensitivity of the PM risk estimates to different model specifications.
3 Of particular importance is the reemergence of model specification issues related to control for
4 weather effects with results of reanalyses highlighting the sensitivity of modeling outcomes to
5 kinds and numbers of weather-related variables included in base models. Related to this, several
6 reanalyses also examined the sensitivity of results to varying the degrees of freedom for
7 smoothing of weather and temporal trends. PM risk estimates were often reduced when more
8 degrees of freedom were given to model temporal trends. While at present there is no consensus
9 as to what constitutes an “adequate” extent of smoothing (from an epidemiologic viewpoint), the
10 overall assessment of PM risk estimates should take into consideration the range of sensitivity of
11 results to this aspect of model specification.

12 *Confounding and effect modification by other pollutants.* Numerous new short-term PM
13 exposure studies not only continue to report significant associations between various PM indices
14 and mortality, but also between gaseous pollutants (O₃, SO₂, NO₂, and CO) and mortality.
15 In most of these studies, simultaneous inclusions of gaseous pollutants in the regression models
16 did not meaningfully affect the PM-effect size estimates. This was the case for the NMMAPS
17 90 cities study with regard to the overall combined U.S. regional and nationwide risk estimates
18 derived for that study. The issue of confounding is discussed further in Section 8.4.

19 *Fine and coarse particle effects.* Newly available studies provide generally positive (and
20 often statistically significant) PM_{2.5} associations with mortality, with effect size estimates falling
21 in the range reported in the 1996 PM AQCD. New results from Germany appear to implicate
22 both ultrafine (nuclei-mode) and accumulation-mode fractions of urban ambient fine PM as
23 being important contributors to increased mortality risks. As to the relative importance of fine
24 and coarse particles, in the 1996 PM AQCD there was only one acute mortality study (Schwartz
25 et al., 1996a) that examined this issue. The results of that study of six U.S. cities suggested that
26 fine particles (PM_{2.5}), were associated with daily mortality, but not coarse particles (PM_{10-2.5}),
27 except for in Steubenville, OH.. Now, eight studies have analyzed both PM_{2.5} and PM_{10-2.5} for
28 their associations with mortality. While the results from some of these new studies (e.g., the
29 Santa Clara County, CA analysis [Fairley, 1999]) did suggest that PM_{2.5} was more important
30 than PM_{10-2.5} in predicting mortality fluctuations, other studies (e.g., Phoenix, AZ analyses
31 [Clyde et al., 2000; Mar et al., 2000; Smith et al., 2000]) suggest that PM_{10-2.5} may also be

1 important in at least some locations. Seasonal dependence of size-related PM component effects
2 observed in some of the studies complicates interpretations.

3 *Chemical components of PM.* Several new studies have examined the role of specific
4 chemical components of PM. The studies conducted in U.S., Canadian, and European cities
5 showed mortality associations with specific fine particle components of PM, including sulfate,
6 nitrate, and CoH; but their relative importance varied from city to city, likely depending on their
7 levels (e.g., no clear associations in those cities where H⁺ and sulfate levels were very low, i.e.,
8 circa non-detection limits). The results of several studies that investigated the role of crustal
9 particles, although somewhat mixed, overall do not appear to support associations between
10 crustal particles and mortality (see also the discussion, below, of source-oriented evaluations).

11 *Source-oriented evaluations.* Several studies conducted source-oriented evaluations of PM
12 components using factor analysis. The results from these studies generally indicated that several
13 combustion-related fine particle source-types are likely associated with mortality, including
14 motor vehicle emissions, coal combustion, oil burning, and vegetative burning. The crustal
15 factor from fine particles was not associated with total non-accidental mortality in the Harvard
16 Six Cities data, and the soil (i.e., crustal) factor from fine particles in the Phoenix data was not
17 associated with cardiovascular mortality. Thus, the results of source-oriented evaluations most
18 clearly appear to implicate fine particles of anthropogenic origin as being important in
19 contributing to increased mortality, but not short-term exposures to crustal materials in U.S.
20 ambient environments.

21 *Cause-specific mortality.* Findings for new results concerning cause-specific mortality
22 comport well with those for total (non-accidental) mortality, the former showing generally larger
23 effect size estimates for cardiovascular, respiratory, and/or combined cardiorespiratory excess
24 risks than for total mortality risks. An analysis of specific cardiovascular causes in a large
25 population (The Netherlands) suggested that specific causes of deaths (such as heart failure)
26 were more strongly associated with PM (and other pollutants) than total cardiovascular
27 mortality.

28 *Lags.* In general, maximum effect sizes for total mortality appear to be obtained with 0-1
29 day lags, with some studies indicating a second peak for 3-4 days lags. There is also some
30 evidence that, if effects distributed over multiple lag days are considered, the effect size may be

1 larger than for any single maximum-effect-size lag day. Lags are discussed further in
2 Section 8.4.

3 *Threshold.* Few new short-term mortality studies explicitly address the issue of thresholds.
4 One study that analyzed Phoenix, AZ data (Smith et al., 2000) did report some limited evidence
5 suggestive of a possible threshold for PM_{2.5}. Also, several different analyses of larger PM₁₀ data
6 sets across multiple cities (Dominici, et al., 2002; Daniels et al., 2000; and reanalysis by
7 Dominici et al., 2003) generally provide only limited, if any, support to indicate a threshold for
8 PM₁₀ mortality effects. Threshold issues are discussed further in Section 8.4.
9

10 **8.2.3 Mortality Effects of Long-Term Exposure to Ambient** 11 **Particulate Matter**

12 **8.2.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document**

13 *8.2.3.1.1 Aggregate Population Cross-Sectional Chronic Exposure Studies*

14 Mortality effects associated with chronic, long-term exposure to ambient PM have been
15 evaluated in cross-sectional studies and, more recently, in prospective cohort studies. A number
16 of older cross-sectional studies from the 1970s provided indications of increased mortality
17 associated with chronic (annual average) exposures to ambient PM, especially with respect to
18 fine mass or sulfate (SO₄⁻²) concentrations. These cross-sectional studies were discussed in
19 detail in Section 12.4.1.2 of the 1996 PM AQCD. However, questions unresolved at the time
20 regarding the adequacy of statistical adjustments for other potentially important covariates (e.g.,
21 cigarette smoking, economic status, etc.) across cities tended to limit the degree of confidence
22 that was placed by the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) on such
23 purely “ecological” studies or on quantitative estimates of PM effects derived from them.
24 Evidence comparing the toxicities of specific PM components was relatively limited, although
25 the sulfate and acid components were discussed in detail in the 1986 PM AQCD.
26

27 *8.2.3.1.2 Prospective Cohort Chronic Exposure Studies*

28 Prospective cohort studies of mortality associated with chronic exposures to air pollution
29 of outdoor origins have yielded especially valuable insights into the adverse health effects of
30 long-term PM exposures. Such cohort studies using subject-specific information about relevant
31 covariates (such as cigarette smoking, occupation, etc.) typically are capable of providing more

1 certain findings of long-term PM exposure effects than are purely “ecological studies” (Künzli
2 and Tager, 1997). The new, better designed cohort studies, as discussed below, have largely
3 confirmed the magnitude of PM effect estimates derived from past cross-sectional studies.

4 The extensive Harvard Six-Cities Study (Dockery et al., 1993) and the initial American
5 Cancer Society (ACS) Study (Pope et al., 1995) agreed in their findings of statistically
6 significant positive associations between fine particles and excess mortality, although the ACS
7 study did not evaluate the possible contributions of other air pollutants. Neither study
8 considered multi-pollutant models, although the Six-City study did examine various PM and
9 gaseous pollutant indices (including total particles, $PM_{2.5}$, SO_4^{-2} , H^+ , SO_2 , and ozone), and found
10 that sulfate and $PM_{2.5}$ fine particles were most strongly associated with mortality. The excess
11 RR estimates originally reported for total mortality in the Six-Cities study (and 95 percent
12 confidence intervals, CI) per increments in PM indicator levels were: Excess RR = 18%
13 (CI: 6.8%, 32%) for $20 \mu g/m^3 PM_{10}$; excess RR = 13.0% (CI: 4.2%, 23%) for $10 \mu g/m^3 PM_{2.5}$;
14 and excess RR = 13.4% (CI: 5.1%, 29%) for $5 \mu g/m^3 SO_4^{-2}$. The estimates for total mortality
15 derived from the ACS study were excess RR = 6.6% (CI: 3.5%, 9.8%) for $10 \mu g/m^3 PM_{2.5}$ and
16 excess RR 3.5% (CI: 1.9%, 5.1%) for $5 \mu g/m^3 SO_4^{-2}$. The ACS pollutant RR estimates were
17 smaller than those from the Six-Cities study, although their 95% confidence intervals overlap.

18 In some cases in these studies, the life-long cumulative exposure of the study cohorts
19 included distinctly higher past PM exposures, especially in cities with historically higher PM
20 levels (e.g., Steubenville, OH); but more current PM measurements were used to help estimate
21 the chronic PM exposures. In the ACS study, the pollutant exposure estimates were based on
22 concentrations at the start of the study (during 1979-1983). In addition, the average age of the
23 ACS cohort was 56, which could overestimate the pollutant RR estimates and perhaps
24 underestimate the life-shortening associated with PM associated mortality. Still, although
25 caution must be exercised regarding use of the reported quantitative risk estimates, the Six-Cities
26 and ACS prospective cohort studies provided consistent evidence of significant mortality
27 associations with long-term exposure to ambient PM.

28 The Six-Cities cohort was preselected by the investigators to be a representative population
29 for the U.S. midwest / eastern regions of the country heavily-impacted by both coal combustion
30 and motor vehicle effluents. By contrast, the ACS study cohort was drawn from a large pool of
31 volunteers who happened to live in communities where several years of fine particle and/or

1 sulfate ambient air concentration data were available. It is important to note that the ACS had a
2 relatively small proportion of people with less than high school education (12% vs. 28% for
3 Six-Cities) and, by inference, better diets and access to good health care than an average U.S.
4 population. To the extent that the mortality impact is lower in the better educated portion of the
5 population, the mortality experience of the ACS cohort likely provides an underestimate for the
6 U.S. population as a whole.

7 In contrast to the Six-Cities and ACS studies, early results reported by Abbey et al. (1991)
8 and Abbey et al. (1995a) from another prospective cohort study, the Adventist Health Study on
9 Smog (AHSMOG), reported no significant mortality effects of previous PM exposure in a
10 relatively young cohort of California nonsmokers. However, these analyses used TSP as the PM
11 exposure metric, rather than more health-relevant PM metrics such as PM_{10} or $PM_{2.5}$, included
12 fewer subjects than the ACS study, and considered a shorter follow-up time than the Six-Cities
13 study (ten years versus 15 years for the Six-Cities study). Further, the AHSMOG study included
14 only nonsmokers (indicated by the Six-Cities Study as having lower pollutant RR's than
15 smokers), suggesting that a longer follow-up time than considered in the past (10 years) might be
16 required to have sufficient power to detect significant pollution effects than would be needed in
17 studies that include smokers (such as the Six-Cities and ACS studies). Thus, greater emphasis
18 was placed in the 1996 PM AQCD on the results of the Six-Cities and ACS studies.

19 Overall, the previously available chronic PM exposure studies collectively indicated that
20 increases in mortality are associated with long-term exposure to ambient airborne particles; and
21 effect size estimates for total mortality associated with chronic PM exposure indices appeared to
22 be much larger than those reported from daily mortality PM studies. This suggested that a major
23 fraction of the reported mortality relative risk estimates associated with chronic PM exposure
24 likely reflects cumulative PM effects above and beyond those exerted by the sum of acute
25 exposure events (i.e., assuming that the latter are fully additive over time). The 1996 PM AQCD
26 (Chapter 12) reached several conclusions concerning four key questions about the prospective
27 cohort studies, as noted below:
28
29

1 (1) Have potentially important confounding variables been omitted?

2 “While it is not likely that the prospective cohort studies have overlooked plausible
3 confounding factors that can account for the large effects attributed to air pollution,
4 there may be some further adjustments in the estimated magnitude of these effects as
5 individual and community risk factors are included in the analyses.” These include
6 individual variables such as education, occupational exposure to dust and fumes, and
7 physical activity, as well as ecological (community) variables such as regional
8 location, migration, and income distribution. Further refinement of the effects of
9 smoking status may also prove useful.”

3 (2) Can the most important pollutant species be identified?

4 “The issue of confounding with co-pollutants has not been resolved for the
5 prospective cohort studies . . . Analytical strategies that could have allowed greater
6 separation of air pollutant effects have not yet been applied to the prospective cohort
7 studies.” The ability to separate the effects of different pollutants, each measured as a
8 long-term average on a community basis, was clearly most limited in the Six Cities
9 study. The ACS study offered a much larger number of cities, but did not examine
10 differences attributable to the spatial and temporal differences in the mix of particles
and gaseous pollutants across the cities. The AHSMOG study constructed time- and
location-dependent pollution metrics for most of its participants that might have
allowed such analyses, but no results were reported.

5 (3) Can the time scales for long-term exposure effects be evaluated?

6 “Careful review of the published studies indicated a lack of attention to this issue.
7 Long-term mortality studies have the potential to infer temporal relationships based
8 on characterization of changes in pollution levels over time. This potential was
9 greater in the Six Cities and AHSMOG studies because of the greater length of the
10 historical air pollution data for the cohort [and the availability of air pollution data
throughout the study]. The chronic exposure studies, taken together, suggest that
there may be increases in mortality in disease categories that are consistent with long-
term exposure to airborne particles, and that at least some fraction of these deaths are
likely to occur between acute exposure episodes. If this interpretation is correct, then
at least some individuals may experience some years of reduction of life as a
consequence of PM exposure.”

7 (4) Is it possible to identify pollutant thresholds that might be helpful in health assessments?

8 “Model specification searches for thresholds have not been reported for prospective
9 cohort studies. . . . Measurement error in pollution variables also complicates the
10 search for potential threshold effects. . . . The problems that complicate threshold
detection in the population-based studies have a somewhat different character for the
long-term studies.”

9

10

8.2.3.2 New Prospective Cohort Analyses of Mortality Related to Chronic Particulate Matter Exposures

Considerable further progress has been made towards addressing the above issues. As an example, extensive reanalyses (Krewski et al., 2000) of the Six-Cities and ACS Studies (sponsored by HEI), indicate that the published findings of the original investigators (Dockery et al., 1993; Pope et al., 1995) are based on substantially valid data sets and statistical analyses. The HEI reanalysis project demonstrated that small corrections in input data have very little effect on the findings and that alternative model specifications further substantiate the robustness of the originally reported findings. In addition, some of the above key questions have been further investigated by Krewski et al. (2000) via sensitivity analyses (in effect, new analyses) for the Six City and ACS studies data sets, including consideration of a much wider range of confounding variables. Newly published analyses of ACS data for more extended time periods (Pope et al., 2002) further substantiate original findings and also provide much clearer, stronger evidence for ambient PM exposure relationships with increased lung cancer risk. Newer published analyses of AHSMOG data (Abbey et al., 1999; Beeson et al., 1998) also extend the ASHMOG findings and show some analytic outcomes different from earlier analyses reported out from the study. Results from the Veterans' Administration- Washington University (hereafter called "VA") prospective cohort study are also now available (Lipfert et al., 2000b).

8.2.3.2.1 Health Effects Institute Reanalyses of the Six-Cities and ACS Studies

The overall objective of the HEI "Particle Epidemiology Reanalysis Project" was to conduct a rigorous and independent assessment of the findings of the Six Cities (Dockery et al., 1993) and ACS (Pope et al., 1995) Studies of air pollution and mortality. The following description of approach, key results, and conclusions is largely extracted from the Executive Summary of the HEI final report (Krewski et al., 2000). The HEI-sponsored reanalysis effort was approached in two steps:

- Part I: Replication and Validation. The Reanalysis Team sought to test (a) whether the original studies could be replicated via a quality assurance audit of a sample of the original data and (b) whether the original numeric results could be validated.
- Part II: Sensitivity Analyses. The Reanalysis Team tested the robustness of the original analyses to alternate risk models and analytic approaches.

1 The Part I audit of the study population data for both the Six Cities and ACS Studies and of
2 the air quality data in the Six Cities Study revealed that data were of generally high quality with
3 few exceptions. In both studies, a few errors were found in the data coding for and exclusion of
4 certain subjects; but when those subjects were included in the analyses, they did not materially
5 change the results from those originally reported. Because the air quality data used in the ACS
6 Study could not be audited, a separate air quality database was constructed for the sensitivity
7 analyses in Part II.

8 The Reanalysis Team was able to replicate the original results for both studies using the
9 same data and statistical methods as used by the original investigators, as shown in Table 8-5.
10 The Reanalysis Team confirmed the original point estimates. For the Six Cities Study, they
11 reported the excess relative risk of mortality from all causes associated with an increase in fine
12 particles of $10 \mu\text{g}/\text{m}^3$ to be 14%, close to the 13% reported by the original investigators. For the
13 ACS Study, they reported the relative risk of all-cause mortality associated with a $10 \mu\text{g}/\text{m}^3$
14 increase in fine particles to be 7.0% in the reanalysis, close to the original 6.6% value.

15 The Part II sensitivity analysis applied an array of different models and variables to
16 determine whether the original results would remain robust to different analytic assumptions and
17 model specifications. The Reanalysis Team first applied the standard Cox model used by the
18 original investigators and included variables in the model for which data were available from
19 both original studies, but had not been used in the published analyses (e.g., physical activity,
20 lung function, marital status). The Reanalysis Team also designed models to include interactions
21 between variables. None of these alternative models produced results that materially altered the
22 original findings.

23 Next, for both the Six Cities and ACS Studies, the Reanalysis Team investigated the
24 possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of
25 the population. These analyses did not find differences in PM-mortality associations among
26 subgroups based on various personal characteristics (e.g., including gender, marital status,
27 smoking status, and exposure to occupational dusts and fumes). However, estimated effects of
28 fine particles did vary with educational level: the association between an increase in fine
29 particles and mortality tended to be higher for individuals without a high school education than
30 for those with more education. The Reanalysis Team postulated that this finding could be
31 attributable to some unidentified socioeconomic effect modifier. The authors concluded “The

TABLE 8-5. COMPARISON OF SIX CITIES AND AMERICAN CANCER SOCIETY (ACS) STUDY FINDINGS FROM ORIGINAL INVESTIGATORS AND HEALTH EFFECTS INSTITUTE REANALYSIS

Type of Health Effect & Location	Indicator	Mortality Risk per Increment in PM ^a	
		Total Mortality Excess Relative Risk (95% CI)	Cardiopulmonary Mortality Excess Relative Risk (95% CI)
Original Investigators' Findings			
Six City ^b	PM _{2.5}	13% (4.2%, 23%)	18% (6.0%, 32%)
Six City ^b	PM _{15/10}	18% (6.8%, 32%)	e
ACS Study ^c	PM _{2.5}	6.6% (3.5%, 9.8%)	12% (6.7%, 17%)
HEI reanalysis Phase I: Replication			
Six City Reanalysis ^d	PM _{2.5}	14% (5.4%, 23%)	19% (6.5%, 33%)
	PM ₁₅	19% (6.1%, 34%)	20% (2.9%, 41%)
ACS Study Reanalysis ^d	PM _{2.5}	7.0% (3.9%, 10%)	12% (7.4%, 17%)
	PM ₁₅ (dichot)	4.1% (0.9%, 7.4%)	7.3% (3.0%, 12%)
	PM ₁₅ (SSI)	1.6% (-0.8%, 4.1%)	5.7% (2.5%, 9.0%)

^a Estimates calculated on the basis of differences between the most-polluted and least-polluted cities, scaled to increments of 20 µg/m³ increase for PM₁₀ and 10 µg/m³ increments for PM₁₅ and PM_{2.5}.

^b Dockery et al. (1993).

^c Pope et al. (1995).

^d Krewski et al. (2000).

^e Results presented only by smoking category subgroup.

1 Reanalysis Team found little evidence that questionnaire variables had led to confounding in
 2 either study, thereby strengthening the conclusion that the observed association between fine
 3 particle air pollution and mortality was not the result of a critical covariate that had been
 4 neglected by the Original Investigators.” (Krewski et al., 2000, pp. 219-220).

5 In the ACS study, the Reanalysis Team tested whether the relationship between ambient
 6 concentrations and mortality was linear. They found some indications of both linear and
 7 nonlinear relationships, depending upon the analytic technique used, suggesting that the shapes
 8 of the concentration-response relationships warrant additional research in the future.

9 One of the criticisms of both original studies has been that neither analyzed the effects of
 10 change in pollutant levels over time. In the Six Cities Study, for which such data were available,

1 the Reanalysis Team tested whether effect estimates changed when certain key risk factors
2 (smoking, body mass index, and air pollution) were allowed to vary over time. In general, the
3 reanalysis results did not change when smoking and body mass index were allowed to vary over
4 time. The Reanalysis Team did find for the Six Cities Study, however, that when the general
5 decline in fine particle levels over the monitoring period was included as a time-dependent
6 variable, the association between fine particles and all-cause mortality was reduced (Excess
7 RR = 10.4% (CI: 1.5, 20). This would be expected, because the most polluted cities would likely
8 have the greatest decline as pollution controls were applied, and it is likely indicative of the
9 effectiveness of control measures in reducing source emissions importantly contributing to the
10 toxicity of ambient PM in those cities. Despite this adjustment, the PM_{2.5} effect estimate
11 continued to be positive and statistically significant.

12 To test the validity of the original ACS air quality data, the Reanalysis Team constructed
13 and applied its own air quality dataset from available historical data. In particular, sulfate levels
14 with and without adjustment were found to differ by about 10% for the Six Cities Study. Both
15 the original ACS Study air quality data and the newly constructed data set contained sulfate
16 levels inflated by 50% due to artifactual sulfate. For the Six Cities Study, the relative risks of
17 mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS Study,
18 adjusting for artifactual sulfate resulted in slightly higher relative risks of all-cause mortality and
19 from cardiopulmonary disease compared with unadjusted data, while the relative risk of
20 mortality from lung cancer was lower after the data had been adjusted. Thus, the Reanalysis
21 Team found essentially the same results as the original Harvard Six-Cities and ACS studies,
22 even after using independently developed pollution data sets and adjusting for sulfate artifact.

23 Because of the limited statistical power to conduct most model specification sensitivity
24 analyses for the Six Cities Study, the Reanalysis Team conducted most of its sensitivity analyses
25 using only the ACS Study data set that considered 151 cities. When a range of city-level
26 (ecologic) variables (e.g., population change, measures of income, maximum temperature,
27 number of hospital beds, water hardness) were included in the analyses, the results generally did
28 not change. The only exception was that associations with fine particles and sulfate were
29 reduced when city-level measures of population change or SO₂ were included in the model.

30 A major product of the Reanalysis Project is the determination that both pollutant variables
31 and mortality appear to be spatially correlated in the ACS Study data set. If not identified and

1 modeled correctly, spatial correlation could cause substantial errors in both the regression
2 coefficients and their standard errors. The Reanalysis Team identified several methods for
3 addressing this, each of which resulted in some reduction in the estimated regression
4 coefficients. The full implications and interpretations of spatial correlations in these analyses
5 have not been resolved and were noted to be an important subject for future research.

6 When the Reanalysis Team sought to take into account both underlying variation from city
7 to city (random effects) and variation from the spatial correlation between cities, positive
8 associations were still found between mortality and sulfates or fine particles. Results of various
9 models, using alternative methods to address spatial autocorrelation and including different
10 ecologic covariates, found fine particle-mortality associations that ranged from 1.11 to 1.29 (the
11 RR reported by original investigators was 1.17) per 24.5 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$. With the
12 exception of SO_2 , consideration of other pollutants in these models did not alter the associations
13 found with sulfates. The authors reported stronger associations for SO_2 than for sulfate, which
14 suggests that artifactual sulfate was “picking up” some of the SO_2 association-perhaps because
15 the sulfate artifact is in part proportional to the prevailing SO_2 concentration (Coutant, 1977).
16 The Reanalysis Team did not use data adjusted for artifactual sulfate for most alternative
17 analyses. When they did use adjusted sulfate data, relative risks of mortality from all causes and
18 cardiopulmonary disease increased. This suggests that more analyses with adjusted sulfate
19 might result in somewhat higher relative risks for sulfate. The Reanalysis Team concluded:
20 “it suggests that uncontrolled spatial autocorrelation accounts for 24% to 64% of the observed
21 relation. Nonetheless, all our models continued to show an association between elevated risks of
22 mortality and exposure to airborne sulfate” (Krewski et al., 2000, p. 230).

23 In summary, the reanalyses generally confirmed the original investigators’ findings of
24 associations between mortality and long-term exposure to PM, while recognizing that increased
25 mortality may be attributable to more than one ambient air pollution component. Regarding the
26 validity of the published Harvard Six-Cities and ACS Studies, the HEI Reanalysis Report
27 concluded that “Overall, the reanalyses assured the quality of the original data, replicated the
28 original results, and tested those results against alternative risk models and analytic approaches
29 without substantively altering the original findings of an association between indicators of
30 particulate matter air pollution and mortality.”

1 Villeneuve et al. (2002) used Poisson regression models in further analyses of the Harvard
2 Six City study cohort to evaluate relationships between fixed-in-time and time-dependent
3 measures of PM_{2.5} and the risk of mortality among adult, Caucasian participants. The RR of
4 mortality using the Poisson method based upon city-specific exposures that remained constant
5 during the follow up was 1.31 (CI: 1.12, 1.52), similar to results derived from the Cox model
6 used in the original analysis. However, the authors report that the RR of mortality due to PM_{2.5}
7 exposure decreased when time-dependent measures of air pollution were modeled (Table 8-6).
8 Specifically, when the mean PM_{2.5} level within each city during each period of follow-up was
9 modeled, the RR was 1.16 (CI: 1.02, 1.32). The authors noted that “there were considerable
10 variations in mortality rates across the calendar periods that were modeled,” and that “the
11 magnitude of these variations in mortality rates may have dampened any real PM_{2.5} effect on
12 mortality.”

13 Similar results were observed by Villeneuve et al. (2002) irrespective of the exposure
14 window considered. They used various time-dependent indices that denoted (a) exposures
15 received in the last two years of follow-up and (b) exposures lagged 3 to 4 and ≥ 5 years. Effect
16 modification was evaluated by fitting interaction terms that consisted of PM_{2.5} exposure and
17 individual risk factors (body mass index, education, smoking, age, gender, and occupational
18 exposure to dusts). The significance of this term was formally tested by constructing a
19 likelihood ratio test statistic. An interaction effect between PM_{2.5} exposure and age was seen
20 ($p < 0.05$), and they therefore presented stratified analysis by age group (< 60 , ≥ 60 years).
21 For each index of PM_{2.5}, the RR of all-cause mortality was more pronounced among subjects
22 < 60 years old. There was no effect modification between PM_{2.5} and the other individual risk
23 factors. The RR for PM-associated mortality did not depend on when exposure occurred in
24 relation to death, possibly because of little variation between the time-dependent city-specific
25 PM_{2.5} exposure indices ($r > 0.90$) and the fact that the rank ordering of the cities changed little
26 during follow-up. Villeneuve et al. (2002) concluded that the “attenuated risk of mortality that
27 was observed with a time-dependent index of PM_{2.5} is due to the combined influence of city-
28 specific variations in mortality rates and decreasing levels of air pollution that occurred during
29 follow-up.”

**TABLE 8-6. RELATIVE RISK^a OF ALL-CAUSE MORTALITY FOR
SELECTED INDICES OF EXPOSURE TO FINE PARTICULATE MATTER
(per 18.6 µg/m³) BASED ON MULTIVARIATE POISSON REGRESSION ANALYSIS,
BY AGE GROUP, FOR HARVARD SIX CITY STUDY DATA^B**

Model	PM _{2.5} Exposure City Specific Index	Age Group (years)		
		Total	< 60	≥ 60
1	Exposure to PM _{2.5} remained fixed over the entire follow up period.	1.31 (1.12 – 1.52)	1.89 (1.32 – 2.69)	1.21 (1.02 – 1.43)
2	Exposure to PM _{2.5} defined according to 13 calendar periods (no smoothing). ^a	1.19 (1.04 – 1.36)	1.52 (1.15 – 2.00)	1.11 (0.95 – 1.29)
3	Exposure to PM _{2.5} defined according to 13 calendar periods (smoothed). ^b	1.16 (1.02 – 1.32)	1.43 (1.10 – 1.85)	1.09 (0.93 – 1.26)
4	Time dependent estimate of PM _{2.5} received during the previous two years.	1.16 (1.02 – 1.31)	1.42 (1.09 – 1.82)	1.08 (0.94 – 1.25)
5	Time dependent estimate of PM _{2.5} received 3 - 5 years before current year.	1.14 (1.02 – 1.27)	1.35 (1.08 – 1.87)	1.08 (0.95 – 1.22)
6	Time dependent estimate of PM _{2.5} received > 5 years before current year.	1.14 (1.05 – 1.23)	1.34 (1.11 – 1.59)	1.09 (0.99 – 1.20)

^aRelative risks were adjusted by age, gender, body mass, index, education, number of years smoked (at baseline), occupational exposures and number of cigarettes smoked weekly.

^bFor each city, exposure to PM_{2.5} was estimated for 13 calendar periods using loglinear regression based on annual mean PM_{2.5} levels. The calendar periods used were: 1970-1978, 1979, 1981, . . . 1989, and 1990+. PM_{2.5} associations with all-cause mortality assessed for male Caucasian participants in Six Cities Study.

Source: Villeneuve et al. (2002).

1 8.2.3.2.2 *The ACS Study Extension*

2 Pope et al. (2002) extended the analyses (Pope et al., 1995) and reanalyses (Krewski et al.,
3 2000) of the ACS CPS-II cohort to include an additional nine years of follow-up data. The new
4 study has a number of advantages over the previous analyses, in that it (a) doubles the follow-up
5 time from seven to sixteen years and triples the number of deaths; (b) expands the ambient air
6 pollution data substantially, including two recent years of fine particle data and adding data on
7 gaseous co-pollutants; (c) improves statistical adjustments for occupational exposure;
8 (d) incorporates data on dietary covariates believed to be important factors in mortality,
9 including total fat consumption, and consumption of vegetables, citrus fruit, and high-fiber
10 grains; and (e) uses recent developments in non-parametric spatial smoothing and random effects
11 statistical models as input to the Cox proportional hazards model. Each participant was

1 identified with a specific metropolitan area, and mean pollutant concentrations were calculated
2 for all metropolitan areas with ambient air monitors in the one to two years prior to enrollment.
3 Ambient pollution during the follow-up period was extracted from the AIRS data base.
4 No network of PM_{2.5} monitoring existed in the United States between the early 1980s and the
5 late 1990s. In an attempt to estimate the concentration during this period, the integrated average
6 of PM_{2.5} concentrations during 1999-2000 was averaged with the earlier 1979-1983 period. For
7 the 51 cities where paired data were available, the concentrations of PM_{2.5} were lower in 1999-
8 2000 than in 1979-1983 for most cities. Mean PM_{2.5} levels for the two periods were highly
9 correlated ($r = 0.78$), and the rank order of the cities by relative pollution levels remained nearly
10 the same. Analyses based on the early period would likely provide the best estimate of PM_{2.5}-
11 associated risks, as shown in Figures 8-8 and 8-9. Averages of daily averages of the gaseous
12 pollutants were used except for ozone, where the average daily 1-hour maximum was calculated
13 for the whole year and for the typical peak ozone quarter (July, August, September). Mean
14 sulfate concentrations for 1990 were calculated from archived quartz filters, virtually eliminating
15 the historical sulfate artifact leading to overestimation of sulfate concentrations.

16 The Krewski et al. (2000), Burnett et al. (2001a), and Pope et al. (2002) studies were
17 concerned that survival times of participants in nearby locations might not be independent of
18 each other, due to missing, unmeasured, or mis-measured risk factors or their surrogates that
19 may be spatially correlated with air pollution, thus violating an important assumption of the Cox
20 proportional hazards model. Thus, model fitting proceeded in two stages, the first of which was
21 an adjusted relative risk model with a standard Cox proportional hazards model including
22 individual-specific covariates and indicator variables for each metropolitan area, but not air
23 pollutants. In the second stage, the adjusted log(relative risks) were fitted to fine particle
24 concentrations or other air pollutants by a random effects linear regression model.

25 Models were estimated separately for each of four mortality (total, cardiopulmonary, lung
26 cancer, and causes other than cardiopulmonary or lung cancer deaths) endpoints for the entire
27 follow-up period and for fine particles in three time periods (1979-1983, 1999-2000, and the
28 average of the mean concentrations in these two periods). The results are shown in Table 8-7.
29 Figures 8-7, 8-8, and 8-9 show the results displayed in Figures 2, 3, and 5 of Pope et al. (2002).
30 Figure 8-7 shows that a smooth non-parametric model can be reasonably approximated by a
31 linear model for all-cause mortality, cardiopulmonary mortality, and other mortality; but the

TABLE 8-7. SUMMARY OF RESULTS FROM THE EXTENDED ACS STUDY*

Cause of death	PM _{2.5} , average over 1979-1983	PM _{2.5} , average over 1999-2000	PM _{2.5} , average over all seven years
All causes	4.1% (0.8, 7.5%)	5.9% (2.0, 9.9%)	6.2% (1.6, 11.0%)
Cardiopulmonary	5.9% (1.5, 10.5%)	7.9% (2.3, 14.0%)	9.3% (3.3, 15.8%)
Lung cancer	8.2% (1.1, 15.8%)	12.7% (4.1, 21.9%)	13.5% (4.4, 23.4%)
Other	0.8% (-3.0, 4.8%)	0.9% (-3.4, 5.5%)	0.5% (-4.8, 6.1%)

*Adjusted mortality excess risk ratios (95% confidence limits) per 10 $\mu\text{g}/\text{m}^3$ PM_{2.5} by cause of death associated with each of the multi-year averages of fine particle concentrations. The multi-year average concentrations are used as predictors of cause-specific mortality for all of the 16 years (1982-1998) of the ACS follow-up study. The excess risk ratios are obtained from the baseline random effects Cox proportional hazards models adjusted for age, gender, race, smoking, education, marital status, BMI, alcohol consumption, occupational dust exposure, and diet. Based on Table 2 in Pope et al. (2002) and more precise data from authors (G. Thurston, personal communication, March 13, 2002).

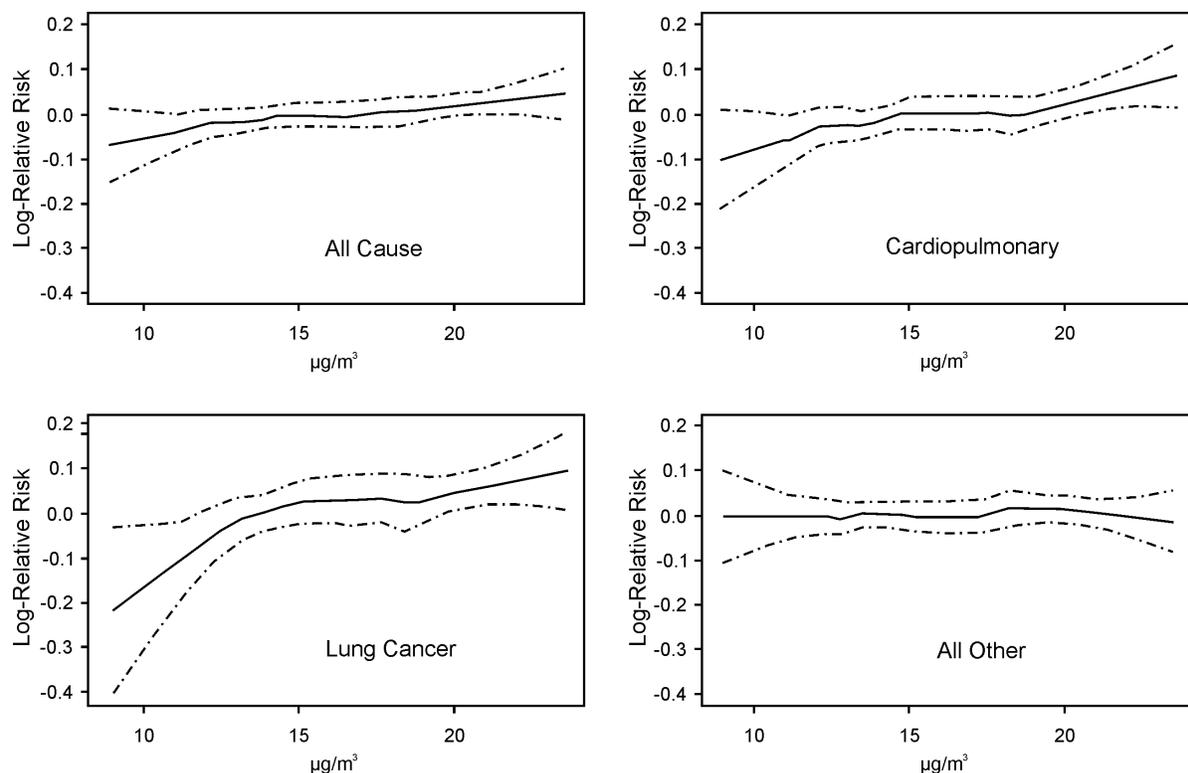


Figure 8-7. Natural logarithm of relative risk for total and cause-specific mortality per 10 $\mu\text{g}/\text{m}^3$ PM_{2.5} (approximately the excess relative risk as a fraction), with smoothed concentration-response functions. Based on Pope et al. (2002) mean curve (solid line) with pointwise 95% confidence intervals (dashed lines).

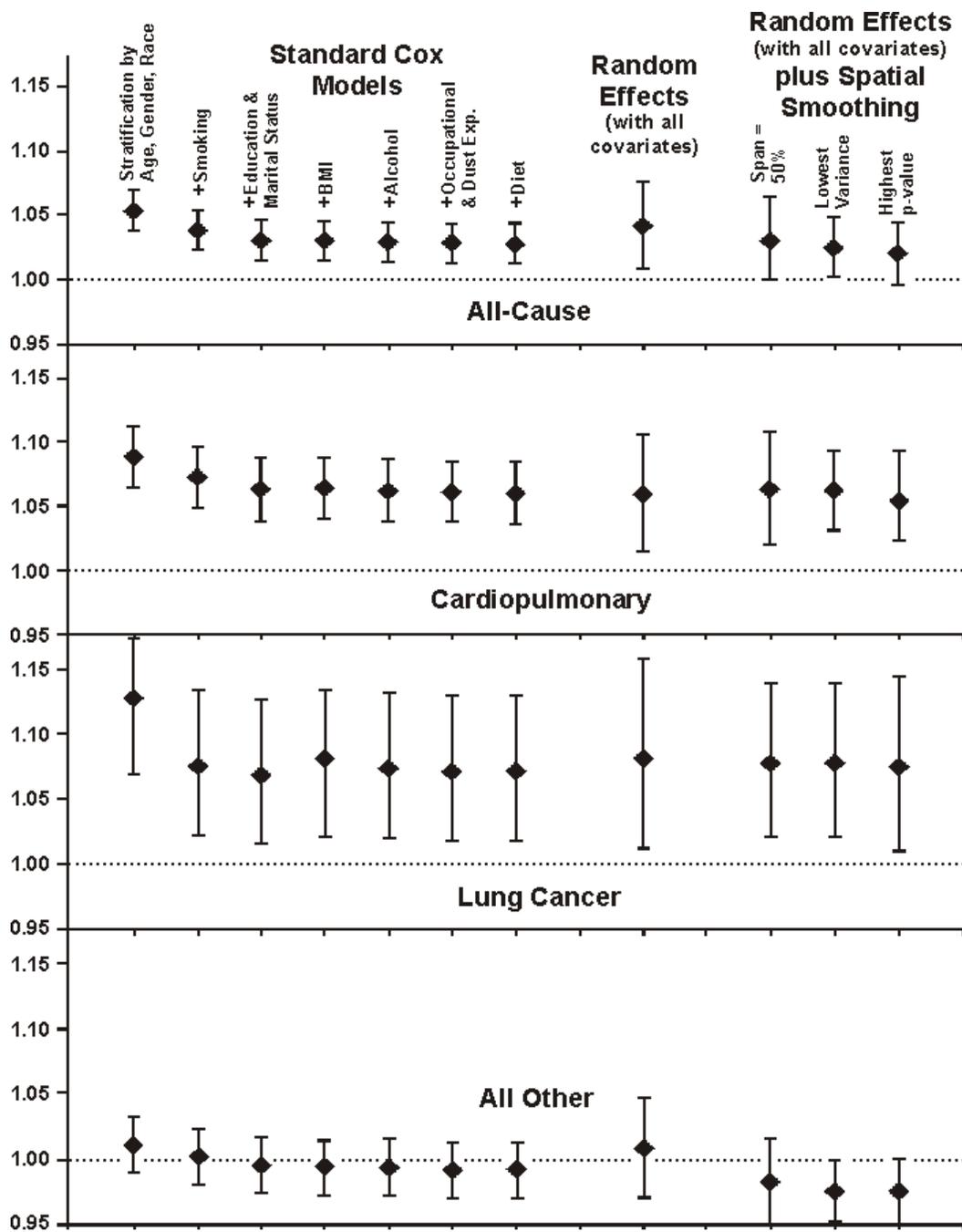


Figure 8-8. Relative risk of total and cause-specific mortality per 10 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$, derived for means of 1979-1983 $\text{PM}_{2.5}$ data for various cities, using alternative statistical models. The standard Cox models are built up in a sequential stepwise manner from the baseline model stratified by age, gender, and race by adding additional covariates. The random effects model allows for additional city-to-city variation, and the spatial smoothing models show the effects of increasingly aggressive adjustment for spatial correlation.

Source: Based on Pope et al. (2002).

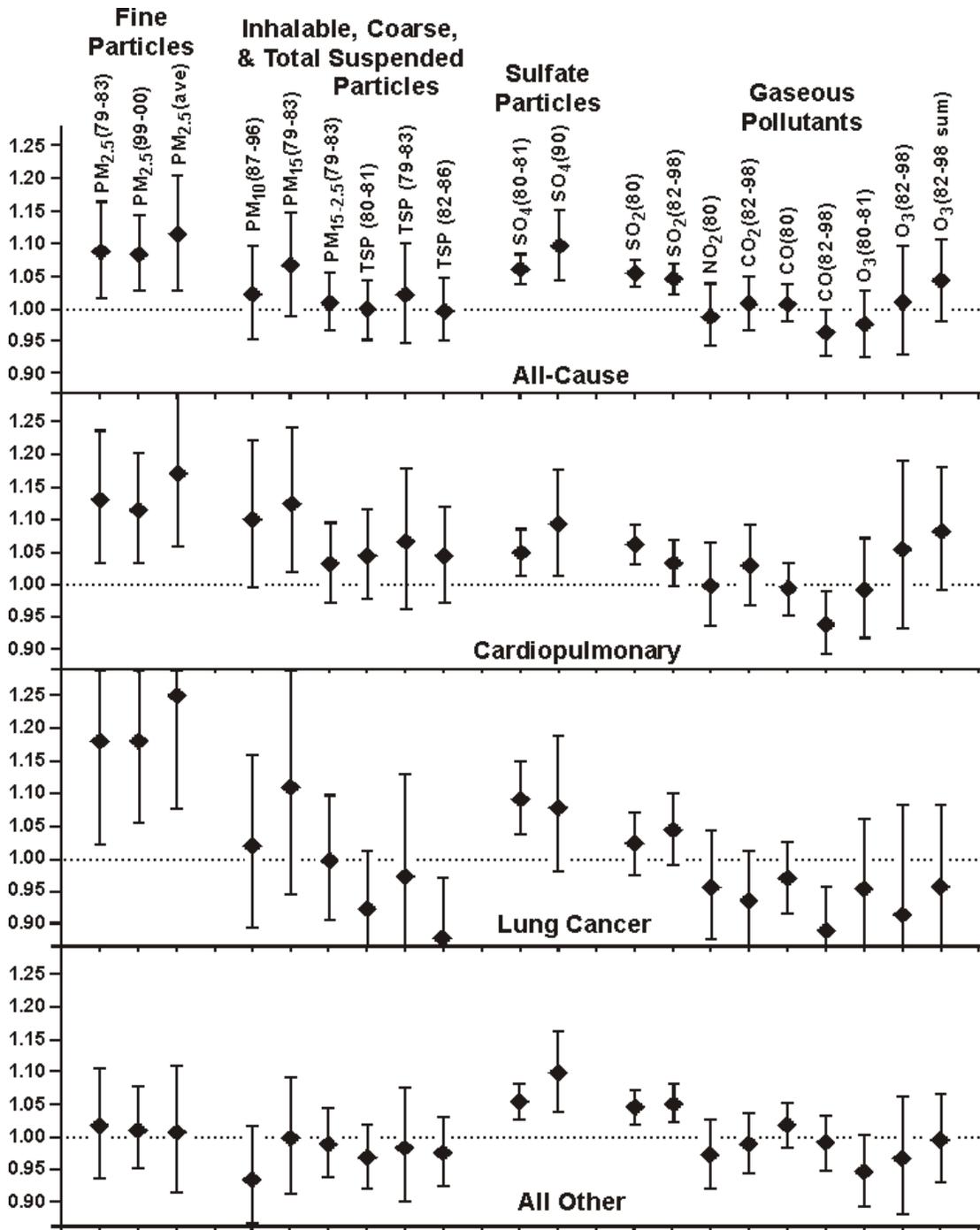


Figure 8-9. Relative risk of total and cause-specific mortality for particle metrics and gaseous pollutants over different averaging periods (years 1979-2000 in parentheses).

Source: Based on Pope et al. (2002).

1 log(relative risk) model for lung cancer appears to be non-linear, with a steep linear slope up to
2 an annual mean concentration of about $13 \mu\text{g}/\text{m}^3$ and a flatter linear slope at fine particle
3 concentrations $> 13 \mu\text{g}/\text{m}^3$.

4 Figure 4 in Pope et al. (2002) shows results for the stratified first-stage models: ages
5 < 60 and > 69 yr are marginally significant for total mortality; ages > 70 are significant for
6 cardiopulmonary mortality; and ages 60-69 for lung cancer mortality. Men are at significantly
7 higher risk for total and lung cancer mortality than are women, but slightly less so for
8 cardiopulmonary mortality (although still significant). Log (RR) decreases significantly from
9 individuals with less than to those with more than a high school education, replicating findings
10 in Krewski et al. (2000), but with twice the time on study. Including smoking status showed
11 increased fine particle RR for cardiopulmonary and lung cancer mortality in never-smokers and
12 least effect in current smokers; however, for total mortality, significant or near-significant effects
13 occurred in both current and never-smokers, but not former smokers.

14 The second-stage random effects models on the right side of Figure 8-8 have much wider
15 confidence intervals than the first-stage models, but are still statistically significant for total,
16 cardiopulmonary, and lung cancer mortality. Spatial smoothing decreased the magnitude and
17 significance of the fine particle effect for total mortality. For cardiopulmonary mortality, spatial
18 smoothing increased the magnitude of the RR and its significance by reducing the width of the
19 confidence intervals in the “50%-span” and “lowest variance” smoothing methods. For lung
20 cancer mortality, spatial smoothing little changed the magnitude of the RR, but increased its
21 significance by reducing the width of confidence intervals in the “50%-span” and “lowest
22 variance” smoothing methods.

23 Figure 8-9 shows statistically significant relationships between fine particles and total,
24 cardiopulmonary, and lung cancer mortality no matter which averaging span was used for $\text{PM}_{2.5}$
25 and slightly larger effect estimates for the average concentration of the 1979-1983 and
26 1999-2000 intervals. PM_{15} for 1979-1983 is significantly associated with cardiopulmonary
27 mortality and marginally with total mortality; whereas 1987-1996 PM_{15} is not quite significantly
28 associated with cardiopulmonary mortality. Coarse particles ($\text{PM}_{15-2.5}$) and TSP are not
29 significantly associated with any endpoint, but are positively associated with cardiopulmonary
30 mortality. Sulfate particles are very significantly associated with all endpoints, including
31 mortality from all other causes, but only marginally for lung cancer mortality using 1990 filters.

1 Figure 8-9 also shows highly positive significant relationships between SO₂ and total,
2 cardiopulmonary, and other-causes mortality, but a weaker SO₂ association with lung cancer
3 mortality. Only ozone using only the third quarter for 1982-1998 showed a marginally
4 significant relationship with cardiopulmonary mortality, but not the year-round average.
5 The other criteria pollutants, CO and NO₂, are neither significantly nor positively related to any
6 mortality endpoint, unlike some findings for acute PM exposure-mortality studies.

7 This paper confirms that the general pattern of findings for the first seven years of the
8 study (Pope et al., 1995; Krewski et al., 2000) can be reasonably extrapolated to the patterns that
9 remain present with twice the length of time on study and three times the number of deaths.
10 As shown later in Table 8-11, the excess relative risk estimate (95% CI) per 10 µg/m³ PM_{2.5} for
11 total mortality in the original ACS study (Pope et al., 1995) was 6.6% (CI: 3.6, 9.9%); in the
12 ACS reanalysis (Krewski et al., 2000) it was 7.0% (CI: 3.9, 10%); and, in the extended ACS data
13 set (Pope et al., 2002), it was 4.1% (CI: 0.8, 7.5%) using the 1979-1983 data and 6.2% (CI: 1.6,
14 11%) using the average of the 1979-1983 and 1999-2000 data. The excess relative risk estimate
15 (95% CI) per 10 µg/m³ PM_{2.5} for cardiopulmonary mortality in the original ACS study (Pope
16 et al., 1995) was 12% (CI: 6.7, 17%); in the ACS reanalysis (Krewski et al., 2000), it was 12%
17 (CI: 7.4, 17%); and, in the extended ACS data set (Pope et al., 2002), it was 5.9% (CI: 1.5, 10%)
18 using the 1979-1983 data and 9.3% (CI: 3.3, 16%) using the average of the 1979-1983 and 1999-
19 2000 data. Thus, the additional data and statistical analyses reported by Pope et al. (2002) yield
20 somewhat smaller estimates than the original study (Pope et al., 1995), but are similar to
21 estimates from the (Krewski et al. (2000) reanalysis of the original ACS data set.

22 The Pope et al. (2002) study also considered the PM risks by subgroup characteristics. The
23 risks were generally found (although not significantly so) to be somewhat higher for males than
24 females. The PM_{2.5} relative risks also tended to be higher for non-smokers than smokers. This is
25 consistent with the fact that smokers would have a much higher baseline risk, especially for lung
26 cancer, and would tend to have lower air pollution-mortality risk when viewed relative to the
27 much higher smoker baseline risk. PM_{2.5} mortality relative risks also tended to be higher for
28 those with less education, which may be due to related socioeconomic factors or, more likely, to
29 the generally greater inter-state mobility of higher-educated persons. Since the MSA was
30 assumed unchanged from that at the start of the study, this would tend to weaken the association
31 for higher education subjects, as the MSA-based exposure information would tend to have less

1 accuracy in that highly mobile group. This may indicate that the less-educated group RR
2 estimates may be more indicative of the true PM_{2.5} effects (i.e., as their exposure information is
3 likely to be more accurate) and, therefore, that the overall study PM_{2.5} RR estimates (which
4 include the highly-educated) may be biased somewhat low.

5 Based on the above patterns of results, the authors drew the following conclusions:

- 6 (1) The apparent association between long-term exposure to fine particle pollution and
mortality persists with longer follow-up as the participants in the cohort grow older and
more of them die.
- 7 (2) The estimated fine particle effect on cardiopulmonary and cancer mortality remained
relatively stable even after adjustment for smoking status, although the estimated effect
was larger and more significant for never-smokers versus former or current smokers.
The estimates were relatively robust against inclusion of many additional covariates:
education, marital status, body mass index (BMI), alcohol consumption, occupational
exposure, and dietary factors. However, the data on individual risk factors were
collected only at the time of enrollment and have not been updated, so that changes in
these factors since 1982 could introduce risk-factor exposure mis-classification and
consequent loss of precision in the estimates that might limit the ability to characterize
time dependency of effects. Moreover, it is noteworthy that this study found education to
be an effect modifier, with larger and more statistically significant PM effect estimates
for persons with less education. This may be due to the fact that less-education is a
marker for lower socioeconomic status and, hence, poorer health status and greater
pollution susceptibility. These results may also reflect that the mobility of the less-
educated may provide better estimates of exposure in this study (with no follow up of
address changes) than for the more mobile well-educated. In either case, because this
cohort has a much higher percentage of well-educated persons than the general public,
the education effect modification seen suggests that the overall PM effect estimates are
likely underestimated by this study cohort than are likely to be found for the general
public.
- 8 (3) Additional assessments for potential spatial or regional differences not controlled in the
first-stage model were evaluated. If there are unmeasured or inadequately modeled risk
factors that differ across locations or are spatially clustered, then PM risk estimates may
be biased. If the clustering is independent or random or independent across areas, then
adding a random-effects component to the Cox proportional hazards model could address
the problem. However, if location is associated with air pollution, then the spatial
correlation may be evaluated using non-parametric smoothing methods. No significant
spatial auto-correlation was found after controlling for fine particles. Even after
adjusting for spatial correlation, estimated PM_{2.5} effects were significant and persisted for
cardiopulmonary and lung cancer mortality and were borderline significant for total
mortality, but with much wider confidence intervals after spatial smoothing.

- 1 (4) Fine particles (PM_{2.5}) were associated with elevated total, cardiopulmonary, and lung
cancer mortality risks, but not with other-cause mortality. PM₁₀ for 1987-1996 and PM₁₅
for 1979-1983 were just significantly associated with cardiopulmonary mortality, but
neither PM_{10-2.5} nor TSP were associated with total or any cause-specific mortality.
All endpoints but lung cancer mortality were very significantly associated with sulfates,
except for lung cancer with 1990 sulfate data. All endpoints except lung cancer mortality
were significantly associated with SO₂ using 1980 data, as were total and other mortality
using the 1982-1998 SO₂ data; but cardiopulmonary and lung cancer mortality had only a
borderline significant association with the 1982-1998 SO₂ data. None of the other
gaseous pollutants showed significant positive associations with any endpoint. Thus,
neither coarse thoracic particles nor TSP were significantly associated with mortality; nor
were CO and NO₂ on a long-term exposure basis.
- 2 (5) The concentration-response curves estimated using non-parametric smoothers were all
monotonic and nearly linear (except for lung cancer). However, the shape of the curve
may become non-linear at much higher concentrations.
- 3 (6) The excess risk from PM_{2.5} exposure is much smaller than that estimated for cigarette
smoking for current smokers in the same cohort (Pope et al., 1995): RR = 2.07 for total
mortality, RR = 2.28 for cardiopulmonary mortality, and RR = 9.73 for lung cancer
mortality. In the more polluted areas of the United States, the relative risk for substantial
obesity (a known risk factor for cardiopulmonary mortality) is larger than that for PM_{2.5},
but the relative risk from being moderately overweight is somewhat smaller.

4

5 **8.2.3.2.3 AHSMOG Analyses**

6 The Adventist Health Study of Smog (AHSMOG), another major U.S. prospective cohort
7 study of chronic PM exposure-mortality effects, started with enrollment in 1977 of 6,338
8 non-smoking non-Hispanic white Seventh Day Adventist residents of California, ages 27 to
9 95 years. All had resided for at least 10 years within 5 miles (8 km) of their then-current
10 residence locations, either within one of the three major California air basins (San Diego,
11 Los Angeles, or San Francisco), or else were part of a random 10% sample of Adventist Health
12 Study participants living elsewhere in California. The study has been extensively described and
13 its initial results reported earlier (Hodgkin et al., 1984; Abbey et al., 1991; Mills et al., 1991).

14 In the more recent AHSMOG analyses (Abbey et al., 1999), the mortality status of subjects
15 after ~15 years of follow-up (1977-1992) was determined by various tracing methods and 1,628
16 deaths (989 female, 639 male) were found in the cohort. This 50% percent increase during the
17 follow-up period (versus previous AHSMOG reports) notably enhances the power of the latest
18 analyses over past published ones. Of 1,575 deaths from all natural (non-external) causes, 1,029

1 were cardiopulmonary, 135 were non-malignant respiratory (ICD9 codes 460-529), and 30 were
 2 lung cancer (ICD9 code 162) deaths. Abbey et al. (1999) also created another death category,
 3 contributing respiratory causes (CRC), which included any mention of nonmalignant respiratory
 4 disease as an underlying or “contributing cause” on the death certificate. Numerous analyses
 5 were done for the CRC category, due to the large numbers and relative specificity of respiratory
 6 causes as a factor in the deaths. Education was used to index socioeconomic status, rather than
 7 income. Physical activity and occupational exposure to dust were also used as covariates. Cox
 8 proportional hazard models adjusted for a variety of covariates or stratified by sex were used.
 9 The “time” variable used in most of the models was survival time from date of enrollment,
 10 except that age on study was used for lung cancer effects due to the expected lack of short-term
 11 effects. Many covariate adjustments were evaluated, yielding results for all non-external
 12 mortality as shown in Table 8-8.

TABLE 8-8. RELATIVE RISK OF MORTALITY FROM ALL NONEXTERNAL CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE ASHMOG STUDY

Pollution Index	Pollution Increment	Females			Males		
		RR	LCL	UCL	RR	LCL	UCL
PM ₁₀ > 100, cl/yr	30 days/yr	0.958	0.899	1.021	1.082	1.008	1.162
PM ₁₀ mean	20 µg/m ³	0.95	0.873	1.033	1.091	0.985	1.212
SO ₄ mean	5 µg/m ³	0.901	0.785	1.034	1.086	0.918	2.284
O ₃ > 100 ppb, b/yr	551 h/yr (IQR)	0.9	0.8	1.02	1.14	0.98	1.32
SO ₂ mean	3.72 (IQR)	1	0.91	1.1	1.05	0.94	1.18

LCL = Lower 95% confidence limit UCL Upper 95% confidence limit

Source: Abbey et al. (1999).

1 As for cause-specific mortality analyses of the AHSMOG data, positive and statistically
 2 significant effects on deaths with underlying contributing respiratory causes were also found for
 3 30 day/yr > 100 µg/m³ PM₁₀ (RR = 1.14, CI: 1.03, 1.56) in models that included both sexes and

1 adjustment for age, pack-years of smoking, and BMI. Subsets of the cohort had elevated risks:
 2 (a) former smokers had higher RR's than never-smokers (RR for PM₁₀ exceedances for never-
 3 smokers was marginally significant by itself); (b) subjects with low intake of anti-oxidant
 4 vitamins A, C, E had significantly elevated risk of response to PM₁₀, whereas those with
 5 adequate intake did not (suggesting that dietary factors or, possibly, other socioeconomic or life
 6 style factors for which they are a surrogate may be important covariates); and (c) there also
 7 appeared to be a gradient of PM₁₀ risk with respect to time spent outdoors, with those who had
 8 spent at least 16 h/wk outside being at greater risk from PM₁₀ exceedances. The extent to which
 9 time spent outdoors is a surrogate for other variables or is a modifying factor reflecting temporal
 10 variation in exposure to ambient air pollution is not clear, e.g., if the males spent much more
 11 time outdoors than the females, outdoor exposure time could be confounded with gender. When
 12 the cardiopulmonary analyses are broken down by gender (Table 8-9), the RR's for female
 13 deaths were generally smaller than that for males, but none of the risks for PM indices or
 14 gaseous pollutants were statistically significant at $p < 0.05$.

TABLE 8-9. RELATIVE RISK OF MORTALITY FROM CARDIOPULMONARY CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE ASHMOG STUDY

Pollution Index	Pollution Increment	Females			Males		
		RR	LCL	UCL	RR	LCL	UCL
PM ₁₀ > 100, d/yr	30 days/yr	0.929	0.857	1.007	1.062	0.971	1.162
PM ₁₀ mean	20 µg/m ³	0.933	0.836	1.042	1.082	0.943	1.212
SO ₄ mean	5 µg/m ³	0.95	0.793	1.138	1.006	0.926	1.086
O ₃ > 100 ppb, h/yr	551 h/yr (IQR)	0.88	0.76	1.02	1.06	0.87	1.29
O ₃ mean	10 ppb	0.975	0.865	1.099	1.066	0.92	1.236
SO ₂ mean	3.72 (IQR)	1.02	0.9	1.15	1.01	0.86	1.18

LCL = Lower 95% confidence limit

UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

1 The AHSMOG cancer analyses yielded very mixed results (Table 8-10) for lung cancer
 2 mortality. For example, RR's for lung cancer deaths were statistically significant for males for
 3 PM₁₀ and O₃ metrics, but not for females. In contrast, such cancer deaths were significant for
 4 mean NO₂ only for females (but not for males), but lung cancer metrics for mean SO₂ were
 5 significant for both males and females. This pattern is not readily interpretable, but is reasonably
 6 attributable to the very small numbers of cancer-related deaths (18 for females and 12 for males),
 7 resulting in wide RR confidence intervals and very imprecise effects estimates.
 8
 9

TABLE 8-10. RELATIVE RISK OF MORTALITY FROM LUNG CANCER BY AIR POLLUTANT AND BY GENDER FOR AN ALTERNATIVE COVARIATE MODEL

Pollution Index	Pollution Increment	Smoking Category	Females			Males		
			RR	LCL	UCL	RR	LCL	UCL
PM ₁₀ > 100, d/yr	30 days/yr	All ¹	1.055	0.657	1.695	1.831	1.281	2.617
PM ₁₀ mean	20 µg/m ³	All	1.267	0.652	2.463	2.736	1.455	5.147
NO ₂ mean	19.78 (IQR)	All	2.81	1.15	6.89	1.82	0.93	3.57
O ₃ >100 ppb, h/yr	551 h/yr (IQR)	All	1.39	0.53	3.67	4.19	1.81	9.69
		never smoker				6.94	1.12	43.08
		past smoker				4.25	1.5	12.07
O ₃ mean	10 ppb	All	0.805	0.436	1.486	1.853	0.994	3.453
SO ₂ mean	3.72 (IQR)	All	3.01	1.88	4.84	1.99	1.24	3.2
		never smoker	2.99	1.66	5.4			

¹All = both never smokers and past smokers.

LCL = Lower 95% confidence limit.

UCL = Upper 95% confidence limit.

Source: Abbey et al. (1999).

1 The analyses reported by Abbey et al. (1999) attempted to separate PM₁₀ effects from those
2 of other pollutants by use of two-pollutant models, but no quantitative findings from such
3 models were reported. Abbey et al. did mention that the PM₁₀ coefficient for CRC remained
4 stable or increased when other pollutants were added to the model. Lung cancer mortality
5 models for males evaluated co-pollutant effects in detail and indicated that NO₂ was
6 non-significant in all two-pollutant models, but other pollutant coefficients were stable. The
7 PM₁₀ and O₃ effects remained stable when SO₂ was added, suggesting possible independent
8 effects, but PM₁₀ and O₃ effects were hard to separate because these pollutants were highly
9 correlated in this study. Again, the very small number of lung cancer observations and likely
10 great imprecision of reported effects estimates markedly limit the weight that should be accorded
11 to these cancer results.

12 Other analyses, by Beeson et al. (1998), evaluated essentially the same data as in Abbey
13 et al. (1999), but focused on lung cancer incidence (1977-1992). There were only 20 female and
14 16 male lung cancer cases among the 6,338 subjects. Exposure metrics were constructed to be
15 specifically relevant to cancer, those being the annual average of monthly exposure indices from
16 January, 1973 through ensuing months but ending 3 years before date of diagnosis (thus
17 representing a 3-year lag between exposure and diagnosis of lung cancer). The covariates in the
18 Cox proportional hazards model were pack-years of smoking and education, and the time
19 variable was attained age. Many additional covariates were evaluated for inclusion, but only
20 ‘current use of alcohol’ met criteria for inclusion in the final model. Pollutants evaluated were
21 PM₁₀, SO₂, NO₂, and O₃. No interaction terms with the pollutants proved to be significant,
22 including outdoor exposure times. The RR estimates for male lung cancer cases were:
23 (a) positive and statistically significant for all PM₁₀ indicators; (b) positive and mostly
24 significant for O₃ indicators, except for mean O₃, number of O₃ exceedances > 60 ppb, and in
25 former smokers; (c) positive and significant for mean SO₂, except when restricted to proximate
26 monitors; and (d) positive but not significant for mean NO₂. When analyses are restricted to the
27 use of air quality data within 32 km of the residences of subjects, the RR for PM₁₀ over the IQR
28 of 24 µg/m³ in the full data set is 5.21 (or RR=1.99 per 10 µg/m³ PM₁₀). The female RR’s were
29 all much smaller than for males, their being significant for mean SO₂ but not for any indicator of
30 PM₁₀ or O₃.

1 The AHSMOG investigators also attempted to compare effects of fine versus coarse
2 particles (McDonnell et al, 2000). For AHSMOG participants living near an airport (n = 3,769),
3 daily PM_{2.5} levels were estimated from airport visibility using previously-described methods
4 (Abbey et al, 1995b). Given the smaller numbers of subjects in these subset analyses, it is not
5 necessarily surprising that no pollutants were found to be statistically significant, even based on
6 analysis for the male subset near airports (n = 1266). It is important to caveat that (a) the PM_{2.5}
7 exposures were estimated from visibility measurements (increasing exposure measurement error)
8 and yielded a very uneven and clustered distribution of estimated exposures and; (b) the PM_{10-2.5}
9 values were calculated from the differencing of PM₁₀ and PM_{2.5}, likely adding yet even more
10 measurement error for the coarse particle (PM_{10-2.5}) variable.

11 12 ***8.2.3.2.4 The EPRI-Washington University Veterans' Cohort Mortality Study***

13 Lipfert et al. (2000b) reported preliminary results from large-scale mortality analyses for a
14 prospective cohort of up to ~70,000 men assembled by the U.S. Veterans Administration (VA)
15 in the mid-1970s at 32 VA clinics. The VA study group was not originally formed to study air
16 pollution, but was later linked to air pollution data collected separately. The study that led to the
17 development of this clinical cohort (Veterans Administration Cooperative Study Group on
18 Antihypertensive Agents, 1970; 1967) was a “landmark” VA cooperative study demonstrating
19 that anti-hypertensive treatment markedly decreased morbidity and mortality (Perry et al., 1982).
20 The clinical cohort itself involved actual clinical rather than research settings. Lipfert et al.
21 (2001b) noted: “This cohort differs from a general male population in being limited to
22 hypertensive patients and it differs from the cohorts that are randomized into large-scale multi-
23 center trials since it contains a broad spectrum of subjects including many with various
24 co-morbidities.”

25 The VA study cohort was male, middle-aged (51 ± 12 years) and included a larger
26 proportion of African-Americans (35%) than the U.S. population as a whole and a large
27 percentage of current or former smokers (81%). The cohort was selected at the time of
28 recruitment as being mildly to moderately hypertensive, with screening diastolic blood pressure
29 (DBP) in the range 90 to 114 mm Hg (mean 96, about 7 mm more than the U.S. population
30 average) and average systolic blood pressure (SBP) of 148 mm Hg. The subjects had all been
31 healthy enough to be in the U.S. armed forces at one time. As stated by Lipfert et al. (2000b),

1 “Twelve percent had a pulmonary abnormality on physical examination, 9% were diabetic;
2 19% had a history of heart disease; 7% had a history of stroke, and 56% had a positive
3 cardio-renal family history.” Contextual socioeconomic variables were also assembled at the
4 ZIP-code and county levels. The ZIP-code level variables were average education, income, and
5 racial mix. County-level variables included altitude, average annual heating-degree days,
6 percentage Hispanic, and socioeconomic indices. Census-tract variables included poverty rate
7 and racial mix.

8 Detailed exposure information was obtained by averaging air quality data by year for each
9 county of residence at the time of entry to the study. County-wide air pollution variables
10 included TSP, PM₁₀, PM_{2.5}, PM₁₅, PM_{15-2.5}, SO₄, O₃, CO, and NO₂. The VA PM_{2.5} pollutant data
11 were derived from the same data set as used in the ACS study; that PM_{2.5} data set (103 counties
12 with monitors) was much smaller than the VA TSP data set (1,379 counties). In the 1,379
13 counties with TSP data, there were 67,537 subjects. For PM₁₀, during the period 1989-96, there
14 were 59,053 subjects; for PM_{2.5} during 1979-81, there were 26,067 subjects; for PM_{2.5} during
15 1982-84, there were 29,177; for PM₁₅ during 1979-81, there were 26,067; for PM₁₅ during
16 1982-84, there were 29,177; for PM_{15-2.5} during 1979-81, there were 26,067; and for PM_{15-2.5}
17 during 1982-84, there were 29,177. Lipfert et al. (2000b) stated “The IP data used here were
18 derived from 103 monitors,” and “Matching at the county level substantially reduces the errors
19 in estimated exposures incurred by averaging across an entire metropolitan area.” Lipfert et al.
20 (2000b) also indicated: “In this study, the mortality risks were based on the mean concentration
21 of pollutants less estimated background weighted by the number of subjects in each county. . . .
22 Background is estimated as the mean concentration less 3 standard deviations. In the few cases
23 for which this value was negative (indicating a skewed distribution) the background was taken as
24 zero.”

25 Besides considering average exposures over the entire period, three sequential mortality
26 follow-up periods (1976-81, 1982-88, 1989-96) were also evaluated in separate statistical
27 analyses that related mortality in each of those periods to air pollution in different preceding,
28 concurrent, or subsequent periods (i.e., up to 1975, 1975-81, 1982-88, and 1989-86, for TSP in
29 the first three periods, PM₁₀ for the last, and NO₂, 95th percentile O₃, and 95th percentile CO for
30 all four periods). Mortality in the above-noted periods was also evaluated in relation to SO₄ in
31 each of the same four periods noted for NO₂, O₃, and CO, and to PM_{2.5}, PM₁₅, and PM_{15-2.5} in

1 1979-81 and 1982-84. Thus, Lipfert et al. (2000b) stated: “With the baseline and final model,
2 deaths during each of the three most recent exposure periods were considered separately,
3 yielding up to 12 combinations of exposure and mortality periods for each pollutant.
4 Associations between concurrent air quality and mortality periods were considered to relate to
5 acute responses, associations with prior exposures were considered to be emblematic of initiation
6 of chronic diseases and preexposure mortality associations could only be indirect (temporality
7 violated by design), that is, noncausal, and the results of intercorrelation or spurious
8 associations.”

9 Results from the VA study are shown in Table 8-11 for various PM indices. Three caveats
10 were expressed by Lipfert et al. (2000b): “First, the different pollutants, both among species and
11 among time period within species, may represent different locations because of missing data.
12 Second, the relative high fraction of mortality within this cohort may have depleted it of
13 susceptible individuals in the late periods of follow-up. Finally, all of the personal
14 characteristics of each subject were determined only at the entry to the study. It is quite likely
15 that many of those characteristics will have changed during the 21 years of follow-up.” Lipfert
16 et al. (2000b) concluded that this may be reason to regard the results for the 1976-1981 period as
17 the most credible. Within a column of this table, the cohort remains unchanged, but the pollutant
18 differs; however, since missing data vary by pollutant, there are also small changes in the
19 population considered. Within a row of the table the pollutant remains constant, but the cohort is
20 “successively depleted in the passage of time.”

21 In Table 8-11 the column at the far right under the heading “single period” presents
22 regression results from separate model runs for which mortality for the entire follow-up period
23 was regressed against each exposure period for the purpose of comparison with the segmented
24 mortality analysis and with previous cohort studies (Dockery et al., 1993; Pope et al., 1995; and
25 Abbey et al., 1999a). The single-period analysis represents an aggregated approach to exposure
26 when the follow-up periods are short, say a few years; thus, the exposure aggregation error may
27 be small but the study will have reduced power because of the smaller number of deaths. For
28 longer follow-up periods, say 10 yr or more, it becomes important to consider the timing of
29 death relative to exposure in order to preclude attributing associated mortality to subsequent
30 exposure. In the present study, the “indirect” cells of the matrix tend to occur early in the
31 follow-up period while the “delayed” cells tend to occur later.

TABLE 8-11. PARTICULATE MATTER EFFECTS ON MORTALITY BY EXPOSURE AND MORTALITY PERIOD WITH ECOLOGICAL VARIABLES FOR THE VETERANS COHORT STUDY EXPRESSED AS EXCESS MORTALITY

	Exposure Period	deaths 1976-81	deaths 1982-88	deaths 1989-1996	single period ^A
TSP	up to 1975	-0.351 ^D	-0.81^D	-1.49^D	-0.18
TSP	1975-81	0.078 ^C	-0.680 ^D	-2.49^D	0.41
TSP	1982-88	2.060^T	1.08 ^C	-0.20 ^D	0.94
PM ₁₀	1989-96	7.060^T	4.33^T	3.43 ^C	3.92
PM _{2.5}	1979-81	-5.28 ^C	-10.07^D	-15.35^D	0.27
PM _{2.5}	1982-84	0.236 ^T	-6.11^C	-10.78^D	-0.06
PM ₁₅ -PM _{2.5}	1979-81	-4.27 ^C	-1.99 ^D	-9.20^D	0.68
PM ₁₅ -PM _{2.5}	1982-84	-11.00^T	-7.91^C	-12.64^D	-3.64
PM ₁₅	1979-81	-3.03 ^C	-3.79^D	-7.65^D	0.3
PM ₁₅	1982-84	-4.46^T	-5.99^C	-9.73^D	-1.54

A - Mortality for the entire followup period (1976-1996) regressed against each exposure period

C - Concurrent

D - Delayed

T - Temporality violated by design

All excess mortality in units of percent per 10 ug/m³. Bold italic print indicates significant at p < 0.05.

Source: Lipfert et al. (2000b).

1 Lipfert et al (2000b) stated that “The use of specific exposure periods improve the
2 precision of the exposure estimates. Response to PM_{2.5} and PM₁₅ differ greatly between the
3 single period and the segmented periods; that is thus a prime example of the value of the
4 segmented analysis in revealing such details. The single mortality period response without
5 ecological variables are qualitatively similar to what has been reported before (SO₄²⁻ > PM_{2.5} >
6 PM₁₅) but the segmented analysis shows that responses to all of the IP variables are negative,
7 some significantly so.”

8 Lipfert et al (2000b) also stated that specific attention must be given to significant negative
9 associations between pollution and mortality, which they indicated may be indicative of
10 confounding or an incomplete model specification. They also noted “It is possible that the

1 indirect responses may simply reflect random variation and collinearity among time periods.”
2 For example, the correlation between PM_{2.5} concentrations the 1979-81 and 1982-84 exposure
3 periods was 0.69. The study found some responses that were consistent with previous studies
4 but only in the absence of ecological covariates in the model or when responses were aggregated
5 across the entire period of follow-up. The results from this study indicate that peak ozone was
6 the only pollutant with constant positive concurrent response. Lipfert et al. (2000b) state that
7 these overall findings were the result of a more detailed consideration of exposure timing.

8 It should be noted that the preliminary screening models used proportional hazards
9 regression models (Miller et al., 1994) to identify age, SBP, DBP, BMI (nonlinear), age and race
10 interaction terms, and present or former smoking as baseline predictors, with one or two
11 pollution variables added. In the final model using 233 terms (of which 162 were interactions of
12 categorized SBP, DBP, and BMI variables with age), the most significant non-pollution
13 variables were SBP, DBP, BMI, and their interactions with age, smoking status, average
14 education, race, poverty, and height. Also, Lipfert et al. (2000b) noted that the mortality risk
15 associated with current cigarette smoking (1.43) that they found was lower than reported in other
16 studies. The most consistently positive effects were found for O₃ and NO₂ exposures in the
17 immediately preceding years. This study used peak O₃ rather than mean O₃, as was done in
18 some other cohort studies. This may account for the higher O₃ and NO₂ effects here. While the
19 PM analyses considering segmented (shorter) time periods gave differing results (including
20 significant negative mortality coefficients for some PM metrics), when methods consistent with
21 past studies were used (i.e., many- year average PM concentrations), similar results were
22 reported: the authors found that “(t)he single-mortality-period responses without ecological
23 variables are qualitatively similar to what has been reported before (SO₄ ≥ PM_{2.5} > PM₁₅).” With
24 ecological variables included, a significant PM effect was that for TSP for 1982-1988 exposure
25 for the single period. Overall, the authors concluded that “the implied mortality risks of long-
26 term exposure to air pollution were found to be sensitive to the details of the regression model,
27 the time period of exposure, the locations included, and the inclusion of ecological as well as
28 personal variables.”

29 In a follow-up study of the Veterans' Cohort Study, Lipfert et al. (2003) investigated the
30 importance of blood pressure (BP) as a covariate in studies of long-term associations between air
31 quality and mortality. The aims of the article were to summarize quantitative relationships

1 between BP and mortality, to discuss the available information on associations between air
2 quality and BP, and to present results of a proportional hazard regression sensitivity analysis for
3 the Veterans' Cohort. The relationship between BP and air quality was considered by reviewing
4 the literature, by deleting variables from the Veterans' Study proportional hazards regression
5 models, and by stratifying the analyses of that cohort by diastolic blood pressure (DBP) level.
6 The literature review found BP to be an important predictor of survival and found small transient
7 associations between air quality and BP that may be either positive or negative. The regression
8 model sensitivity runs indicate that the reported VA model associations with air pollution are
9 robust to the deletion of the BP variables for the entire cohort. For stratified regressions, the
10 confidence intervals for the air pollution-mortality associations overlapped for the two DBP
11 groups. The authors, Lipfert et al. (2003), concluded that there is scant evidence that air
12 pollution affects blood pressure in either healthy or impaired subjects. They went on to note that
13 the inclusion of BP variables is not strictly essential to derive valid estimates of air pollution
14 responses, concluding overall that the associations between air quality and mortality are not
15 mediated through blood pressure.

17 ***8.2.3.2.5 Relationship of Six Cities, ACS, AHSMOG, and VA Study Findings***

18 This section compares findings from the earlier Six Cities study (Dockery et al., 1993), the
19 ACS study (Pope et al., 1995), the HEI reanalyses of the latter two studies, the extension of the
20 ACS study (Pope et al., 2002), the more recent AHSMOG mortality analyses (Abbey et al.,
21 1999; McDonnell et al., 2000) and the VA study (Lipfert et al., 2000b). In comparing
22 prospective cohort studies, some key issues for consideration are: (1) cohort size and
23 characteristics; (2) study design; and (3) air quality data used in exposure characterization.
24 Table 8-12 compares the estimated RR for total, cardiopulmonary, and cancer mortality among
25 the studies.

26 The number of subjects in these studies varies greatly: 8,111 subjects in the Six-Cities
27 Study; 295,223 subjects in the 50 fine particle ($PM_{2.5}$) cities and 552,138 subjects in the
28 151 sulfate cities of the ACS Study; 6,338 in the AHSMOG Study; and 26,000 in the VA study
29 for $PM_{2.5}$. This may partially account for differences among their results.

30 The Six City and AHSMOG studies were designed specifically as prospective studies to
31 evaluate long-term effects of air pollution and included concurrent air pollution measurements.

TABLE 8-12. COMPARISON OF EXCESS RELATIVE RISKS OF LONG-TERM MORTALITY IN THE HARVARD SIX CITIES, ACS, AHSMOG, AND VA STUDIES

Study	PM ¹	Total Mortality		Cardiopulmonary Mortality		Lung Cancer Mortality	
		Ex. RR ²	95% CI	Ex. RR	95% CI	Ex. RR	95% CI
Six City ³	PM _{2.5}	13%	(4.2, 23%)	18%	(6.0, 32%)	18%	(-11, 57%)
Six City New ⁴	PM _{2.5}	14%	(5.4, 23%)	19%	(6.5, 33%)	21%	(-8.4, 60%)
ACS ⁵	PM _{2.5}	6.6%	(3.5, 9.8%)	12%	(6.7, 17%)	1.2%	(-8.7, 12%)
ACS New ⁶	PM _{2.5}	7.0%	(3.9, 10%)	12%	(7.4, 17%)	0.8%	(-8.7, 11%)
ACS New	PM _{15-2.5}	0.4%	(-1.4, 2.2%)	0.4%	(-2.2, 3.1%)	-1.2%	(-7.3, 5.1%)
ACS New	PM _{10/15} Dicot	4.1%	(0.9, 7.4%)	7.3%	(3.0, 12%)	0.8%	(-8.1, 11%)
ACS New	PM _{10/15} SSI	1.6%	(-0.8, 4.1%)	5.7%	(2.5, 9.0%)	-1.6%	(-9.1, 6.4%)
ACS Extend. ⁷	PM _{2.5} 1979-1983	4.1%	(0.8, 7.5%)	5.9%	(1.5, 10%)	8.2%	(1.1, 16%)
ACS Extend.	PM _{2.5} 1999-2000	5.9%	(2.0, 9.9%)	7.9%	(2.3, 14%)	12.7%	(4.1, 22%)
ACS Extend.	PM _{2.5} Avg.	6.2%	(1.6, 11%)	9.3%	(3.3, 16%)	13.5%	(4.4, 23%)
AHSMOG ⁸	PM _{10/15}	2.1%	(-4.5, 9.2%)	0.6%	(-7.8, 10%)	81%	(14, 186%)
AHSMOG ⁹	PM _{2.5}	8.5%	(-2.3, 21%)	23%	(-3.0, 55%)	39%	(-21, 150%)
AHSMOG ⁹	PM ₁₀ -PM _{2.5}	5.2%	(-8.3, 21%)	20%	(-13, 64%)	26%	(-38, 155%)
VA ¹⁰	PM _{2.5} PM _{2.5}	0.3% ¹¹ -10% ¹²	NS ¹³ SS ¹⁴				
VA ¹⁰	PM _{15-2.5} PM _{15-2.5}	0.7% ¹¹ -2.0% ¹²	NS ¹³ NS ¹³				
VA ¹⁰	PM ₁₅ PM 15	0.7% ¹¹ -7.6 ¹²	NS ¹³ SS ¹⁴				

¹ Increments are 10 µg/m³ for PM_{2.5} and PM_{10/15-2.5} and 20 µg/m³ for PM_{10/15}.

² Ex. RR (excess relative risk, percent) = 100 * (RR - 1) where the RR has been converted from the highest-to-lowest range to the standard increment (10 or 20) by the equation RR = exp(log(RR for range) × (standard increment) / range).

³ From Dockery et al. (1993); Krewski et al. (2000), Part II, Table 21a, original model.

⁴ From Krewski et al. (2000), Part I, Table 21c.

⁵ From Krewski et al. (2000), Part I, Table 25a.

⁶ From Krewski et al. (2000), Part I, Table 25c.

⁷ From Pope et al. (2002).

⁸ From Abbey et al. (1999), pooled estimate for males and females.

⁹ From McDonnell et al. (2000), two-pollutant (fine and coarse) models; males only.

¹⁰ From Lipfert et al. (2000b), Males only, exposure period 1979-1981 from Table 7. Standard errors not provided.

¹¹ Single period mortality (1976-1996).

¹² Mortality from 1982-88.

¹³ Reported by author to be non-significant.

¹⁴ Reported to be statistically significant.

1 The ACS study was also a prospective study, using air pollution data obtained at about the
2 approximate time of enrollment but not subsequently (Pope et al., 1995) and it evaluated air
3 pollution effects among a cohort originally recruited to study factors affecting cancer rates. The
4 extended ACS study incorporated much more air pollution data, including TSP data back to the
5 1960s and more recent fine particle data. The VA study was originally designed to evaluate the
6 efficacy of hypertension treatments in male military veterans with hypertension.

7 The Six-Cities cohort was pre-selected, by the investigators, to be a representative
8 population, at least for the region of the country that was (is) heavily impacted by both coal
9 combustion and motor vehicle effluents. By contrast, the ACS study cohort was drawn from a
10 large pool of volunteers who happened to live in communities where several years of fine
11 particle and/or sulfate ambient air concentration data were available. The AHSMOG cohort is
12 drawn from non-smoking, non-Hispanic white Seventh Day Adventist residents of California.
13 The VA cohort also presents a narrow population (only male veterans having a very high
14 percentage of prior smoking, all of whom were diagnosed as hypertensive). Of these four cohort
15 studies, the ACS and Six Cities studies are thusly more broadly representative of U.S.
16 populations.

17 The estimated mean risk of cigarette smoking in the VA cohort ($RR = 1.43$) was smaller
18 than that of the Six City cohort ($RR = 1.59$) and the ACS cohort ($RR = 2.07$ for current
19 smokers). Some possible differences include the higher proportion of former or current smokers
20 in the VA cohort (81%) versus 51% in the ACS study and 42 to 53% in the Six City study.
21 A possibly more important factor may be the difference in education levels, as only 12% of the
22 ACS participants had less than a high school education vs 28% of the Six City cohort. Education
23 level was not reported for the VA Cohort; however, education differences may be associated
24 with smoking behavior (more smokers among the less-educated). The ACS, Six Cities and
25 AHSMOG investigators used Cox Proportional Hazards models to estimate relationships
26 between mortality and long-term PM exposure; in the VA study, linear regression models were
27 used. All incorporated potentially confounding variables, such as body mass index or smoking
28 history; however, as described previously, the VA study included a large number of covariates
29 and interaction terms in the models. The VA study also differed from the other three studies in
30 emphasizing analyses using subsets of air quality and mortality data.

1 As described in more detail in section 8.4.6.4, the Harvard Six Cities study used
2 dichotomous samplers to measure fine and coarse fraction particles for approximately seven
3 years in each city. AHSMOG investigators relied on available PM monitoring data, initially
4 using TSP, then PM₁₀ data, and more recently including PM_{2.5} data estimated from airport
5 visibility measurements. Both the VA and ACS studies used PM_{2.5} data from the same data set,
6 the IP Network which consisted of 157 sites. For the VA study, the cohort was between 26,000
7 and 29,000 for the two exposure periods derived from 103 monitors and for the ACS study, the
8 cohort was 359,000 in 61 MSAs for one exposure period 1979-1983. Both studies may have
9 potentially used up to 61 sites in common, but the VA study breaks the average level into two
10 periods, whereas the ACS study averages the level across the entire time period. For the cities in
11 common, the same data were used to relate an exposure estimate to the county in the VA study
12 and to the Metropolitan Statistical Areas (MSAs) in the ACS study. Thus differences in the base
13 for deriving exposure estimates for the subjects may have contributed to possible differences
14 between the representativeness of exposures used in the county or the MSA.

15 Section 3.2.5 and Appendix 3A discuss spatial variability in PM_{2.5} at multiple sites within
16 MSAs across the United States for 27 MSAs. MSA sites may include those in one to several
17 counties. Consistency of PM_{2.5} values between multiple sites within individual MSAs used to
18 derive annual averages for PM_{2.5} can vary by MSAs. The annual averages for many counties
19 differ by 1-2 µg/m² across MSAs. In some counties with several monitors, differences between
20 individual monitors can range from 1-2 µg/m² to 4-6 µg/m², at times, for annual averages.

21 It is noteworthy that estimated PM effects observed in the VA study appeared to be more
22 negative in the later years of the study rather than in the earlier years. As noted earlier, this may
23 also be due to cohort depletion. The participants in the VA Cohort clearly formed an “at-risk”
24 population, and the results by Vasan et al. (2001) make more plausible the hypothesis stated by
25 Lipfert et al. (2000b, p. 62) that “. . . the relatively high fraction of mortality within this cohort
26 may have depleted it of susceptible individuals in the later periods of follow-up.”

27 The Six Cities study found significant associations of PM_{2.5} with total and cardiopulmonary
28 (but not lung cancer) mortality, but not with coarse particle indicators. In the Krewski et al.
29 (2000) reanalysis of the ACS study data, significant associations were found for both PM_{2.5} and
30 PM₁₅ (excess relative risks of 6.6% for a 10 µg/m³ increase in PM_{2.5} and 4% for a 20 µg/m³
31 increase in annual PM_{10/15}). The results most recently reported for the AHSMOG study (Abbey

1 et al., 1999; McDonnell et al., 2000) used PM_{10} as its PM mass index and found some significant
2 associations with total mortality and deaths with contributing respiratory causes, even after
3 controlling for potentially confounding factors (including other pollutants). In further
4 investigation of the results found for PM_{10} among males, McDonnell et al. (2000) reported larger
5 associations with $PM_{2.5}$ than $PM_{10-2.5}$ for males in the AHSMOG cohort, though none of the 11
6 $PM_{2.5}$ associations reached statistical significance. For the VA study, few statistically significant
7 associations were found with PM indicators; in fact, some statistically significant negative
8 associations were reported for some subset analyses. Where significant positive associations
9 were reported, they were generally for the subset of mortality data from the early years of the
10 study. The authors note that these were sometimes analyses using mortality data that preceded
11 the air quality measurements; it is important to note, however, that the design of these studies
12 uses available air quality data to characterize long-term pollution concentrations, not as a
13 measure of latency or lag period in effects.

14 There is no clear consistency in relationships among PM effect sizes, gender, and smoking
15 status across these studies. The AHSMOG study cohort is a primarily nonsmoker group while
16 the VA study cohort had a large proportion of smokers and former smokers in an all-male
17 population. The ACS results show similar and significant associations with total mortality for
18 both “never smokers” and “ever smokers”, although the ACS cohort may include a substantial
19 number of long-term former smokers with much lower risk than current smokers. The Six Cities
20 study cohort shows the strongest evidence of a higher PM effect in current smokers than in non-
21 smokers, with female former smokers having a higher risk than male former smokers. This
22 study suggests that smoking status may be viewed as an effect modifier for ambient PM, just as
23 smoking may be a health effect modifier for ambient O_3 (Cassino et al., 1999).

24 When the ACS study results are compared with the AHSMOG study results for SO_4^{-2}
25 ($PM_{10-2.5}$ and PM_{10} were not considered in the ACS study, but were evaluated in ACS reanalyses
26 [Krewski et al., 2000; Pope et al, 2002]), the total mortality effect sizes per $15 \mu g/m^3 SO_4^{-2}$ for
27 the males in the AHSMOG population fell between the Six-Cities and the ACS effect-size
28 estimates for males (RR = 1.28 for AHSMOG male participants; RR=1.61 for Six-Cities Study
29 male non-smokers; and RR = 1.10 for never smoker males in the ACS study), and the AHSMOG
30 study 95% confidence intervals encompass both of those other studies’ sulfate RR’s.

1 In considering the results of these studies together, statistically significant associations are
2 reported between fine particles and mortality in the ACS and Six Cities analyses, inconsistent
3 but generally positive associations with PM were reported in the AHSMOG analyses, and
4 distinctly inconsistent results were reported in the VA study. Based on several factors – the
5 larger study population in the ACS study, the larger air quality data set in the Six Cities study,
6 the more generally representative study populations used in the Six Cities and ACS studies, and
7 the fact that these studies have undergone extensive reanalyses – the greatest weight should be
8 placed on the results of the ACS and Six Cities cohort studies in assessing relationships between
9 long-term PM exposure and mortality. The results of these studies, including the reanalyses
10 results for the Six Cities and ACS studies and the results of the ACS study extension, provide
11 substantial evidence for positive associations between long-term ambient PM (especially fine
12 PM) exposure and mortality.

13 14 **8.2.3.2.6 *The S-Plus GAM Convergence Problem and Cohort Studies***

15 The long-term pollution-mortality study results discussed above in this section were
16 unaffected by the GAM default convergence issue reported by Dominici et al. (2002) and
17 discussed earlier in this chapter, because they did not use such a model specification. Instead,
18 the cohort studies of long-term PM exposures used Cox Proportional Hazards models. For
19 example, in the recent Pope et al. study (2002), the baseline models were random effects Cox
20 Proportional Hazards models without the inclusion of nonparametric smooths. However, Pope
21 et al. (2002) did include a non-parametric spatial smooth in the model as part of a more extended
22 sensitivity analysis to evaluate more aggressive control of spatial differences in mortality. They
23 found that the estimated pollution-mortality effects were not sensitive to this additional spatial
24 control, so final reported results did not include the smooth; and this study's results, like those
25 from other cohort studies discussed above, were unaffected by the S-Plus convergence issue.

26 27 **8.2.3.3 Studies by Particulate Matter Size-Fraction and Composition**

28 **8.2.3.3.1 *Six Cities, ACS, AHSMOG and VA Study Results***

29 Ambient PM consists of mixtures that may vary in composition over time and from place
30 to place. This should logically affect the relative toxicity of PM indexed by mass at different
31 times or locations. Some semi-individual chronic exposure studies have investigated relative

1 roles of various PM components in contributing to observed air pollution associations with
 2 mortality. However, only a limited number of the chronic exposure studies have included direct
 3 measurements of chemical-specific constituents of the PM mixes indexed by mass measurements
 4 used in their analyses.

5 As shown in Table 8-13, the Harvard Six-Cities Study (Dockery et al., 1993) results
 6 indicated that the PM_{2.5} and SO₄⁻² RR associations (as indicated by their respective 95% CI's and
 7 t-statistics) were more consistent than those for the coarser mass components. Further, the
 8 effects of sulfate and non-sulfate PM_{2.5} are quite similar. Acid aerosol (H⁺) exposure was also
 9 considered by Dockery et al. (1993), but only less than one year of measurements collected near
 10 the end of the follow-up period were available in most cities; consequently, the Six-Cities results
 11 were much less conclusive for the acidic component of PM than for the other PM metrics
 12 measured over many years during the study.

TABLE 8-13. COMPARISON OF ESTIMATED RELATIVE RISKS FOR ALL-CAUSE MORTALITY IN SIX U.S. CITIES ASSOCIATED WITH THE REPORTED INTER-CITY RANGE OF CONCENTRATIONS OF VARIOUS PARTICULATE MATTER METRICS

PM Species	Concentration Range (µg/m ³)	Relative Risk Estimate	RR 95% CI	Relative Risk t-Statistic
SO ₄ ⁼	8.5	1.29	(1.06-1.56)	3.67
PM _{2.5} - SO ₄ ⁼	8.4	1.24	(1.16-1.32)	8.79
PM _{2.5}	18.6	1.27	(1.06-1.51)	3.73
PM _{15-2.5}	9.7	1.19	(0.91-1.55)	1.81
TSP-PM ₁₅	27.5	1.12	(0.88-1.43)	1.31

Source: Dockery et al. (1993); U.S. Environmental Protection Agency (1996a).

1 Table 8-14 presents comparative PM_{2.5} and SO₄⁻² results from the ACS study, indicating
 2 that both had substantial, statistically significant effects on all-cause and cardiopulmonary
 3 mortality. On the other hand, the RR for lung cancer was notably larger (and substantially
 4 more significant) for SO₄⁻² than PM_{2.5} (not significant).

TABLE 8-14. COMPARISON OF REPORTED SO₄⁻² AND PM_{2.5} RELATIVE RISKS FOR VARIOUS MORTALITY CAUSES IN THE AMERICAN CANCER SOCIETY (ACS) STUDY

Mortality Cause	SO ₄ ⁻² (Range = 19.9 µg/m ³)			PM _{2.5} (Range = 24.5 µg/m ³)		
	Relative Risk	RR 95% CI	RR t-Statistic	Relative Risk	RR 95% CI	RR t-Statistic
All Cause	1.15	(1.09-1.22)	4.85	1.17	(1.09-1.26)	4.24
Cardiopulmonary	1.26	(1.15-1.37)	5.18	1.31	(1.17-1.46)	4.79
Lung Cancer	1.35	(1.11-1.66)	2.92	1.03	(0.80-1.33)	0.38

Source: Pope et al. (1995).

1 The most recent AHSMOG analyses also considered SO₄⁻² as a PM index for all health
2 outcomes studied except lung cancer, but SO₄⁻² was not as strongly associated as PM₁₀ with
3 mortality (as shown in Table 8-8) and was not statistically significant for any mortality category.

4 Also, extensive results from the VA study were reported in Lipfert et al. (2000b) for
5 various components: TSP, PM₁₀, PM_{2.5}, PM_{15-2.5}, PM₁₅, SO₄⁻². There were no significant positive
6 effects for any exposure period concurrent or preceding any of the segmented mortality periods
7 for any PM component, unlike for O₃. On the other hand, the SO₄⁻² levels during the 1979-81
8 and 1982-84 exposure periods were significantly associated with deaths aggregated across all the
9 segmented follow-up mortality periods (1976-1996). The first exposure period was associated
10 with 4.9% increase and the latter with a 6.7% increase in the aggregated (“single period” in
11 Lipfert et al 2000b terminology) total, non-accidental mortality risk per 10 µg/m³ SO₄⁻²
12 increment.

13 Harvard Six Cities, ACS, and AHSMOG study results are compared in Table 8-15 (total
14 mortality) and Table 8-16 (cause-specific mortality). Results for the VA study are not shown in
15 Tables 8-15 and 8-16 as the VA cohort is all male and largely consists of current or former
16 smokers (81%) and is thusly not comparable to the total or male non-smoker populations of the
17 other studies. Also, results for females are not presented, as the overall effects were driven
18 largely by males (female associations generally being statistically nonsignificant).

TABLE 8-15. COMPARISON OF TOTAL MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM ₁₀ (50 µg/m ³)	Six Cities	All	1.50 ^a ; 1.53 ^b	2.94 ^a ; 3.27 ^b
		Male Nonsmoker	1.28 ^a	0.81 ^a
	AHSMOG	Male Nonsmoker	1.24	1.61
PM _{2.5} (25 µg/m ³)	Six Cities	All	1.36 ^a ; 1.38 ^b	2.94 ^a ; 3.73 ^b
		Male Nonsmoker	1.21 ^a	0.81 ^a
	ACS (50 cities)	All	1.17	4.35
		Male Nonsmoker	1.25	1.96
SO ₄ = (15 µg/m ³)	Six Cities	All	1.50 ^a ; 1.57 ^b	2.94 ^a ; 3.67 ^b
		Male Nonsmoker	1.35	0.81 ^a
	ACS (151 cities)	All	1.11	5.11
		Male Nonsmoker	1.1	1.59
		AHSMOG	Male Nonsmoker	1.28
Days/yr. with PM ₁₀ > 100 µg/m ³ (30 days)	AHSMOG	Male Nonsmoker	1.08	2.18
PM _{10-2.5} (25 µg/m ³)	Six Cities	All	1.81 ^a ; 1.56 ^b	2.94 ^{a,c} 1.81 ^b
		Male Nonsmoker	1.43 ^a	0.81 ^a

^a Method 1 compares Portage versus Steubenville (Table 3, Dockery et al., 1993).

^b Method 2 is based on ecologic regression models (Table 12-18, U.S. Environmental Protection Agency, 1996a).

^c Method 1 not recommended for PM_{10-2.5} analysis, due to high concentration in Topeka.

1 Estimates for Six Cities parameters were calculated in two ways: (1) mortality RR for the
2 most versus least polluted city in Table 3 of Dockery et al. (1993), adjusted to standard
3 increments; and (2) ecological regression fits in Table 12-18 of U.S. Environmental Protection
4 Agency (1996a). The Six Cities study of eastern and mid-western U.S. cities suggests a strong
5 and highly significant relationship for fine particles and sulfates, a slightly weaker but still
6 highly significant relationship to PM₁₀, and a marginal relationship to PM_{10-2.5}. The ACS study
7 looked at a broader spatial representation of cities, and found a stronger statistically significant

TABLE 8-16. COMPARISON OF CARDIOPULMONARY MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM ₁₀ (50 µg/m ³)	Six Cities	All	1.744 ^a	2.94 ^a
	AHSMOG	Male Nonsmoker	1.219	1.12
		Male Non-CRC ^c	1.537	2.369
PM _{2.5} (25 µg/m ³)	Six Cities	All	1.527 ^a	2.94 ^a
	ACS (50 cities)	All	1.317	4.699
		Male	1.245	3.061
		Male Nonsmoker	1.245	1.466
SO ₄ = (15 µg/m ³)	Six Cities	All	1.743 ^a	2.94 ^a
	ACS (151 cities)	All	1.19	5.47
		Male	1.147	3.412
		Male Nonsmoker	1.205	2.233
	AHSMOG	Male Nonsmoker	1.279	0.072
		Male Non.-CRC ^c	1.219	0.357
Days/yr. with PM ₁₀ > 100 (30 days)	AHSMOG	Male Nonsmoker	1.082	1.31
		Male Non.-CRC ^c	1.188	2.37
PM _{10-2.5} (25 µg/m ³)	Six Cities	All	2.251 ^a	2.94 ^{a,b}

^a Method 1 compares Portage versus Steubenville (Table 3, Dockery et al., 1993).

^b Method 1 not recommended for PM_{10-2.5} analysis due to high concentration in Topeka.

^c Male non. - CRC = AHSMOG subjects who died of any contributing non-malignant respiratory cause.

1 relationship to PM_{2.5} than to sulfate (no other pollutants were examined). The AHSMOG study
2 at California sites (where sulfate levels are typically low) found significant effects in males for
3 PM₁₀ 100 µg/m³ exceedances and a marginal effect of mean PM₁₀, but no PM effects for females
4 or with sulfates. On balance, the overall results shown in Tables 8-15 and 8-16 suggest
5 statistically significant relationships between long-term exposures to PM₁₀, PM_{2.5}, and/or sulfates
6 and excess total and cause-specific cardiopulmonary mortality.

1 The prospective cohort long-term PM exposure studies conducted to date collectively
2 appear to confirm earlier cross-sectional study indications that the fine mass component of PM₁₀
3 (and usually especially its sulfate constituent) are more strongly correlated with mortality than is
4 the coarse PM_{10-2.5} component. However, the greater precision of PM_{2.5} population exposure
5 measurement (both analytical and spatial) relative to PM_{10-2.5} makes conclusions regarding their
6 relative contributions to observed PM₁₀-related associations less certain than if the effect of their
7 relative errors of measurement could be addressed.

8 9 **8.2.3.3.2 *Lipfert and Morris (2002): An Ecological Study***

10 Although the use of prospective cohort studies in assessing the long-term exposure effects
11 of particles and gases is preferred, additional useful information may be derived from ecological
12 studies. In particular, repeated cross-sectional studies may provide another tool for examining
13 changes in air-pollution-attributable mortality over time. Lipfert and Morris (2002) carried out
14 cross-sectional regressions for five time periods using data on mortality, air pollution including
15 various measures of PM, O₃, NO₂, SO₂, CO, climate, and sociodemographic factors using
16 county-level data. Data were available for TSP and gaseous co-pollutants as far back as 1960
17 and for PM_{2.5}, PM₁₅, and SO₄⁻ from the inhalable particulate network (IPN). The authors
18 investigated longitudinal and spatial relations between air pollution and age-specific mortality
19 using 3- to 5-year subsets of data from 1960 to the end of 1997, with the addition of PM_{2.5} data
20 from 1999.

21 One of the key features of this study is the presentation of attributable risk estimates for
22 different age groups across varying time periods. It is important to note that cross-sectional
23 studies such as this one do not directly investigate temporality or latency of effects. One or more
24 years of pollution measurements are used as estimates of long-term pollution concentrations for
25 the communities. Lipfert and Morris (2002) note that PM_{2.5} data from the two available time
26 periods (1979-1984 and 1999) were well correlated ($r=0.71$)² and, in fact, used the 1999 data for
27 “back-extrapolation” of data for some of the counties where data were not available in

² Pope et al. (2002) also reported a strong correlation ($r = 0.78$) between PM_{2.5} concentrations averaged over 1979-1983 and 1999-2000 in the extended analysis for the ACS cohort.

1 1979-1984³. The different time periods may provide data that more or less adequately represent
2 long-term PM concentrations, and it is more important that the measurements reflect long-term
3 trends than that the PM concentrations predate the mortality data by any specific time period.
4 While well-motivated, the use of multiple mortality and pollution time periods clearly reduces
5 the power of any individual analysis.

6 The counties included in any given analysis varied by time period based on available data.
7 Lipfert and Morris (2002) stated that “the number of counties with valid air quality data vary
8 substantially...by pollutant and over time” and that they attempted to differentiate “among many
9 air quality variables that differ according to species, timing, and in some cases measurement
10 technology.” They stated, “Environmental monitoring coverage increased substantially during
11 this period [1970-1974] (1258 counties had TSP data) and air quality began to improve in major
12 cities in response to emission controls and use of clean fuels.” There have also been changes in
13 the measurement of PM (e.g., TSP, PM₁₀, and PM_{2.5}) over time as well as changes in the location
14 of monitors as they were sited for different purposes.

15 An interesting conclusion drawn by Lipfert and Morris (2002) is that pollution-mortality
16 relationships vary across age groups, with stronger effects among younger age groups. It is
17 important, however, to note that the results of this study are presented as attributable risks; with
18 attributable risk defined as the mortality risk based on the mean concentration of the pollutant
19 and the mean mortality rate. A problem with attributable risk arises when one compares the
20 risks of different age groups. In Table 8-17, it can be seen that among the young a higher
21 percentage of mortality is reduced by reducing air pollution, as reflected in the higher
22 attributable risks. However, with the more standard presentation of risk per 10 µg/m³ change in
23 PM_{2.5}, the risk increases for older age groups.

24 Lipfert and Morris (2002) also reported that they generally found that risk estimates were
25 highest for pollution estimates in the earlier time periods and decreased in analyses using more
26 recent pollution and mortality data. This can be seen in Table 8-17, where statistically
27 significant associations are reported for all but the youngest age group using 1989-1991
28 mortality data, but with 1995-1997 data the associations were smaller and only significant for

³ It appears that the extrapolated data were used in the main analyses. EPA observes that it was difficult to interpret the methodological discussions in the paper and obtained further information via personal communication with the author.

TABLE 8-17. PERCENT ATTRIBUTABLE RISK OF MORTALITY (from Lipfert and Morris, 2000) AND RISK ESTIMATES CALCULATED PER 10 µg/m³ PM_{2.5}. SELECTED TIME PERIODS FOR MORTALITY DATA OF 1989-91 AND 1995-97 WITH PM_{2.5} DATA FROM THE IP NETWORK DATA (1979-84) FOR COUNTIES IN THE U.S. WITH IP NETWORK MONITORS.

Age	1989-91 Mortality Data				1995-97 Mortality Data			
	Lipfert and Morris results		EPA estimates (per 100,000)		Lipfert and Morris results		EPA estimates (per 100,000)	
	Attributable risk ^A	SE	Mortality Rate	Risk Estimate ^B	Attributable Risk ^A	SE	Mortality Rate	Risk Estimate ^B
15-44	5.2	4.9	70	4	4.2	3.6	74	3
45-64	7.9*	2.4	778	62	5.4*	2.7	701	38
65-74	3.7*	1.2	2643	98	1.1	1.4	2577	27
75-84	2.0*	1	5943	119	1.5	1.9	5885	88
≥ 85	2.1*	0.8	15145	316	1.6	1.4	15795	246

*P < 0.05

^A adapted from Lipfert and Morris (2002) Tables 7 and 8; converted to %attributable risk per 10 µg/m³.

^B risk estimate = (coefficient)(10 µg/m³ PM_{2.5}) per 100,000 over a 3-yr period; where coefficient = [(AR) (mean mortality rate)]/(mean PM_{2.5} concentration). Mortality rates per 100,000 over a 3-yr period from Table 1 and mean PM_{2.5} concentration (19.19 µg/m³) from Table 2 of Lipfert and Morris (2002).

1 one age group. The same pattern can be seen for TSP, PM₁₀, and PM_{2.5} as summarized in
 2 Figure 7 in the authors' report (Lipfert and Morris, 2002). The authors concluded that mortality
 3 responses to air pollution have been decreasing over time for PM and several other pollutants.

4 In any cross-sectional study, exposure misclassification and confounding are important
 5 issues to consider in interpreting the results. For all studies discussed in this section, exposure is
 6 characterized by pollution concentration averaged for a given geographic region. In cohort
 7 studies, some information is generally available on participants' residence histories but in cross-
 8 sectional studies the exposure level is assigned based on the subjects' location according to the
 9 death record. Between the years 1995-2000, approximately 20% of people aged 5 to 64 moved
 10 to a different state. Older adults were slightly less mobile as a group, with 18.8% of those
 11 65 and older moving to a different state; the rate was 21.2% for adults aged 65-74 and declined
 12 with greater age, though there was some evidence of return migration at advanced ages of
 13 85 years and older (U.S. Census Bureau, 2003). To address potential confounding, the authors

1 used county-level data on a variety of risk factors, using stepwise regression methods to select
2 the best-fitting model, then apparently used the residuals from these models to evaluate
3 relationships with air pollution concentrations. While an impressive list of variables were
4 included in these analyses, it must be noted that there can be considerable variation in
5 socioeconomic or personal risk factors across areas within a given county as well as from county
6 to county.

7 The inhalable particle network data used in Lipfert and Morris (2002) is basically the same
8 air quality data set used in analyses for the ACS and VA study cohorts. A major distinction, of
9 course, is that individual health data were used in the cohort studies, but only county-level data
10 for the cross-sectional study. Lipfert and Morris (2002) noted reasonable agreement with Pope
11 et al. (1995) and Dockery et al. (1993), but observed that the VA study analyses (Lipfert et al.,
12 2000b) “found apparent beneficial effects of PM_{2.5}...whereas the present study does not.” While
13 subject to the limitations of cross-sectional analyses, the Lipfert and Morris study reports
14 associations between fine particles and mortality that are generally similar to those from the
15 large cohort studies, although it is difficult to compare the quantitative results across studies.
16 Interpreting the results of the many subset analyses conducted is difficult, but the results of
17 analyses across time periods would appear to indicate reduced mortality risk with pollution from
18 more recent time periods.

19 20 ***8.2.3.3 Mortality and Chronic Exposure to Traffic-Related Ambient PM***

21 Although not a study of PM mass, a recent study of the potential mortality effects of long-
22 term exposure to PM air pollution conducted in the Netherlands gives insight into the potential
23 role of long-term effects of PM from traffic origins in the PM mass-mortality association. Hoek
24 et al (2002) aimed to assess the relation between traffic-related air pollution and mortality in
25 participants of the Netherlands Cohort Study on Diet and Cancer (NLCS), an ongoing study.
26 They investigated a random sample of 5000 middle-aged people (aged 55-69 years) from the full
27 cohort of the NLCS study during 1986 to 1994. Long-term exposure to traffic-related air
28 pollutants using black smoke (BS) and nitrogen dioxide (NO₂) as indicators, was estimated for
29 participants' 1986 home address. The authors noted that, in the Netherlands, BS is primarily
30 derived from diesel emissions, while NO₂ is from all motorized vehicles. However, the authors
31 did not consider tracers for other sources of PM; so, this study did not investigate or preclude

1 effects from other PM source categories. This long-term study is unique in that it examined
2 within-metropolitan-area small-scale variations in exposures. Exposure was characterized by
3 interpolation, based on the measured regional and urban background concentration, as well as
4 using an indicator variable for living near major roads.

5 Associations between exposure to air pollution and (cause specific) mortality were
6 assessed with Cox's proportional hazards models, with adjustment for potential confounders.
7 Cardiopulmonary mortality was associated with living near a major road (relative risk 1.95, 95%
8 CI 1.09-3.52) and with background plus local BS (1.71, 1.10-2.67), but not as significantly with
9 the estimated ambient background BS concentration (1.34, 0.68-2.64) or background plus local
10 NO₂ (1.81, 0.98-3.34). The relative risk for living near a major road was 1.41 (0.94-2.12) for
11 total deaths. The fact that BS exposure was statistically significantly associated with
12 cardiopulmonary deaths, but not NO₂, suggests a greater role for diesel particles in the reported
13 associations with living near major roads than for traffic in general. Non-cardiopulmonary, non-
14 lung cancer deaths were unrelated to air pollution (1.03, 0.54-1.96 for living near a major road);
15 but, discussing the lung cancer results, the authors noted that “the number of cases was small in
16 our study, leading to wide CIs.” The authors considered the potential role of residual
17 confounding factors, finding that the unadjusted effects estimates were consistently similar to the
18 effects after adjustment for confounders, and concluding that residual confounding was very
19 unlikely to account for the association between living near a major road and mortality. The
20 authors conclude that long-term exposure to traffic-related air pollution may shorten life
21 expectancy, but note that the local scale PM is mostly characterized by fresh emissions high in
22 ultrafines, while the (more weakly associated) background aerosol is more aged. These
23 differences in ambient PM characteristics may therefore account for the apparent local traffic
24 PM toxicity, rather than its specific source.

25 26 **8.2.3.4 Recent PM-Mortality Intervention Studies**

27 Although many studies have reported short-term associations between PM indices and
28 mortality, a largely unaddressed question remains as to the extent to which reductions in ambient
29 air PM actually lead to reductions in deaths attributable to PM. This question is not only
30 important in terms of “accountability” from the regulatory point of view, but it is also a scientific

1 question that challenges the predictive validity of statistical models and their underlying
2 assumptions used thus far to estimate excess mortality due to ambient PM.

3 The opportunities to address this question are rare. However, at the time of the 1996
4 PM AQCD, one situation seemed to offer good possibilities for a PM-mortality intervention
5 study — that being the Utah Valley situation evaluated by Pope et al. (1992). In the Pope et al.
6 (1992) analysis of daily mortality and PM₁₀ in Utah Valley, the study period contained the
7 13-month steel mill closure mentioned earlier (during which time PM₁₀ concentrations averaged
8 35 µg/m³ versus 50 µg/m³ when the mill was opened). Pope et al. (1992) noted that, based on
9 the PM₁₀ slope they obtained for the entire study period (~4.5 years), a 2.3% higher death rate
10 would be predicted for the period when the mill was opened, based on the higher PM₁₀ levels
11 during this period. The actual excess deaths observed per day for the period when the mill was
12 open turned out to be 3.2% higher than during the period when the mill was closed. Thus, the
13 study did suggest some internal consistency between lower death rates during the intervention
14 period versus the rest of the study period. Pope's (1989) study of children's respiratory
15 admissions in Utah Valley before and after the steel mill closure also provided evidence of
16 decreased morbidity resulting from lower PM₁₀ concentrations during the mill closure.

17 Two more recent mortality intervention studies have examined: (1) the impact of a ban on
18 coal sale in Dublin, Ireland (Clancy et al., 2002); and (2) the impact of a regulation to use fuel
19 oil with low sulfur content in Hong Kong (Hedley et al., 2002). These regulations were enforced
20 across very short time frames and, as such, they provided opportunities to observe any change in
21 mortality rate before and after the intervention.

22 Clancy et al. (2002) examined the impact of the ban on coal sales that took place in
23 September 1990 in the city of Dublin, Ireland. They assessed the ban's impact on mortality by
24 conducting Poisson regression of the standardized mortality rate during 72 months before and
25 after the ban on coal sales (13 years total study period), adjusting for temperature on the same
26 day and previous days, mean relative humidity and previous days, day-of-week, respiratory
27 epidemics, and directly standardized deaths rates in the rest of Ireland. The impact of the ban
28 was estimated by an indicator variable of the post-ban period. They also reported means for
29 black smoke (BS), SO₂, temperature and relative humidity before and after the ban by season,
30 as well as age-standardized deaths rates before and after the ban by seasons. A substantial
31 reduction (35.6 µg/m³ reduction, or 70% for all seasons) in BS, especially for winter season

1 (63.8 $\mu\text{g}/\text{m}^3$ reduction) was observed. The reduction for SO_2 was less (34% reduction). The
2 post-ban means of age-standardized mortality rates were significantly lower for total (non-
3 accidental), cardiovascular, and respiratory categories for all seasons combined and especially
4 for the winter season. In contrast, the mean of the other mortality categories slightly increased
5 for spring and fall (but decreased for summer). The Poisson regression results with adjustments
6 for time-varying covariates showed statistically significant ($p < 0.05$) reductions in age-
7 standardized mortality rate for total (-5.7% [-7.2, -4.1]), cardiovascular (-10.3% [-12.6,
8 -8.0]), and respiratory (-15.5% [-19.1, -11.6]) mortality, but not mortality for other causes
9 (1.7% [-0.7, 4.2]). The results without adjustments for other time-varying covariates showed
10 larger reductions.

11 Clancy et al. compared their mortality reduction estimates to the projected reduction based
12 on APHEA 1 study (Katsouyanni et al., 1997) results. They noted that the BS mortality
13 regression coefficient from APHEA 1 results would have translated to only a 2.1% reduction in
14 total deaths had they been applied to the Dublin data where a BS concentration reduction of 35.6
15 $\mu\text{g}/\text{m}^3$ was observed, compared to a 5.7% decrease that Clancy and colleagues estimated for the
16 intervention period in their analysis. They also noted that the actual reduction (~3.2% when the
17 PM_{10} average was 15 $\mu\text{g}/\text{m}^3$ lower than the period when the mill was operating) in average
18 deaths during the steel mill closure in Utah Valley, as noted by Pope et al. (1992) would have
19 translated to 8.0% had it been applied to the BS reduction in the Dublin data (assuming $\text{BS} \approx$
20 PM_{10}), which was the same as their unadjusted estimate (8.0%). It should be noted, however,
21 that the reduction estimate in Clancy et al.'s study is the "average" reduction comparing the two
22 6-yr periods before and after the ban of coal sales. In contrast, most time-series studies,
23 including APHEA, estimate excess mortality risk in response to a short-term change, usually for
24 mortality on a single day or a few days. As discussed in Section 8.4.5, there is some suggestive
25 evidence that risk estimates based on a single- or a few-day exposures may underestimate the
26 possible multi-day effects. The apparent lack of the evidence for "harvesting" (see Section
27 8.4.9.1) further suggests that the excess risk (or reduction) estimates based on the prevailing
28 time-series study design may not predict longer-term effects. Therefore, comparisons of
29 estimates of reduction in mortality due to interventions and predicted reductions based on results
30 of time-series studies are not straightforward; and it may not be surprising that Clancy et al.'s
31 estimate of mortality reduction was larger than predicted based on PM coefficients derived from

1 most time-series studies. Clancy et al.'s study nevertheless provides suggestive evidence that a
2 substantial reduction in PM leads to a significant reduction in mortality.

3 Hedley et al. (2002) assessed the impact on mortality rate of the restriction on use of low
4 sulfur (not more than 0.5%) fuel oil implemented in July 1990 in Hong Kong. Changes in trends
5 in deaths were estimated using Poisson regression of monthly mortality rate between 1985 and
6 1995, adjusting for trends, seasonal cycles (by sine/cosine terms), temperature, and relative
7 humidity, with stratification by the two five-year pre- and post-intervention periods. They also
8 estimated a measure of warm to cool season change in death rates relative to the mean by fitting
9 monthly deaths as a function of sine and cosine terms for each of the five years after the
10 intervention and by cause (total, respiratory, cardiovascular, neoplasms, and others) and by age
11 groups (all ages, age 15-64, age 65 and older). Interestingly, although SO₂ did decrease
12 substantially (~50%), PM₁₀ levels did not change at all after the intervention. Even sulfate
13 levels, while reported to be lower by ~ 20% for the first 2 years after the intervention, were
14 unchanged five years after the intervention, apparently due to regional influences. O₃ showed an
15 increasing trend during the study period. The seasonal mortality analysis results show that the
16 apparent reduction in seasonal death rate occurred only during the first winter, and this was
17 followed by a rebound (i.e., higher than expected) in the following winter. This pattern was seen
18 for total, respiratory, and cardiovascular categories. Based on the Poisson regression of the
19 monthly mortality data analysis, the average annual trend in death rate significantly declined
20 after the intervention for all cause (2.1%), respiratory (3.9%), and cardiovascular causes (2.0%).
21 Hedley et al. also estimated expected average gain in life expectancy per year due to the lower
22 SO₂ level to be 20 days for females and 41 days for males.

23 Interpreting Hedley et al.'s results is somewhat complicated by an upward trend noted by
24 them in mortality across the intervention point, due to increased population size and aging. The
25 results suggest that such an upward trend is less steep after the introduction of low sulfur fuel.
26 While their Poisson regression model of monthly deaths does adjust for trend and seasonal
27 cycles, the regression model does not specifically address the influence of influenza epidemics.
28 Since the magnitude of influenza epidemics can change from year to year, the included
29 sine/cosine terms will not necessarily fit the year-to-year variation. This issue also applies to the
30 analysis of warm to cool season change in death rates. The most prominent feature of the time-
31 series plot (or the fitted annual cycle of monthly deaths) presented in Hedley et al.'s paper is the

1 lack of a winter peak for respiratory and all cause mortality during the year immediately
2 following the intervention. Much could be made out of this lack of a winter peak, but no
3 discussion of potential impact of (or a lack of) influenza epidemics is provided. These issues
4 make the interpretation of the estimated decline in upward trend of mortality rate or the apparent
5 lack of winter peak difficult. In any case, since the intervention did not result in the reduction of
6 PM (PM₁₀ in this case), this study does not provide direct information on the impact of PM
7 intervention.

8 The Clancy et al. and Hedley et al. studies share a similar situation in which regulations
9 caused a sudden reduction in PM and/or SO₂. Both studies estimated reductions in mortality rate
10 before and after an intervention (6-year periods in Clancy et al. study, and 5-year periods in
11 Hedley et al. study). Both studies attempted to adjust for unmeasured secular changes in social
12 or other variables that can affect the trend in mortality rate by direct standardization or in the
13 regression models. The challenge of these analyses is that, unlike regular time-series mortality
14 analyses in which only the associations in short-term fluctuations are estimated by filtering out
15 the longer-wave fluctuations, the parameter that is being estimated is in the longer-wave length
16 where effective sample size of “events” can be small. For example, the number of influenza
17 epidemics in these data is “small”, and yet their magnitude can vary substantially from year to
18 year, making their influence on the average statistics of long-wave events possibly large.
19 Furthermore, because the regular short-term daily time-series studies specifically filter out these
20 long-wave events, it may not be appropriate to directly compare projected risk reductions based
21 on PM risk coefficients derived from the daily time-series studies with estimated mortality
22 reductions based on these intervention studies. Clearly, there is much uncertainty between
23 mortality risk estimates derived from daily time-series studies versus those derived from cohort
24 studies (that may be capturing the very long-term effects). The intervention studies appear to
25 capture the risk (reduction) in a time scale that is in between these two types of studies.

26 In summary, Clancy et al.’s intervention study suggests evidence of mortality reduction in
27 response to reduced levels of PM. Hedley et al.’s intervention study also presents an unusual
28 case, where SO₂ levels declined substantially but PM levels did not, and the SO₂ decrease was
29 paralleled by decrements in mortality. As such, these intervention studies are valuable in
30 drawing conclusions that imply likely causal relationships underlying the observed mortality
31 decrements occurring in concert with declines in ambient PM and/or SO₂ levels. However, they

1 are not particularly useful for quantification of risk; and quantitative comparisons of risk
2 reductions seen in intervention studies versus risk reductions projected from results of time-
3 series studies are not particularly appropriate.

4 5 **8.2.3.5 Salient Points Derived from Analyses of Chronic Particulate Matter Exposure** 6 **Mortality Effects**

7 A review of the studies summarized in the previous PM AQCD (U.S. Environmental
8 Protection Agency, 1996a) indicates that past epidemiologic studies of chronic PM exposures
9 collectively indicated that increases in mortality are associated with long-term exposure to
10 airborne particles of ambient origins. The PM effect size estimates for total mortality from these
11 studies also indicate that a substantial portion of these deaths reflected cumulative PM effects
12 above and beyond those exerted by acute exposure events.

13 The HEI-sponsored reanalyses of the ACS and Harvard Six-Cities studies (Krewski et al.,
14 2000) “replicated the original results, and tested those results against alternative risk models and
15 analytic approaches without substantively altering the original findings of an association
16 between indicators of particulate matter air pollution and mortality.” Several questions,
17 including the questions (1-4) posed at the outset of this Section (8.2.3) were investigated by the
18 Krewski et al. (2000) sensitivity analyses for the Six City and ACS studies data sets. Key results
19 emerging from the HEI reanalyses and other new chronic PM mortality studies are as follow:

20 (1) A much larger number of confounding variables and effects modifiers were considered
21 in the Reanalysis Study than in the original Six City and ACS studies. The only significant air
22 pollutant other than $PM_{2.5}$ and SO_4 in the ACS study was SO_2 , which greatly decreased the $PM_{2.5}$
23 and sulfate effects when included as a co-pollutant (Krewski et al., 2000, Part II, Tables 34-38).
24 A similar reduction in particle effects occurred in any multi-pollutant model with SO_2 . The most
25 important new effects modifier was education. The AHSMOG study also suggested that other
26 metrics for air pollution, and other personal covariates such as time spent outdoors and
27 consumption of anti-oxidant vitamins, might be useful. Both individual-level covariates and
28 ecological-level covariates shown in (Krewski et al., 2000, Part II, Table 33) were evaluated,
29 including whether or not the observations are independent or spatially correlated.

30 (2) Specific attribution of excess long-term mortality to any specific particle component or
31 gaseous pollutant was refined in the reanalysis of the ACS study. Both $PM_{2.5}$ and sulfate were

1 significantly associated with excess total mortality and cardiopulmonary mortality and to about
2 the same extent whether the air pollution data were mean or median long-term concentrations or
3 whether based on original investigator or Reanalysis Team data. The association of mortality
4 with PM_{15} was much smaller, though still significant; and the associations with the coarse
5 fraction ($PM_{15-2.5}$) or TSP were even smaller and not significant. The lung cancer effect was
6 significant only for sulfate with the original investigator data or for new investigators with
7 regional sulfate artifact adjustment for the 1980-1981 data (Krewski et al., 2000, Part II,
8 Table 31). Associations of mortality with long-term mean concentrations of criteria gaseous
9 co-pollutants were generally non-significant except for SO_2 (Krewski et al., 2000, Part II,
10 Tables 32, 34-38), which was highly significant, and for cardiopulmonary disease with warm-
11 season ozone. However, the regional association of SO_2 with SO_4 and SO_2 with $PM_{2.5}$ was very
12 high; and the effects of the separate pollutants could not be distinguished. Krewski et al. (2000,
13 p. 234) concluded that, “Collectively, our reanalyses suggest that mortality may be associated
14 with more than one component of the complex mix of ambient air pollutants in urban areas of
15 the United States.” In the most recent extension of the ACS study, Pope et al. (2002) confirmed
16 the strong association with SO_2 but found little evidence of effects for long-term exposures to
17 other gaseous pollutants.

18 (3) The extensive temporal data on air pollution concentrations over time in the Six City
19 Study allowed the Reanalysis Team to evaluate time scales for mortality for long-term exposure
20 to a much greater extent than was reported in Dockery et al. (1993). The first approach was to
21 estimate the log-hazard ratio as a function of follow up time using a flexible spline-function
22 model (Krewski et al., 2000, Part II, Figures 2 and 3). The results for both SO_4^{-2} and $PM_{2.5}$
23 suggest very similar relationships, with larger risk after initial exposure decreasing to 0 after
24 about 4 or 5 years, and a large increase in risk at about 10 years follow-up time.

25 The analyses of the ACS Study proceeded somewhat differently, with less temporal data
26 but many more cities. Flexible spline regression models for $PM_{2.5}$ and sulfate as function of
27 estimated cumulative exposure (not defined) were very nonlinear and showed quite different
28 relationships (Krewski et al., 2000, Part II, Figures 10 and 11). The $PM_{2.5}$ relationship shows the
29 mortality log-hazard ratio increasing up to $\sim 15 \mu g/m^3$ and relatively flat above $\sim 22 \mu g/m^3$, then
30 increasing again. The sulfate relationship is almost piecewise linear, with a low near- zero slope
31 below $\sim 11 \mu g/m^3$ and a steep increase above that concentration.

1 A third approach evaluated several time-dependent PM_{2.5} exposure indicators in the
2 Six City Study: (a) constant (at the mean) over the entire follow-up period; (b) annual mean
3 within each of the 13 years of the study; (c) city-specific mean concentration for the earliest
4 years of the study (i.e., very long-term effect); (d) exposure estimate in 2 years preceding death;
5 (e) exposure estimate in 3 to 5 years preceding death; and (f) exposure estimate > 5 years
6 preceding death. The time-dependent estimates (a-e) for mortality risk are generally similar and
7 statistically significant (Krewski et al., 2000, Part II, Table 53), with RR of 1.14 to 1.19 per
8 24.5 µg/m³ being much lower than the risk of 1.31 estimated for exposure at the constant mean
9 for the period. Thus, it is highly likely the duration and time patterns of long-term exposure
10 affect the risk of mortality; and further study of this question (along with that of mortality
11 displacement from short-term exposures) would improve estimates of life-years lost from PM
12 exposure.

13 (4) The Reanalysis Study also advanced our understanding of the shape of the relationship
14 between mortality and PM. Again using flexible spline modeling, Krewski et al. (2000, Part II,
15 Figure 6) found a visually near-linear relationship between all-cause and cardiopulmonary
16 mortality residuals and mean sulfate concentrations, near-linear between cardiopulmonary
17 mortality and mean PM_{2.5}, but a somewhat nonlinear relationship between all-cause mortality
18 residuals and mean PM_{2.5} concentrations that flattens above ~20 µg/m³. The confidence bands
19 around the fitted curves are very wide, however, neither requiring a linear relationship nor
20 precluding a nonlinear relationship if suggested by reanalyses. An investigation of the mortality
21 relationship for other indicators may be useful in identifying a threshold, if one exists, for
22 chronic PM exposures.

23 (5) With regard to the role of various PM constituents in the PM-mortality association,
24 past cross-sectional studies have generally found the fine particle component, as indicated either
25 by PM_{2.5} or sulfates, to be the PM constituent most consistently associated with mortality. While
26 relative measurement errors of various PM indicators must be further evaluated as a possible
27 source of bias in these estimate comparisons, the Six-Cities and AHSMOG prospective cohort
28 studies both indicate that the fine mass components of PM are more strongly associated with
29 mortality effects of chronic PM exposure than are coarse fraction indicators.

30 (6) The spatial regression methods suggested that part of the relation between sulfate and
31 mortality was probably due to some unobserved variable or group of confounding variables.

1 In particular, they found that the sulfate-associated effect drops from a relative risk of 1.25 with
2 the Independent Cities Model to 1.19 with the Regional Adjustment Model, but all models
3 continued to show an association between elevated risks of mortality and exposure to airborne
4 sulfate.

5 (7) The newly available (2002) ACS study extension more than doubles the original
6 follow-up period (now to 16 y versus 7 earlier); and it both (a) confirms the original ACS study
7 findings of significant associations between long-term $PM_{2.5}$ exposures and increased
8 cardiopulmonary mortality risks and (b) provides the strongest evidence to date for increased
9 lung cancer risk associations with ambient fine particles measured as $PM_{2.5}$.

10

1 **8.3 MORBIDITY EFFECTS OF PARTICULATE MATTER EXPOSURE**

2 The effects of ambient PM on morbidity endpoints are assessed below in subsections
3 focused on: (a) effects of acute ambient PM exposure on cardiovascular morbidity; (b) effects of
4 short-term PM exposure on the incidence of respiratory and other medical visits and hospital
5 admissions; and (c) short- and long-term PM exposure effects on lung function and respiratory
6 symptoms in asthmatics and non-asthmatics.

7 8 **8.3.1 Cardiovascular Morbidity Effects Associated with Acute Ambient** 9 **Particulate Matter Exposure**

10 **8.3.1.1 Introduction**

11 Very little information specifically addressing cardiovascular morbidity effects of acute
12 PM exposure existed at the time of the 1996 PM AQCD. Since then, a significantly expanded
13 body of literature has emerged, both on the ecologic relationship between ambient particles and
14 cardiovascular hospital admissions and associations of PM exposures with changes in various
15 physiological and/or biochemical measures. The latter studies are particularly important in that
16 they are suggestive of possible mechanisms underlying PM cardiovascular effects. However, it
17 should be noted that the mechanistic interpretation of the cardiovascular physiology results
18 observed to date (some of which are conflicting) remain unclear, as discussed in more detail in
19 Chapter 7.

20 This section begins with a brief summary of key findings from the 1996 PM AQCD on
21 acute cardiovascular effects of PM. Next, key new studies are reviewed in the two categories
22 noted above, i.e., ecologic time-series studies and individual-level studies of physiological
23 measures of cardiac function and/or biochemical measures in blood as they relate to ambient
24 pollution. This is followed by discussion of several issues of importance for interpreting the
25 available data, including identification of potentially susceptible subpopulations, roles of
26 environmental co-factors such as weather and other air pollutants, temporal lags in the
27 relationship between exposure and outcome, and the relative importance of various size-
28 classified PM components (e.g., PM_{2.5}, PM₁₀, PM_{10-2.5}).

1 **8.3.1.2 Summary of Key Findings on Cardiovascular Morbidity from the 1996**
2 **Particulate Matter Air Quality Criteria Document**

3 Just two studies were available for review in the 1996 PM AQCD that provided results for
4 acute cardiovascular (CVD) morbidity outcomes (Schwartz and Morris, 1995; Burnett et al.,
5 1995). Both studies were of ecologic time-series design and used standard statistical methods.
6 Analyzing four years of data on the ≥ 65 year old Medicare population in Detroit, MI, Schwartz
7 and Morris (1995) reported significant associations between PM_{10} and ischemic heart disease
8 admissions, controlling for environmental covariates. Based on analysis of admissions data from
9 168 hospitals throughout Ontario, Canada, Burnett et al. (1995) reported significant associations
10 between fine particle sulfate concentrations (as well as other air pollutants) and daily
11 cardiovascular admissions. The relative risk due to sulfate particles was slightly larger for
12 respiratory than for cardiovascular hospital admissions. The 1996 PM AQCD concluded on the
13 basis of these studies that: “There is a suggestion of a relationship to heart disease, but the
14 results are based on only two studies, and the estimated effects are smaller than those for other
15 endpoints” (U.S. Environmental Protection Agency, 1996a, p. 12-100). The PM AQCD also
16 stated that acute effects on CVD admissions had been demonstrated for elderly populations (i.e.,
17 ≥ 65), but that insufficient data existed to assess relative effects on younger populations.

18 When viewed alongside the more extensive literature on acute CVD mortality that was
19 available at the time, the evidence from ecologic time-series studies reviewed in the 1996 PM
20 AQCD was consistent with acute health risks of PM being larger for cardiovascular and
21 respiratory causes than for other causes. Given the tendency for end-stage disease states to
22 include both respiratory and cardiovascular impairment, and the associated diagnostic overlap
23 that often exists, it was not possible on the basis of these studies alone to determine which of the
24 two organ systems, if either, was more critically affected.

25
26 **8.3.1.3 New Particulate Matter-Cardiovascular Morbidity Studies**

27 ***8.3.1.3.1 Acute Hospital Admission Studies***

28 Salient methodological features and results of numerous newly available studies that
29 examine associations between daily measures of ambient PM and daily hospital admissions for
30 cardiovascular disease are summarized in Table 8B-1 (see Appendix 8B). As discussed earlier
31 in Sections 8.1.4 and 8.2.2, many studies published since 1995 used GAM with default

1 convergence criteria. Several of those studies have been reanalyzed by original investigators
2 using GAM with more stringent convergence criteria and GLM with parametric smooths, such as
3 natural splines (NS) or penalized splines (PN). Again, since the extent of possible bias in PM
4 effect-size estimates caused by the default criteria setting in the GAM models is difficult to
5 estimate for individual studies, the discussion here focuses mainly on the studies that either did
6 not use GAM Poisson models or those GAM studies which have been reanalyzed using more
7 stringent convergence criteria and/or alternative approaches. Newly available U.S. and Canadian
8 studies on relationships between short-term PM exposure and hospital admissions or emergency
9 visits that meet these criteria are summarized in Table 8-18, along with a few non-North
10 American studies. Reanalyses studies are indicated in Table 8-18 by indentation of the reference
11 citation to the pertinent short communication in the HEI Special Report (HEI, 2003b). The table
12 is organized by first summarizing single-pollutant (PM only) analyses and then multi-pollutant
13 (PM + one or more copollutant) analyses for U.S. and non-U.S. studies.

14 Of much interest are NMMAPS multi-city analyses (Samet et al., 2000a,b; Zanobetti et al.,
15 2000a), as reanalyzed (Zanobetti and Schwartz, 2003a), which provide evidence for significant
16 PM_{10} effects on cardiovascular-related hospital admissions and visits, using a variety of
17 statistical models. These results are supported by another multi-city study (Schwartz, 1999)
18 which, however, has not been reanalyzed with alternative statistical models. Numerous other
19 studies, carried out by individual investigators in a variety of locales, present a more varied
20 picture, especially when gaseous co-pollutants have been analyzed in multipollutant models.
21 Most CVD hospital admissions studies reported to date have used PM_{10} as the main particle
22 measure due to the wide availability of ambient PM_{10} monitoring data.

23 Samet et al. (2000a,b) analyzed daily emergency-only CVD hospital admissions in persons
24 65 and older in relation to PM_{10} in 14 cities from the NMMAPS multi-city study. The cities
25 included Birmingham, AL; Boulder, CO; Canton, OH; Chicago, IL; Colorado Springs, CO;
26 Detroit, MI; Minneapolis/ St. Paul, MN; Nashville, TN; New Haven, CT; Pittsburgh, PA;
27 Provo/Orem, UT; Seattle, WA; Spokane, WA; and Youngstown, OH. The range of years studied
28 encompassed 1985-1994, but this varied by city. Covariates included SO_2 , NO_2 , O_3 , and CO not
29 analyzed directly as regression covariates; rather, individual cities were analyzed first by Poisson
30 regression methods on PM_{10} for lags from 0 to 5 days. An overall PM_{10} risk estimate was then

TABLE 8-18. SUMMARY OF STUDIES OF PM₁₀, PM_{10-2.5}, OR PM_{2.5} EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in µg/m ³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 µg/m ³ PM ₁₀ or 25 µg/m ³ PM _{2.5} *, PM _{10-2.5} **
U.S. Results Without Co-pollutants						
Samet et al. (2000a,b) 14 Cities	Total CVD admissions ≥ 65 yrs	PM ₁₀ Means: 24.4-45.3	none	0 day	Default GAM	5.5% (4.7, 6.2)
Zanobetti and Schwartz, (2003a) 14 Cities		PM ₁₀ Means: 24.4-45.3		0-1 day	Default GAM Strict GAM GLM NS GLM PS	5.9% (5.1-6.7) 4.95% (3.95-5.95) 4.8% (3.55-6.0) 5.0% (4.0-5.95)
Lippmann et al., 2000 Detroit (Wayne County), MI	Ischemic heart disease ≥ 65 yrs	PM ₁₀ : 31(19) PM _{2.5} : 18 (11) PM _{10-2.5} : 13 (7)	none	2 day	Default GAM Default GAM Default GAM	8.9% (0.5-18.0) 4.3% (-1.4-10.4)* 10.5% (2.75-18.9)**
Ito 2003 Detroit (Wayne County), MI		PM ₁₀ : 31(19)			Strict GAM GLM NS	8.0% (-0.3-17.1) 6.2% (-2.0-15.0)
		PM _{2.5} : 18 (11)			Strict GAM GLM NS	3.65% (-2.05-9.7)* 3.0% (-2.7-9.0)*
		PM _{10-2.5} : 13 (7)			Strict GAM GLM NS	10.2% (2.4-18.6)** 8.1% (0.4-16.4)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Dysrhythmias ≥ 65 yrs	PM ₁₀ : 31(19) PM _{2.5} : 18 (11) PM _{10-2.5} : 13 (7)	none	1 day 1 day* 0 day**	Default GAM Default GAM Default GAM	2.9% (-10.8-18.8) 3.2% (-6.5-14.0)* 0.2% (-12.2-14.4)**
Ito 2003 Detroit (Wayne County), MI		PM ₁₀ : 31(19)			Strict GAM GLM NS	2.8% (-10.9-18.7) 2.0% (-11.7-17.7)
		PM _{2.5} : 18 (11)			Strict GAM GLM NS	3.2% (-6.6-14.0)* 2.6% (-7.1-13.3)*
		PM _{10-2.5} : 13 (7)			Strict GAM GLM NS	0.1% (-12.4-14.4)** 0.0% (-12.5-14.3)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Heart Failure ≥ 65 yrs	PM ₁₀ : 31(19) PM _{2.5} : 18 (11) PM _{10-2.5} : 13 (7)	none	0 day 1 day* 0 day**	Default GAM Default GAM Default GAM	9.7% (0.15-20.2) 9.1% (2.4-16.2)* 5.2% (-3.25-14.4)**
Ito 2003 Detroit (Wayne County), MI		PM ₁₀ : 31(19)			Strict GAM GLM NS	9.2% (-0.3-19.6) 8.4% (-1.0-18.7)
		PM _{2.5} : 18 (11)			Strict GAM GLM NS	8.0% (1.4-15.0)* 6.8% (0.3-13.8)*
		PM _{10-2.5} : 13 (7)			Strict GAM GLM NS	4.4% (-4.0-13.5)** 4.9% (-3.55-14.1)**
Morris and Naumova (1998) Chicago, IL	Congestive heart failure ≥ 65 yrs	PM ₁₀ : 41 (23)	none	0 day	GAM not used	3.9% (1.0-6.9)

TABLE 8-18 (cont'd). SUMMARY OF STUDIES OF PM₁₀, PM_{10-2.5}, OR PM_{2.5} EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in µg/m ³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 µg/m ³ PM ₁₀ or 25 µg/m ³ PM _{2.5} *, PM _{10-2.5} **
U.S. Results Without Co-pollutants (cont'd)						
Linn et al. (2000) Los Angeles, CA	Total CVD admissions ≥ 30 yrs	PM ₁₀ : 45 (18)	none	0 day	GAM not used	3.25% (2.04, 4.47)
Moolgavkar (2000b) Cook County, IL	Total CVD admissions ≥ 65 yrs	PM ₁₀ : 35 [‡] (22)	none	0 day	Default GAM	4.2% (3.0, 5.5)
Moolgavkar (2003) Cook County, IL					Strict GAM _{100df} GLM NS _{100df}	4.05% (2.9-5.2) 4.25% (3.0-5.5)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admissions ≥ 65 yrs	PM ₁₀ : 44 [‡] (26) PM _{2.5} : 22 [‡] (16)	none	0 day	Default GAM Default GAM	3.2% (1.2, 5.3) 4.3% (2.5, 6.1)*
Moolgavkar (2003) Los Angeles County, CA		PM ₁₀ : 44 [‡] (26) PM _{2.5} : 22 [‡] (16)			Strict GAM _{30df} Strict GAM _{100df} GLM NS _{100df} Strict GAM _{30df} Strict GAM _{100df} GLM nspline _{100df}	3.35% (1.2-5.5) 2.7% (0.6-4.8) 2.75% (0.1-5.4) 3.95% (2.2-5.7)* 2.9% (1.2-4.6)* 3.15% (1.1-5.2)*
Metzger et al., (2004)*** Atlanta, GA 1993-2000	Total CVD emerg. dept. visits, ≥ 16 yrs	Period 1 PM ₁₀ : 26.3	none	0-2 day avg.	GAM not used	2.3 (-0.4, 5.0)
Metzger et al., (2004) Atlanta, GA 1998-2000	Total CVD emerg. dept. visits, ≥ 16 yrs	Period 2 PM _{2.5} : 17.8 PM _{10-2.5} : 9.1	none	0-2 day avg.	GAM not used	5.1% (-7.9, 19.9) 8.2% (2.6, 14.7) 3.0% (-3.7, 10.3)**
U.S. Results With Co-pollutants						
Lippmann et al., 2000 Detroit (Wayne County), MI	Ischemic heart disease ≥ 65 yrs	PM ₁₀ : 31(19) PM _{2.5} : 18 (11) PM _{10-2.5} : 13 (7)	CO	2 day	Default GAM Default GAM Default GAM	8.5% (-0.45-18.3) 3.7% (-2.4-10.3)* 10.1% (2.25-18.6)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Dysrhythmias ≥ 65 yrs	PM ₁₀ : 31(19) PM _{2.5} : 18 (11) PM _{10-2.5} : 13 (7)	CO	1 day 1 day 0 day	Default GAM Default GAM Default GAM	-1.3% (-15.5-15.4) 0.55% (-9.7-12.0)* -1.0% (-13.4-13.05)**

TABLE 8-18 (cont'd). SUMMARY OF STUDIES OF PM₁₀, PM_{10-2.5}, OR PM_{2.5} EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in µg/m ³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 µg/m ³ PM ₁₀ or 25 µg/m ³ PM _{2.5} *, PM _{10-2.5} **
U.S. Results With Co-pollutants (cont'd)						
Lippmann et al., 2000 Detroit (Wayne County), MI	Heart Failure ≥ 65 yrs	PM ₁₀ : 31(19)	CO	0 day	Default GAM	7.5% (-2.6-18.7)
		PM _{2.5} : 18 (11)		1 day	Default GAM	8.9% (2.2-16.1)*
		PM _{10-2.5} : 13 (7)		0 day	Default GAM	3.9% (-4.7-13.2)**
Morris and Naumova (1998) Chicago, IL	Congestive heart failure ≥ 65 yrs	PM ₁₀ : 41, 23	CO, NO ₂ , SO ₂ , O ₃	0 day	GAM not used	2% (-1-6)
Moolgavkar (2000b) Cook County, IL	Total CVD admissions ≥ 65 yrs	PM ₁₀ : 35, 22	NO ₂	0 day	Default GAM	1.8% (0.4, 3.2)
Moolgavkar (2003) Cook County, IL		PM ₁₀ : 35, 22	CO		Strict GAM _{100df} GLM NS _{100df}	2.95% (1.7-4.2) 3.1% (1.8-4.4)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admissions ≥ 65 yrs	PM ₁₀ : 44 [‡] (26)	CO	0 day	Default GAM	-1.8% (-4.4, 0.9)
		PM _{2.5} : 22 [‡] (16)			Default GAM	0.8% (-1.3, 2.9)*
		PM ₁₀			Strict GAM _{100df} GLM NS _{100df}	-1.3% (-3.8-1.2) -1.1% (-4.2-2.0)
Moolgavkar (2003) Los Angeles County, CA		PM _{2.5}			Strict GAM _{100df} GLM NS _{100df}	1.0% (-1.1-3.3)* 1.45% (-1.1-4.0)*
Non-U.S. Results Without Co-pollutants						
Burnett et al., (1997a) Toronto, Canada	Total CVD admissions all ages	PM ₁₀ : 28, 22	none	1-4 day avg.	GAM not used	12.1% (1.4, 23.8)
		PM _{2.5} : 17, 15				7.2% (-0.6, 15.6)*
		PM _{10-2.5} : 12, 7				20.5% (8.2, 34.1)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	PM ₁₀ : 14.0, 9.0	none	1-3 day avg.	GAM not used	29.3% (p=0.003)
		PM _{2.5} : 8.5, 5.9				14.4% (p = 0.055)*
Atkinson et al. (1999a) Greater London, England	Total emerg. CVD admissions ≥ 65 yrs	PM ₁₀ : 28.5, 90-10 %tile range: 30.7	none	0 day	GAM not used	2.5% (-0.2, 5.3)
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admissions ≥ 65 yrs	PM ₁₀ : 20.7, 8.4	none	1-3 day avg.	GAM not used	12.4% (4.6, 20.9)
Wong et al. (1999a) Hong Kong	Total emerg. CVD admissions ≥ 65 yrs	PM ₁₀ : Median 45.0, IQR 34.8	none	0-2 day avg.	GAM not used	4.1% (1.3, 6.9)

TABLE 8-18 (cont'd). SUMMARY OF STUDIES OF PM₁₀, PM_{10-2.5}, OR PM_{2.5} EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome Measure	Mean PM levels (IQR) in $\mu\text{g}/\text{m}^3$	Co-pollutants Analyzed with PM	Lag Structure	Method	Effect measures standardized to 50 $\mu\text{g}/\text{m}^3$ PM ₁₀ or 25 $\mu\text{g}/\text{m}^3$ PM _{2.5} *, PM _{10-2.5} **
Non-U.S. Results With Co-pollutants						
Burnett et al., (1997a) Toronto, Canada	Total CVD admissions all ages	PM ₁₀ : 28, IQR 22	O ₃ , NO ₂ , SO ₂ , CO	1-4 day avg.	GAM not used	-1.4% (-12.5, 11.2)
		PM _{2.5} : 17, 15				-1.6% (-10.5, 8.2)*
		PM _{10-2.5} : 12, 7				12.1% (-1.9, 28.2)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	PM ₁₀ : 14.0, 9.0	CO, H ₂ S, NO ₂ , O ₃ , SO ₂ , total reduced sulfur	1-3 day avg.	GAM not used	PM ₁₀ not significant; no quantitative results presented
Atkinson et al. (1999a) Greater London, England	Total emerg. CVD admissions \geq 65 yrs	PM ₁₀ : 28.5, 90-10 %tile range: 30.7	NO ₂ , O ₃ , SO ₂ , CO	0 day	GAM not used	PM ₁₀ not significant; no quantitative results presented
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admissions \geq 65 yrs	PM ₁₀ : 20.7, 8.4	SO ₂ , NO ₂ , O ₃ , CO	1-3 day avg.	GAM not used	PM ₁₀ effect robust; no quantitative results presented
Wong et al. (1999a) Hong Kong	Total emerg. CVD admissions \geq 65 yrs	PM ₁₀ : Median 45.0, IQR 34.8	NO ₂ , O ₃ , SO ₂	0-2 day avg.	GAM not used	PM ₁₀ effect robust; no quantitative results presented

* PM_{2.5} entries, **PM_{10-2.5}. All others relate to PM₁₀; †Median.

***Note: Metzger et al (2004) study provides full results for most all participating hospitals versus earlier Tolbert et al (2000) presentation of preliminary results for many fewer hospitals.

1 computed by taking the inverse-variance weighted mean of the city-specific risk estimates. The
 2 city-specific risk estimates for PM₁₀ were also examined for correlations with omitted covariates,
 3 including other pollutants. No relationship was observed between city-specific risk estimates
 4 and measures of socioeconomic status, including percent living in poverty, percent non-white,
 5 and percent college educated. The overall weighted mean risk estimate for PM₁₀ was greatest for
 6 lag 0 and for the mean of lags 0-1. For example, the mean risk estimate for the mean of lags
 7 0-1 was a 5.9% increase in CVD admissions per 50 $\mu\text{g}/\text{m}^3$ PM₁₀ (95% CI: 5.1 - 6.7). The mean
 8 risk was larger in a subgroup of data where PM₁₀ was less than 50 $\mu\text{g}/\text{m}^3$, suggesting the lack of
 9 a threshold. A weakness of this study was its failure to report multipollutant results. The

1 authors argued that confounding by co-pollutants was not present because the city-specific risk
2 estimates did not correlate with city-specific regressions of PM₁₀ on co-pollutant levels.
3 However, the validity of this method for identifying meaningful confounding by co-pollutants at
4 the daily time-series level has not been demonstrated. Thus, it is not possible to conclude from
5 these results alone that the observed PM₁₀ associations were independent of co-pollutants.

6 Samet et al. (2000a,b) reported results based on use of GAM LOESS smoothing to control
7 for time and weather covariates. Data from the 14 city NMMAPs analysis of CVD hospital
8 admissions were reanalyzed by Zanobetti and Schwartz (2003a) using three alternative control
9 methods. A small decrease in overall effects was observed as compared with the original study
10 results. Whereas the original 14 city pooled analysis yielded a 5.9% increase in CVD
11 admissions per 50 µg/m³ increase in mean lags 0 and 1 day PM₁₀ (95% CI: 5.1-6.7%), the
12 reanalysis found 4.95% (3.95-5.95%), 4.8% (3.55-6.0%), and 5.0 (4.0-5.95%) when reanalyzed
13 by GAM with stringent convergence criteria, GLM with natural spline, and GLM with penalized
14 spline, respectively. Based on these results, no change is warranted with regard to overall
15 conclusions for the original published study.

16 Zanobetti et al. (2000a) reanalyzed a subset of 10 cities from among the 14 evaluated by
17 Samet et al. (2000a,b). The same basic pattern of results obtained by Samet et al. (2000a,b) were
18 found, with strongest PM₁₀ associations on lag 0 day, smaller effects on lag 1 and 2, and none at
19 longer lags. The cross-city weighted mean estimate at 0 day lag was excess risk = 5.6% (95%
20 CI 4.7, 6.4) per 50 µg/m³ PM₁₀ increment. For the 0-1 day lag average, excess CVD risk = 6.2%
21 (95% CI 5.4, 7.0) per 50 µg/m³ PM₁₀ increment. Effect-size estimates increased when data were
22 restricted to days with PM₁₀ < 50 µg/m³. As before, no evidence of gaseous (CO, O₃, SO₂)
23 co-pollutant modification of PM effects was seen in the second stage analyses. Again, however,
24 co-pollutants were not tested as independent explanatory variables in the regression analysis.
25 Like the larger NMMAPS morbidity analyses reported by Samet et al. (2000a,b), this sub-study
26 utilized the GAM function in SPlus. These 10 cities were among the 14 cities that Zanobetti and
27 Schwartz (2003a) recently reanalyzed using alternative statistical methods, and the reanalyses
28 results noted above would thus also apply in general here.

29 Janssen et al. (2002), in further analyses of the data set examined above by Samet et al.
30 (2000a,b), evaluated whether differences in prevalence of air conditioning (AC) use and/or the
31 contribution of different sources to total PM₁₀ emissions could partially explain the observed

1 variability in exposure-effect relations in the 14 cities. Cities were characterized and analyzed as
2 either winter- or nonwinter-peaking for the AC analyses. Data on the prevalence of AC from the
3 1993 American Housing Survey of the United States Census Bureau (1995) were used to
4 calculate the percentage of homes with central AC for each metropolitan area. Data on PM₁₀
5 emissions by source category were obtained by county from the U.S. EPA emissions and air
6 quality data web site (U.S. Environmental Protection Agency, 2000a). In an analysis of all
7 14 cities, central AC was not strongly associated with PM₁₀ coefficients. However, separate
8 analysis for nonwinter-peaking and winter-peaking PM₁₀ cities yielded coefficients for CVD-
9 related hospital admissions that decreased significantly with increased percentage of central AC
10 for both groups of cities. There were also significant positive relationships between CVD effects
11 and PM₁₀ percent emissions from highways or from diesel vehicles, suggesting that mobile
12 source particles may have more potent cardiovascular effects than other particle types. For both
13 analyses, similar though weaker, patterns were found for hospitalization for COPD and
14 pneumonia. The authors note that the stronger relationship for hospital admission rates for CVD
15 over COPD and pneumonia may relate to the 10 times higher CVD hospital admissions rate
16 (which would result in a more precise estimate). However, no co-pollutant analyses were
17 reported. The ecologic nature and limited sample size also indicate the need for further study.
18 Because Janssen et al.'s analysis utilized the GAM function in SPlus, Zanobetti et al. (2003a)
19 reanalyzed the main findings from this study using alternative methods for controlling time and
20 weather covariates. While the main conclusions of the study were not significantly altered, some
21 changes in results are worth noting. The effect of air conditioning remained significant for the
22 non-winter PM₁₀-peaking cities. The significance of highway vehicles and diesels on PM₁₀
23 effect sizes remained significant, as did oil combustion. However, the effect of air conditioning
24 use on PM₁₀ effect estimates was less pronounced and no longer statistically significant at $p <$
25 0.05 for the winter PM₁₀-peaking cities using natural splines or penalized splines, in comparison
26 to the original Janssen et al. GAM analysis.

27 Schwartz (1999) extended the analytical approach he had used in Tucson (described below)
28 to eight other U.S. metropolitan areas, limiting analyses to a single county in each location to
29 enhance the representativeness of the air pollution data. The locations analyzed were Chicago,
30 IL; Colorado Springs, CO; New Haven, CT; Minneapolis, MN; St. Paul, MN; Seattle, WA;
31 Spokane, WA; and Tacoma, WA. Again, the analyses focused on total cardiovascular (CVD)

1 hospital admissions among persons ≥ 65 years old. In univariate regressions, remarkably
2 consistent PM_{10} associations with CVD admissions were found across the eight locations, with a
3 $50 \mu\text{g}/\text{m}^3$ increase in PM_{10} being associated with 3.6 to 8.6% increases in admissions. The
4 univariate eight-county pooled PM_{10} effect was 5.0% (CI 3.7-6.4), similar to the 6.1 % effect per
5 $50 \mu\text{g}/\text{m}^3$ observed in the previous Tucson analysis. In a bivariate model that included CO, the
6 pooled PM_{10} effect size diminished somewhat to 3.8% (CI 2.0-5.5) and the CO association with
7 CVD admissions was generally robust to inclusion of PM_{10} in the model. The Schwartz 1999
8 paper used GAM LOESS smoothing with default convergence criteria to control for time and
9 weather covariates. Although no direct reanalyses of this study using alternative statistical
10 methods have been reported, six of the eight cities included in Schwartz (1999) were included in
11 the NMMAPS reanalyses (Zanobetti et al., 2003; Zanobetti and Schwartz, 2003a).

12 Turning to some examples of independent single-city analyses, PM_{10} associations with
13 CVD hospitalizations were also examined in a study by Schwartz (1997), which analyzed three
14 years of daily data for Tucson, AZ linking total CVD hospital admissions for persons ≥ 65 years
15 old with PM_{10} , CO, O_3 , and NO_2 . Only one site monitored daily PM_{10} , whereas multiple sites did
16 so for gaseous pollutants (O_3 , NO_2 , CO). Both PM_{10} and CO were independently (i.e., robustly)
17 associated with CVD-related admissions; but O_3 and NO_2 were not. The percent effect of a
18 $50 \mu\text{g}/\text{m}^3$ increase in PM_{10} changed only slightly from 6.07 (CI 1.12-11.27) to 5.22 (CI 0.17 -
19 10.54) when CO was included in the model along with PM_{10} . The Schwartz 1997 paper utilized
20 GAM smoothing to control for time and weather covariates. To date, no revised results have
21 been reported using alternative statistical methods.

22 Morris and Naumova (1998) reported results for PM_{10} , as well as for O_3 , NO_2 , and SO_2 , in
23 an analysis of four years of congestive heart failure data among people ≥ 65 years old in
24 Chicago, IL. As many as eight monitoring sites were available for calculating daily gaseous
25 pollutant concentrations; however, only one site in Chicago monitored daily PM_{10} . Only same-
26 day results were presented, based on an initial exploratory analysis showing strongest effects for
27 same-day pollution exposure (i.e., lag 0). Associations between hospitalizations and PM_{10} were
28 observed in univariate regressions (3.9% [1.0, 6.9] per $50 \mu\text{g}/\text{m}^3$ PM_{10} increase), but these
29 diminished somewhat in a multi-pollutant model (2.0%, [-1.4, 5.4]). Strong, robust associations
30 were seen between CO and congestive heart failure admissions. These results seem to suggest a
31 more robust association with CO than with PM_{10} . However, the observed differences might also

1 be due in part to differential exposure misclassification for PM₁₀ (monitored at one site) as
2 compared with CO (eight sites). This study did not use GAM functions to control for time and
3 weather covariates.

4 In a study designed to compare the effects of multiple PM indices, Lippmann et al. (2000)
5 analyzed associations between PM₁₀, PM_{2.5}, or PM_{10-2.5} and various categories of CVD hospital
6 admissions (only emergency and urgent admissions) among the elderly (65+ yr) in Detroit on
7 344 days in the period 1992-1994. While no consistent differences were observed in the relative
8 risks for the alternative PM indices, many of the associations involving PM were significant:
9 (a) ischemic heart disease (IHD) in relation to PM indices (i.e., 8.9% [0.5, 18.0] per 50 µg
10 PM₁₀); 10.5% (2.8, 18.9) per 25 µg/m³ PM_{10-2.5}; and 4.3% (-1.4, 10.4) per 25 µg/m³ PM_{2.5} (all at
11 lag 2d); and (b) heart failure (i.e., 9.7% [0.2, 20.2] per 50 µg/m³ PM₁₀); 5.2% (-3.3, 14.4) per
12 25 µg/m³ PM_{10-2.5}; and 9.1% (2.4, 16.2) per 25 µg/m³ PM_{2.5} (the first two at lag 0 d and the latter
13 at lag 1 d). No associations with dysrhythmias were seen however. The PM effects generally
14 were robust when co-pollutants were added to the model. Results for 2-pollutant models
15 involving CO are given in Table 8-16 above. As discussed earlier with regard to the Lippmann
16 et al. (2000) mortality findings, it is difficult to discern whether the observed associations with
17 coarse fraction particles (PM_{10-2.5}) are independently due to such particles or may possibly be
18 attributed to the moderately correlated fine particle (PM_{2.5}) fraction in Detroit. In addition,
19 power was limited by the small sample size. Because GAM was used in the analyses reported in
20 Lippmann et al. (2000), Ito (2003) has recently reported reanalyses results for the Detroit study
21 using GAM with more stringent convergence criteria and GLM with natural splines. PM effect
22 sizes diminished somewhat (up to 30%) and sometimes lost significance. However, these
23 changes tended to affect all PM metrics in a similar fashion. Thus, there was no change in basic
24 conclusions for the original Lippmann et al. (2000) study, i.e., that there was no evidence for
25 stronger effects for one size fraction versus others. Ito (2003) also noted that study results were
26 more sensitive to alternative weather models and degree of smoothing (degrees of freedom used
27 for the smoothing function) than to whether or not GAM, with strict convergence criteria, was
28 used.

29 Tolbert et al. (2000a) initially reported preliminary results for multiple PM indices as they
30 relate to daily hospital emergency department (ED) visits for dysrhythmias (DYS) and all CVD
31 categories for persons aged 16 yrs or older, based on analyses of data from 18 of 33 participating

1 hospitals in Atlanta, GA. During Period 1 of the study (1993-1998), PM₁₀ from the EPA AIRS
2 database was reported to be negatively associated with CVD visits. In a subsequent one-year
3 period (Aug. 1998-Aug. 1999), when data became available from the Atlanta PM supersite,
4 positive but non-significant associations were seen between CVD and PM₁₀ (RR of 5.1% per
5 50 µg/m³ PM₁₀) and PM_{2.5} (RR of 6.1% per 25 µg/m³ PM_{2.5}); and significant positive
6 associations were seen with certain fine particle components, i.e., elemental carbon (p ≤ 0.005)
7 and organic carbon (p ≤ 0.02), and CO (p ≤ 0.005). No multi-pollutant results were reported.
8 Study power was limited due to the short data record in Period 2.

9 More complete analyses for 1993-2000 data from nearly all participating hospitals have
10 recently been reported by Metzger et al. (2004) as part of the ARIES / SOPHIA studies.
11 Metzger et al. (2004) examined the relation between air pollution and cardiovascular outcomes
12 using ambient air quality data and emergency department visits in Atlanta, Georgia from January
13 1, 1993 to August 31, 2000. Daily air quality data for PM₁₀, PM_{2.5}, and PM_{10-2.5} and gaseous
14 criteria pollutants were gathered. Data on 4,407,535 emergency department visits were
15 compiled for 31 hospitals in Atlanta for CVD and related subgroups. Poisson generalized linear
16 models (GLM) controlling for long-term temporal trends and meteorologic conditions with cubic
17 splines were used for the analyses. The results indicate that for an a priori 3-day moving average
18 in single pollutant models, CVD visits were associated with NO₂, CO, PM_{2.5}, organic carbon,
19 elemental carbon, and oxygenated hydrocarbons (but not with O₃ or SO₂). Further analyses
20 suggested that these associations were strongest with same-day pollutant levels. Two pollutant
21 models for PM_{2.5} were generally attenuated. No associations were observed for finger wounds
22 (which served as a control). Neither Tolbert et al. nor Metzger et al. reported any key findings
23 based on GAM analyses.

24 In an analysis of 1992-1995 Los Angeles data, Linn et al. (2000) also found that PM₁₀, CO,
25 and NO₂ were all significantly associated with increased CVD admissions in single-pollutant
26 models among persons aged 30 yr and older. Associations generally appeared to be stronger for
27 CO than for PM₁₀. No PM₁₀ results were presented with co-pollutants in the model.

28 Lastly, Moolgavkar (2000b) analyzed PM₁₀, CO, NO₂, O₃, SO₂ and limited PM_{2.5} data in
29 relation to daily total cardiovascular (CVD) and total cerebrovascular (CrD) admissions for
30 persons aged ≥65 from three urban counties (Cook, IL; Los Angeles, CA; Maricopa, AZ) during
31 1987-1995. Of particular note was the availability of PM_{2.5} data in LA, though only for every

1 sixth day. Consistent with most studies, in univariate regressions, PM₁₀ (and PM_{2.5} in LA) were
2 associated at some lags with CVD admissions in Cook and LA counties, but not in Maricopa
3 county. However, in two-pollutant models in Cook and LA counties, the PM risk estimates
4 diminished substantially and/or were rendered non-significant, whereas co-pollutant (CO or
5 NO₂) risk estimates were less affected. These results suggest that gaseous pollutants, with the
6 exception of O₃, may have been more strongly associated with CVD hospitalizations than were
7 PM indices. These findings were based on an analysis that used GAM functions for time and
8 weather controls. Moolgavkar (2003) reported results of a reanalysis using improved GAM
9 convergence criteria and GLM with natural splines (nspline) and a range of degrees of freedom
10 (30 versus 100) for the smooth function of time. Results were not very sensitive to the use of
11 default versus improved GAM or splines (Table 8-16) but did appear to be more sensitive to
12 degrees of freedom. The nspline results were given only with 100 degrees of freedom. This is
13 an unusually large number, especially for PM_{2.5}, where data were available only every sixth day
14 over a nine year period.

15 The above analyses of daily PM₁₀ and CO in U.S. cities, overall, indicate that elevated
16 concentrations of both PM₁₀ and CO may enhance risk of CVD-related morbidity leading to
17 increased ED visits or hospitalizations. The Lippmann results appear to implicate both PM_{2.5}
18 and PM_{10-2.5} in increased hospital admissions for some categories of CVD among the elderly.

19 **8.3.1.3.2 Studies in Non-U.S. Cities**

21 Four separate analyses of hospitalization data in Canada have been reported by Burnett and
22 coworkers since 1995 (Burnett et al., 1995, 1997a,b, 1999). A variety of locations, outcomes,
23 PM exposure metrics, and analytical approaches were used. The first study (Burnett et al.,
24 1995), reviewed briefly in the 1996 PM AQCD, analyzed six years of data from 168 hospitals in
25 Ontario, CN. Respiratory and CVD hospital admissions were analyzed in relation to sulfate and
26 O₃ concentrations. Sulfate lagged one day was associated with CVD admissions, with an effect
27 of 2.8% (CI 1.8-3.8) increase per 13 µg/m³ SO₄⁻² without O₃ in the model and 3.3% (CI 1.7 - 4.8)
28 with O₃ included. When CVD admissions were split out into sub-categories, larger associations
29 were seen between sulfates and coronary artery disease and heart failure than for cardiac
30 dysrhythmias. Sulfate associations with total admissions were larger for the elderly ≥ 65 yr old

1 (3.5% per 13 $\mu\text{g}/\text{m}^3$) than for those < 65 yr old (2.5% per 13 $\mu\text{g}/\text{m}^3$). There was little evidence
2 for seasonal differences in sulfate associations.

3 Burnett et al. (1997b) analyzed daily congestive heart failure hospitalizations in relation to
4 CO and other air pollutants (O_3 , NO_2 , SO_2 , CoH) in ten large Canadian cities as a replication of
5 an earlier U.S. study by Morris et al. (1995). The Burnett Canadian study expanded upon the
6 previous work both by its size (11 years of data for each of 10 large cities) and by including a
7 measure of PM air pollution (coefficient of haze, CoH); whereas no PM data were included in
8 the earlier Morris et al. study. The Burnett study was restricted to the population ≥ 65 years old.
9 The authors noted that all pollutants except O_3 were correlated, making it difficult to separate out
10 their effects statistically. CoH, CO, and NO_2 measured on the same day as admission (i.e., lag 0)
11 were all strongly associated with congestive heart failure admissions in univariate models.
12 In multi-pollutant models, CO remained a strong predictor, but CoH did not (no gravimetric PM
13 data used).

14 The roles played by size-selected gravimetric and chemically-specified particle metrics as
15 predictors of CVD hospitalizations were explored in analyses of data from metropolitan Toronto
16 for the summers of 1992-1994 (Burnett et al., 1997a). The analyses used dichotomous sampler
17 ($\text{PM}_{2.5}$, PM_{10} , and $\text{PM}_{10-2.5}$), hydrogen ion, and sulfate data collected at a central site as well as
18 O_3 , NO_2 , SO_2 , CO, and CoH data collected at multiple sites in Toronto. Hospital admissions
19 categories included total cardiovascular (i.e., the sum of ischemic heart disease, cardiac
20 dysrhythmias, and heart failure) and total respiratory-related admissions. Model specification
21 with respect to pollution lags was based on evaluation of all lags and averaging times out to
22 4 days prior to admission in exploratory analyses and “best” metrics being chosen on the basis of
23 maximal t-statistics. The relative risks of CVD admissions were positive and generally
24 statistically significant for all pollutants analyzed in univariate regressions, but especially so for
25 O_3 , NO_2 , CoH, and $\text{PM}_{10-2.5}$ (i.e., regression t-statistics > 3). Associations for gaseous pollutants
26 were generally robust to inclusion of PM covariates, whereas the PM indices (aside from CoH)
27 were not robust to inclusion of multiple gaseous pollutants. In particular, $\text{PM}_{2.5}$ was not a robust
28 predictor of CVD admissions in multi-pollutant models: whereas an 25 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$
29 was associated with a 7.2% increase ($t = 1.8$) in CVD admissions in a univariate model, the
30 effect was reduced to -1.6% ($t = 0.3$) in a model that included O_3 , NO_2 , and SO_2 . CoH, like CO
31 and NO_2 , is generally thought of as a measure of primary motor-vehicle emissions during the

1 non-heating season. The authors concluded that “particle mass and chemistry could not be
2 identified as an independent risk factor for exacerbation of cardiorespiratory diseases in this
3 study beyond that attributable to climate and gaseous air pollution.”

4 Burnett et al. (1999) later reported results of a more extensive attempt to explore cause-
5 specific hospitalizations for persons of all ages in relation to a large suite of gaseous and PM air
6 pollutant measures, using 15 years of Toronto data. Cardiovascular admissions were split out
7 into separate categories for analysis: dysrhythmias, heart failure, and ischemic heart disease.
8 Burnett et al. selected only those admissions to acute care treatment hospitals that were
9 considered an emergency or urgent. The analyses also examined several respiratory causes, as
10 well as cerebrovascular and diseases of the peripheral circulation; the latter categories were
11 included because they should show PM associations if one mechanism of PM action is related to
12 increased plasma viscosity, as suggested by Peters et al. (1997a). The PM metrics analyzed were
13 $PM_{2.5}$, PM_{10} , and $PM_{10-2.5}$ estimated from daily TSP and TSP sulfate data, based on a regression
14 analysis for dichotomous sampling data that were available every sixth day during an eight-year
15 subset of the full study period. Although some statistically significant associations with one or
16 another PM metric were found in univariate models, there were no significant PM associations
17 with any of the three CVD hospitalization outcomes in multi-pollutant models. For example,
18 whereas an $25 \mu\text{g}/\text{m}^3$ increase in estimated $PM_{2.5}$ was associated with a 8.05% increase (t-
19 statistic = 6.08) in ischemic heart disease admissions in a univariate analysis, the $PM_{2.5}$
20 association was reduced to 2.25% (n.s.) when NO_2 and SO_2 were included in the model. The
21 gaseous pollutants dominated most regressions. There also were no associations between PM
22 and cerebral or peripheral vascular disease admissions. However, the use of estimated rather
23 than measured PM components limits interpretation of the reported PM results: that is, use of
24 estimated PM exposure metrics should, in general, tend to increase exposure measurement error
25 and thereby tend to decrease effects estimates.

26 The Burnett et al. studies provide some of the most extensive results for PM in conjunction
27 with multiple gaseous pollutants, but the inconsistent use of alternative PM metrics in the
28 various analyses confuses the picture. A general finding appears to be lack of robustness of
29 associations between cardiovascular outcomes and PM in multi-pollutant analyses. This was
30 seen for CoH in the analysis of 10 Canadian cities (Burnett et al., 1997b), for $PM_{2.5}$ and PM_{10} in
31 the analysis of summer data in Toronto (Burnett et al., 1997a), and for linear combinations of

1 TSP and sulfates (i.e., estimated $PM_{2.5}$, PM_{10} , and $PM_{10-2.5}$) in the analysis of 15 years of data in
2 Toronto (Burnett et al., 1999). One exception was the association reported between CVD
3 admissions to 168 Ontario hospitals and sulfate concentrations (Burnett et al., 1995), where the
4 sulfate association was robust to the inclusion of O_3 . Also, although gravimetric PM variables
5 were not robust predictors in the Toronto summer analysis, CoH was (Burnett et al., 1997a),
6 perhaps reflecting the influence of primary motor vehicle emissions. This contrasts, however,
7 with CoH's lack of robustness in the 10-city analysis (Burnett et al., 1997b).

8 Stieb et al., 2000 studied all-age acute cardiac emergency room visits in relation to a rich
9 set of pollution covariates in Saint John, Canada for the period 1992-1996. Daily data were
10 available on $PM_{2.5}$, PM_{10} , fine fraction hydrogen and sulfate ions, CoH, CO, H_2S , NO_2 , O_3 , SO_2 ,
11 and total reduced sulfur. In a multi-pollutant model, neither PM_{10} nor $PM_{2.5}$ were significantly
12 related to total cardiac ED visits, though O_3 and SO_2 were.

13 The APHEA II (Le Tertre et al., 2002) project examined the association between PM_{10} and
14 hospital admissions for cardiac causes in eight European cities. They found a significant PM_{10}
15 effect (0.5%; CI: 0.2, 0.8) on admission for cardiac causes (all ages), as well as for both cardiac
16 causes (0.7%; CI: 0.4, 1.0) and ischemic heart disease (0.8%; CI: 0.3, 1.2) for people over
17 65 years old, the effect per unit of PM_{10} pollution being half that reported for the U.S. NMMAPS
18 reanalyses (Zanobetti and Schwartz, 2003). PM_{10} did not seem to be confounded by O_3 or SO_2 .
19 The PM_{10} effect was reduced when CO was incorporated in the regression model and eliminated
20 when controlling for NO_2 . In contrast to PM_{10} , black smoke was robustly associated with CVD
21 hospital admissions when co-pollutants were introduced into the model. This led the authors to
22 suggest that diesel PM may be especially important. GAM functions were used in the original
23 analysis. In a recent reanalysis using GAM with stringent convergence criteria and GLM with
24 either natural or penalized splines, no marked changes from original results were observed (Le
25 Tertre et al., 2003).

26 Several additional non-U.S. studies, mainly in the U.K., have also been published since the
27 1996 PM AQCD. Most of these studies evaluated co-pollutant effects along with those of PM.
28 Interpretation is hindered somewhat, however, by the failure to report quantitative results for
29 PM_{10} in the presence of co-pollutants. In univariate models, Atkinson et al. (1999a) reported PM
30 associations for persons aged < 65 yr and for persons aged \geq 65 yr. Significant associations
31 were reported for both ambient PM_{10} and black smoke (BS), as well as all other co-pollutants,

1 with daily admissions for total cardiovascular disease and ischemic heart disease for 1992-1994
2 in London, UK, using standard time-series regression methods. In two-pollutant models, the
3 associations with PM₁₀, NO₂, SO₂, and CO were moderated by the presence of BS in the model,
4 but the BS association was robust to co-pollutants. Interpretation is hampered somewhat by the
5 lack of quantitative results for two-pollutant models.

6 In another U.K. study, associations with PM₁₀, and to a lesser extent BS, SO₂, and CO,
7 were reported for analyses of daily emergency hospital admissions for cardiovascular diseases
8 from 1992-1995 for Edinburgh, UK (Prescott et al., 1998). No associations were observed for
9 NO₂ and O₃. Significant PM₁₀ associations for CVD admissions were present only in persons
10 < 65 yrs old. The authors reported that the PM₁₀ associations were unaffected by inclusion of
11 other pollutants; however, results were not shown. On the other hand, no associations between
12 PM₁₀ and daily ischemic heart disease admissions were observed by Wordley and colleagues
13 (1997) in an analysis of two years of daily data from Birmingham, UK. However, PM₁₀ was
14 associated with respiratory admissions and cardiovascular mortality during the same study
15 period. This inconsistency of results across causes and outcomes is difficult to interpret, but may
16 relate in part to the relatively short time-series analyzed. The authors stated that gaseous
17 pollutants did not have significant associations with health outcomes independent of PM, but no
18 results were presented for models involving gaseous pollutants.

19 A study in Hong Kong by Wong et al. (1999a) found associations between CVD
20 admissions and PM₁₀, SO₂, NO₂, and O₃ in univariate models, but did not examine multi-
21 pollutant models. In models including PM₁₀ and dichotomous variables for gaseous pollutants
22 (high versus low concentration), the PM₁₀ effects remained relatively stable. Ye et al. (2001)
23 analyzed a 16 year record of daily emergency hospital visits for July and August in Tokyo
24 among persons age 65 and older. In addition to PM₁₀, the study included NO₂, O₃, SO₂, and CO.
25 Models were built using an objective significance criterion for variable inclusion. NO₂ was the
26 only pollutant found to be significantly associated with angina, cardiac insufficiency, and
27 myocardial infarction hospital visits.

1 ***8.3.1.3.3 Summary of Salient Findings for Acute PM Exposure Effects on CVD Hospital*** 2 ***Admissions***

3 The ecologic time-series studies reviewed here add to a growing body of evidence on acute
4 CVD morbidity effects of PM and co-pollutants. Two U.S. multi-city studies offer the strongest
5 current evidence for effects of PM₁₀ on acute CVD hospital admissions, but uncertainties
6 regarding the possible role of co-pollutants in the larger of the two studies hinders interpretation
7 with respect to independent PM₁₀ effects. Among single-city studies carried out in the U.S. and
8 elsewhere by a variety of investigators (see Table 8-18), less consistent evidence for PM effects
9 is seen. Of particular importance are the possible roles of co-pollutants (e.g., CO) as
10 confounders of the PM effect. Among 13 independent studies that included gravimetrically-
11 measured PM₁₀ and co-pollutants, three reported PM effects that appeared to be independent of
12 co-pollutants (Schwartz, 1997; Lippmann et al., 2000; Prescott et al., 1998); eight reported no
13 significant PM₁₀ effects after inclusion of co-pollutants (Morris and Naumova, 1998;
14 Moolgavkar, 2000b; Tolbert et al., 2000a; Burnett et al., 1997a; Steib et al., 2000; Atkinson
15 et al., 1999a; Wordley et al. (1997); Morgan et al., 1998; Ye et al., 2001); and two studies were
16 unclear regarding independent PM effects (Linn et al., 2000; Wong et al., 1999a). In a recent
17 quantitative review of published results from 12 studies on airborne particles and hospital
18 admissions for cardiovascular disease, Morris (2001) noted that adjustment for co-pollutants
19 consistently reduced the PM₁₀ effect, with reductions ranging from 10 to 320% across studies.
20 Thus, although several studies do appear to provide evidence for PM effects on CVD hospital
21 admissions independent of co-pollutant effects, a number of other studies examining
22 co-pollutants did not find results indicative of independent PM₁₀ effects on CVD hospital
23 admissions.

24 With respect to particle size, only a handful of studies have examined the relative effects of
25 different particle indicators (Lippmann et al., 2000; Burnett et al., 1997a; Metzger et al., 2004;
26 Steib et al., 2000; Moolgavkar, 2000b). Perhaps due to statistical power issues, no clear picture
27 has emerged as to particle-size fraction(s) most associated with acute CVD effects.

28 As discussed above, several studies originally based on statistical analyses involving the
29 SPlus GAM function have reported new results using alternative statistical methods. The
30 reanalyses yielded some slightly reduced effect estimates and/or increased confidence intervals

1 or little or no change resulted in other cases. Thus, based on these new results, the overall
2 conclusions from the cardiovascular hospitalization studies remain the same.

3 Because hospitalization can be viewed as likely reflecting some of the same
4 pathophysiologic mechanisms that may be responsible for acute mortality following PM
5 exposure, it is of interest to assess the coherence between the morbidity results reviewed here
6 and the mortality results reviewed in Section 8.2.2 (Borja-Aburto et al., 1997, 1998; Braga et al.,
7 2001a; Goldberg et al., 2000; Gouveia and Fletcher, 2000; Hoek et al., 2001; Kwon et al., 2001;
8 Michelozzi et al., 1998; Morgan et al., 1998; Pönkä et al., 1998; Schwartz et al., 1996a; Simpson
9 et al., 1997; Wordley et al., 1997; Zeghnoun et al., 2001; Zmirou et al., 1998). The mortality
10 studies reported significant associations between acute CVD mortality and measures of ambient
11 PM, though the PM metrics used and the relative risk estimates obtained varied across studies.
12 The PM measurement methods included gravimetrically analyzed filter samples (TSP, PM₁₀,
13 PM_{2.5}, PM_{10-2.5}), beta gauge (particle attenuation of beta radiation), nephelometry (light
14 scattering), and black smoke (filter reflectance). Where tested, PM associations with acute CVD
15 mortality appeared to be generally more robust to inclusion of gaseous covariates than was the
16 case for acute hospitalization studies (Borja-Aburto et al., 1997, 1998; Morgan et al., 1998;
17 Wordley et al., 1997; Zmirou et al., 1998). Three studies (Braga et al., 2001a; Goldberg et al.,
18 2000; Hoek et al., 2001), as noted in Section 8.2.2, provide data indicating that some specific
19 CVD causes of mortality (such as heart failure) were more strongly associated with air pollution
20 than total CVD mortality; but it was noted that ischemic heart disease (which contributes about
21 half of all CVD deaths) was the strongest contributor to the association between air pollution and
22 cardiovascular mortality. The above-noted results for acute CVD mortality are qualitatively
23 consistent with those reviewed earlier in this section for hospital admissions.

24 Figure 8-10 illustrates PM₁₀ excess risk estimates for single-pollutant models derived from
25 selected U.S. studies of PM₁₀ exposure and total CVD hospital admissions, standardized to a
26 50 µg/m³ exposure to PM₁₀ as shown in Table 8-16. Results are shown both for studies yielding
27 pooled outcomes for multiple U.S. cities and for studies of single U.S. cities. The Zanobetti and
28 Schwartz (2003a) and Samet et al. (2000a) pooled cross-city results for 14 U.S. cities provide the
29 most precise estimate for relationships of U.S. ambient PM₁₀ exposure to increased risk for CVD
30 hospitalization. That estimate, and those derived from most other studies in Figure 8-10,
31 generally appear to confirm likely excess risk of CVD-related hospital admissions for U.S. cities

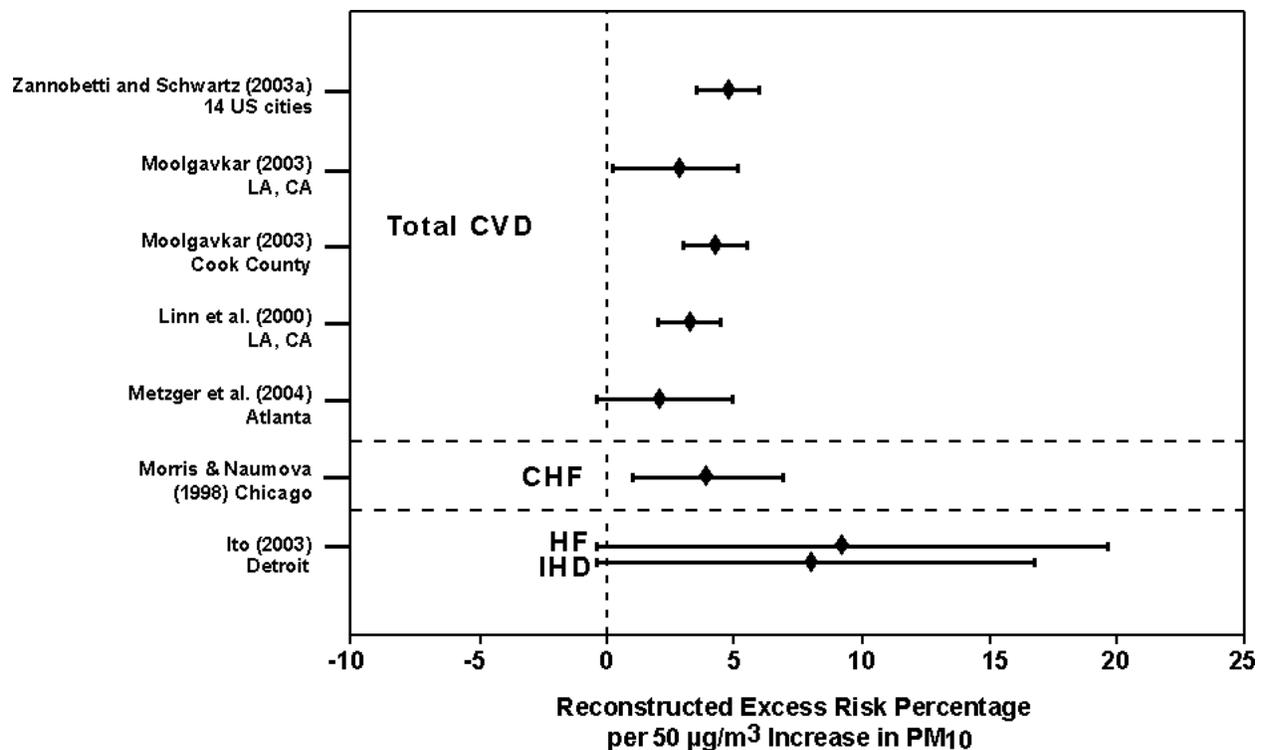


Figure 8-10. Acute cardiovascular hospitalizations and particulate matter exposure excess risk estimates derived from U.S. PM₁₀ studies based on single-pollutant models from GAM strict convergence criteria reanalyses (2003 studies) or alternative (non-GAM) original analyses. Both multi-pollutant models and PM_{2.5} and PM_{10-2.5} results are shown in Table 8-16. CVD = cardiovascular disease. CHF = congestive heart failure. HF = heart failure. IHD = ischemic heart disease.

1 in the range of 3 to 9% per 50 µg/m³ PM₁₀, especially among the elderly (≥ 65 yr). Other
 2 individual-city results (see Table 8-16) from Detroit are also indicative of excess risk being in
 3 the range of approximately 3.0 and 8.1% per 25 µg/m³ of PM_{2.5} or PM_{10-2.5}, respectively, for
 4 ischemic heart disease and 6.8% and 4.9% excess risk per 25 µg/m³ of PM_{2.5} and PM_{10-2.5},
 5 respectively, for heart failure. However, the extent to which PM affects CVD-hospitalization
 6 risks independently of, or together with other co-pollutants (such as CO), remains to be further
 7 resolved.
 8

1 **8.3.1.3.4 Individual-Level Studies of Cardiovascular Effect Markers**

2 Several new studies have evaluated longitudinal associations between ambient PM and
3 cardiovascular effect markers (i.e., physiologic measures of cardiovascular function or
4 biochemical changes in the blood that may be associated with increased cardiac risks).
5 In contrast to the ecologic time-series studies discussed above, these studies measure outcomes
6 and most covariates at the individual level, making it possible to draw conclusions regarding
7 individual risks, as well as to explore mechanistic hypotheses. Heterogeneity of responses
8 across individuals, and across subgroups defined on the basis of age, sex, pre-existing health
9 status, etc., also can be assessed, in principle. While exposure assessment remains largely
10 ecologic (i.e., the entire population is usually assigned the same exposure value on a given day),
11 exposure is generally well characterized in the small, spatially-clustered study populations. The
12 recent studies fall into two broad classes: (1) those addressing heart rate, cardiac rhythm, blood
13 pressure, or other cardiac function indicators; and (2) those addressing blood characteristics.
14 While significant uncertainty still exists regarding the interpretation of results from these new
15 studies, the varied responses that have been reported to be associated with ambient PM and
16 co-pollutants are of much interest in regard to mechanistic hypotheses concerning
17 pathophysiologic processes potentially underlying CVD-related mortality/morbidity effects
18 discussed in preceding sections.

19 ***Cardiac physiology and adverse cardiac events***

20
21 Alterations in heart rate and/or rhythm are thought to reflect pathophysiologic changes that
22 may represent possible mechanisms by which ambient PM exposures may exert acute effects on
23 human health. Decreased heart rate variability, in particular, has been identified as a predictor of
24 increased cardiovascular morbidity and mortality. Several independent studies have recently
25 reported temporal associations between PM exposures and various measures of heart beat
26 rhythm in panels of elderly subjects (Liao et al., 1999; Pope et al., 1999a,b,c; Dockery et al.,
27 1999; Peters et al., 1999a, 2000a; Gold et al. 2000; Creason et al., 2001). Changes in blood
28 pressure may also reflect increases in CVD risks (Linn et al., 1999; Ibald-Mulli et al., 2001).
29 Finally, one important new study (Peters et al., 2001a) has linked acute (2- and 24-h) ambient
30 PM_{2.5} and PM₁₀ concentrations with increased risk of myocardial infarction in subsequent hours
31 and days.

1 Liao et al. (1999) studied 26 elderly subjects (age 65-89 years; 73% female) over three
2 consecutive weeks at a retirement center in metropolitan Baltimore, 18 of whom were classified
3 as “compromised” based on previous cardiovascular conditions (e.g., hypertension). Daily
4 six-minute resting electrocardiogram (ECG) data were collected, and time intervals between
5 sequential R-R intervals recorded. A Fourier transform was applied to the R-R interval data to
6 separate its variance into two major components: low frequency (LF, 0.04-0.15 Hz) and high
7 frequency (HF, 0.15-0.40 Hz). The standard deviation of all normal-to-normal (N-N; also
8 designated R-R) heartbeat intervals (SDNN) was computed as a time-domain outcome variable.
9 PM_{2.5} was monitored indoors by TEOM and outdoors by dichotomous sampler. Outdoor PM_{2.5}
10 levels ranged from 8.0 to 32.2 µg/m³ (mean = 16.1 µg/m³). Regression analyses controlled for
11 inter-subject differences in average variability, allowing each subject to serve as his/her own
12 control. Consistent associations were seen between increases in PM_{2.5} levels (both indoors and
13 outdoors) and decreases in all three outcome variables (LF, HF, SDNN), with associations being
14 stronger for the 18 “compromised” subjects. The short time interval (6 min per day) of
15 measurement for these parameters hampers interpretation of the possible medical significance of
16 the reported positive results; longer or several measurements per day would have allowed for
17 clearer indications of likely underlying perturbation of CV function.

18 Creason et al. (2001) reported results of a subsequent study using similar methods among
19 56 elderly residents of a retirement center in Baltimore County, MD. The 11 men and 45 women
20 ranged in age from 72 to 97 years and were all Caucasian. Associations between ambient PM_{2.5}
21 and decreased HRV were not statistically significant at $p < 0.05$. When two episodic PM_{2.5} days
22 with rainfall were excluded from the 24-day data set, trends associating decreased HRV and
23 PM_{2.5} were present, but did not meet significance at $p < 0.05$. There was no evidence of effects
24 among subsets of subjects with compromised health status as observed previously in the study
25 by Liao et al. (1999). No results were presented for pollutants other than PM_{2.5}.

26 Pope and colleagues (1999c), using ambulatory ECG monitoring, studied HRV and PM₁₀
27 in a panel of six elderly subjects (69-89 years, 5/6 male) and one 23-year old male subject, all
28 compromised by some form of heart disease. SDNN, SDANN, and r-MSSD were used as
29 measures of HRV based on 48-hr holter readings. Daily gravimetric PM₁₀ data from three sites
30 in the study area ranged from ~10 µg/m³ to 130 µg/m³ during the study, with high levels
31 occurring only during the first half of the 1.5 month study period. No co-pollutants (e.g., O₃,

1 CO, NO₂, etc.) were studied. Regression analyses with subject-specific intercepts were
2 performed, with and without control for daily barometric pressure and mean heart rate. Same-
3 day and previous-day ambient PM₁₀ were negatively associated with SDNN and SDANN; and
4 the results were unaffected by inclusion of covariates. Heart rate, as well as r-MSSD, were both
5 positively, but less strongly, associated with PM₁₀. No co-pollutants were studied. The specific
6 heart rate variability findings (i.e., PM associations with decreased SDANN and SDNN and
7 increased r-MSSD) make it difficult to interpret the results or their cardiac health significance.
8 The decreased SDANN and SDNN suggests decreased sympathetic activity, whereas the
9 r-MSSD increase suggests increase parasympathetic (vagal) input to the heart (which is likely
10 protective in terms of risk of ischemic related arrhythmia, but might increase the risk of atrial
11 arrhythmia). These specific HRV findings do not allow clear conclusions as to how PM may be
12 affecting cardiac functioning.

13 The Pope et al. (1999c) study discussed above was nested within a larger cohort of
14 90 subjects who participated in a study of heart rate and oxygen saturation in the Utah Valley
15 (Dockery et al., 1999; Pope et al., 1999b). The investigators hypothesized that decreases in
16 oxygen saturation might occur as a result of PM exposure and that this could be a risk factor for
17 adverse cardiac outcomes. The study was carried out in winter months (mid-November through
18 mid-March), when frequent inversions lead to fine particle episodes. PM₁₀ levels at the three
19 nearest sites averaged from 35 to 43 µg/m³ during the study, and daily 24-h levels ranged from
20 5 to 147 µg/m³. Two populations were studied: 52 retired Brigham Young University
21 faculty/staff and their spouses, and 38 retirement home residents. Oxygen saturation (SpO₂) and
22 heart rate (HR) were measured once or twice daily by an optical sensor applied to a finger.
23 In regression analyses controlling for inter-individual differences in mean levels, SpO₂ was not
24 associated with PM₁₀, but was highly associated with barometric pressure. In contrast, HR
25 association with PM₁₀ significantly increased but significantly decreased with barometric
26 pressure in joint regressions. Including CO in the regressions did not change these basic
27 findings. This was the first study of this type to examine the interrelationships among
28 physiologic measures (i.e., SpO₂ and HR), barometric pressure, and PM₁₀. The profound
29 physiological effects of barometric pressure noted here highlight the importance of carefully
30 controlling for barometric pressure effects in studies of cardiac physiology.

1 Gold and colleagues (2000) obtained somewhat different results in a study of heart rate
2 variability among 21 active elderly subjects, aged 53-87 yr, in a Boston residential community.
3 Resting, standing, exercising, and recovering ECG measurements were performed weekly using
4 a standardized protocol on each subject, which involved 25 min/week of continuous Holter ECG
5 monitoring. Two time-domain measures were extracted: SDNN and r-MSSD (see above for
6 definitions). Heart rate also was analyzed as an outcome. Continuous PM₁₀ and PM_{2.5}
7 monitoring was conducted by TEOM at a site 6 km from the study site and PM data were
8 corrected for the loss of semivolatile mass. Data on CO, O₃, NO₂, SO₂, temperature and relative
9 humidity were available from nearby sites. Outcomes were regressed on PM_{2.5} levels in the
10 0-24 hour period prior to ECG testing, with and without control for HR and temperature. As for
11 the other studies discussed above, declines in SDNN were associated with PM_{2.5} levels, in this
12 case averaged over 4 hours. These associations reached statistical significance at the
13 $p < 0.05$ level only when all testing periods (i.e., resting, standing, exercise) were combined.
14 In contrast to the above studies, both HR and r-MSSD here were negatively associated with
15 PM_{2.5} levels (i.e., lower HR and r-MSSD) when PM_{2.5} was elevated. These associations were
16 statistically significant overall, as well as for several of the individual testing periods, and were
17 unaffected by covariate control. Gold et al. (2003) subsequently reported reanalyses involving
18 temperature with either a GAM function with stringent convergence criteria or a GLM with
19 natural splines, with no substantial changes in results being reported. The negative associations
20 between PM_{2.5} and decreases in both HR and r-MSSD are puzzling, given that decreased HR is
21 indicative of increased parasympathetic tone whereas decreased r-MSSD is reflective of
22 decreased parasympathetic modulation of heart function. This discrepancy raises the possibility
23 that one or another or both of the observed outcomes may be due to chance.

24 Evidence for altered HRV in response to PM_{2.5} exposures comes from two other recent
25 studies. Magari et al. (2001) found significant decreases in SDNN of 1.4% (CI: 2.1, 0.6) per
26 100 ug/m³ 3-hr mean PM_{2.5} in young healthy Boston area boilermakers studied during non-work
27 periods. Another study of 40 boilermakers (including the 20 studied above) analyzed data
28 collected during both work and non-work periods (Magari et al., 2002). That study found a
29 significant 2.7% decrease in SDNN and a 1.0% increase in HR for every 100 ug/m³ increase in
30 4-hr moving average of estimated PM_{2.5}. The larger effect size for the non-work PM exposure
31 study may reflect differing health effects of ambient versus occupational PM composition.

1 These studies are suggestive of PM-related HRV effects in young healthy adults, but use of
2 estimated PM_{2.5} based on light scattering precludes firm quantitative interpretation of exposure
3 levels.

4 Peters et al. (1999a) reported HR results from a retrospective analysis of data collected as
5 part of the MONICA (monitoring of trends and determinants in cardiovascular disease) study in
6 Augsburg, Germany. Analyses focused on 2,681 men and women aged 25-64 years who had
7 valid ECG measurements taken in winter 1984-1985 and again in winter 1987-1988. Ambient
8 pollution variables included TSP, SO₂, and CO. The earlier winter included a 10-day episode
9 with unusually high levels of SO₂ and TSP, but not of CO. Pollution effects were analyzed in
10 two ways: dichotomously comparing the episode and non-episode periods, and continuously
11 using regression analysis. However, it is unclear from the report as to what extent the analyses
12 reflect between-subject versus within-subject effects. A statistically significant increase in mean
13 heart rate was seen during the episode period versus other periods, controlling for cardiovascular
14 risk factors and meteorology. Larger effects were seen in women. In single-pollutant regression
15 analyses, all three pollutants were associated with increased HR.

16 More recently, Ibalid-Mulli et al. (2001) reported similar findings from a study of blood
17 pressure among 2607 men and women aged 25-64 years in the MONICA study. Systolic blood
18 pressure increased on average during an episode of elevated TSP and SO₂, but the effect
19 disappeared after controlling for meteorological parameters (e.g., temperature and barometric
20 pressure). However, when TSP and SO₂ were analyzed as continuous variables, both were
21 associated with elevated systolic blood pressure, controlling for meteorological variables.
22 In two-pollutant models, TSP was more robust than SO₂, and the TSP association was greater in
23 subgroups of subjects with elevated blood viscosity and heart rates.

24 Linn et al. (1999) reported associations between both diastolic and systolic blood pressure
25 and PM₁₀ in a panel study of 30 Los Angeles residents with severe COPD. The relationship was
26 not observed when inside-home PM levels were used in the analyses. Also, no relationship was
27 found between PM levels and heart rate or arrhythmias, based on 48 hours of holter data.

28 In a retrospective study, Peters and colleagues (2000a) examined incidence of cardiac
29 arrhythmias among 100 patients (mean age 62.2 yr.; 79% male) with implanted cardioverter
30 defibrillators followed over a three year period. Shocks from cardioverter defibrillators are
31 frequently used for life-threatening arrhythmias but not always (only ~65-70% are for life-

1 threatening arrhythmias). $PM_{2.5}$ and PM_{10} were measured in South Boston by the TEOM
2 method, along with black carbon, O_3 , CO, temperature and relative humidity; SO_2 and NO_2 data
3 were obtained from another site. The 5th percentile, mean, and 95th percentiles of PM_{10} levels
4 were 7.8, 19.3, and 37.0 $\mu g/m^3$, respectively. The corresponding $PM_{2.5}$ values were 4.6, 12.7,
5 and 26.6 $\mu g/m^3$. Logistic regression was used to analyze events in relation to pollution variables,
6 controlling for between-person differences, seasons, day-of-week, and meteorology in two
7 subgroups: 33 subjects with at least one arrhythmia event and 6 subjects with 10 or more such
8 events. In the larger subgroup, only NO_2 on the previous day, and the mean NO_2 over five days,
9 were significantly associated with arrhythmia incidence. In patients with 10 or more events, the
10 NO_2 associations were stronger. Also, some of the $PM_{2.5}$ and CO lags became significant in this
11 subgroup. Important caveats regarding this study include the fact that the vast majority of
12 cardiovertex defibrillator discharges occurred among a small subset (i.e., 6) of the patients.
13 Also, potentially important variables, e.g., cardiovascular drug usage and anti-arrhythmia drug
14 changes during follow-up, were not reported.

15 An exploratory study of a panel of COPD patients (Brauer et al., 2001) examined several
16 PM indicators in relation to CVD and respiratory health effects. The very low levels of ambient
17 particles (PM_{10} mean = 19 $\mu g/m^3$) and low variability in these levels plus the small sample size
18 of 16 limit the conclusions that can be drawn. Still, for cardiovascular endpoints, single-
19 pollutant models indicated that both systolic and diastolic BP decreased with increasing PM
20 exposure, but this was not statistically significant. Also, 24-h holter monitoring data recorded on
21 7 separate days for each individual did not show any heart rate variability changes associated
22 with PM levels. The size of the ambient PM_{10} effect estimate for ΔFEV_1 was larger than the
23 effect estimate for ambient $PM_{2.5}$ and personal $PM_{2.5}$ but not statistically significant. This initial
24 effort indicated that ambient PM_{10} consistently had the largest effect estimates, whereas while
25 models using personal exposure measurements did not show larger or more consistently positive
26 effect estimates relative to those models using ambient exposure metrics.

27 A potentially important study by Peters et al. (2001a) reported associations between onset
28 of myocardial infarction (MI) and ambient PM (either PM_{10} or $PM_{2.5}$) as studied in a cohort of
29 772 MI patients in Boston, MA. Precise information on the timing of the MI, obtained from
30 patient interviews, was linked with concurrent air quality data measured at a single Boston site.
31 A case crossover design enabled each subject to serve as his/her own control. One strength of

1 this study was its analysis of multiple PM indices and co-pollutants, including real-time PM_{2.5},
2 PM₁₀, the PM_{10-2.5} difference, black carbon, O₃, CO, NO₂, and SO₂. Only PM_{2.5} and PM₁₀ were
3 significantly associated with MI risk in models adjusting for season, meteorological parameters,
4 and day of week. Both the mean PM_{2.5} concentration in the previous two hours and in the
5 24 hours lagged one day were independently associated with MI, with odds ratios of 1.48
6 (CI: 1.09, 2.02) for 25 ug/m³ and 1.62 (CI: 1.13, 2.34) for 20 ug/m³, respectively. PM₁₀
7 associations were similar. The non-significant findings for other pollution metrics should be
8 interpreted in the context of potentially differing exposure misclassification errors associated
9 with the single monitoring site.

10 Checkoway et al. (2000) has reported a Seattle mortality study of PM₁₀ levels and cases of
11 patients experiencing out-of-hospital sudden cardiac death (SCD). They used a case-crossover
12 study design in 362 subjects suffering an SCD episode. They evaluated PM levels over the
13 5 days preceding SCD and compared those levels to levels recorded in the same month and
14 during the same days of the week (Mean PM₁₀ level = 31.9 µg/m³). They evaluated lags of 0 to
15 5 days looking for a correlation, but found no correlation between SCD episodes and PM levels
16 even after controlling for multiple confounding variables. They reported an estimated relative
17 risk at a one day lag of 0.87 (CI: 0.74, 1.01). The HEI (2000) review commentary noted that the
18 authors reported, from their power calculations, that the sample size (362) was not large enough
19 to either find or rule out a relative risk less than 1.5 and that lack of association with PM in this
20 study does not imply that other cardiac or cardiovascular disease outcomes are not associated
21 with PM. These negative findings suggest that PM may not be a risk factor for acute myocardial
22 infarction in previously healthy individuals, or that the pattern and/or mix of PM exposures in
23 Seattle, where woodsmoke may be an important component, may convey lesser risk than
24 observed elsewhere.

25 The above studies present a range of findings regarding possible effects of PM_{2.5} on cardiac
26 rhythm and other cardiac endpoints. However, the studies offer conflicting results, especially
27 with regard to HRV findings. Several studies reported PM levels to be associated with decreases
28 in one or more HR variability measured in elderly subjects with preexisting cardiopulmonary
29 disease, although increased r-MSSD (a measure of high-frequency HR variability) was found to
30 be associated with PM elevations in at least one study (Pope et al., 1999a). Several other found
31 no changes related to PM levels (Creason, et al., 2001) or blood pressure (Brauer et al., 2001).

1 Some recent studies have also reported effects in healthy elderly and young adult populations.
2 All those studies which examined HR found associations with PM most being positive
3 associations; but one (Gold et al., 2000; Gold et al., 2003) reported a negative relationship.
4 Overall, variations in methods used and discrepancies in results obtained across the studies argue
5 for caution in drawing any conclusions yet regarding ambient PM effects on heart rate variability
6 or other ECG measures of cardiovascular parameters.

7 8 ***Viscosity and other blood characteristics***

9 Peters et al. (1997a) state that plasma viscosity, a risk factor for ischemic heart disease, is
10 affected by fibrinogen and other large asymmetrical plasma proteins, e.g., immunoglobulin M
11 and α_2 -macroglobulin. They noted that, in a cohort study (Woodhouse et al., 1994) of elderly
12 men and women, fibrinogen levels were strongly related to inflammatory markers, such as
13 neutrophil count and acute-phase proteins (C-reactive protein and α_1 -antichymotrypsin) and self-
14 reported infections. They further noted that another prospective study (Thompson et al., 1995;
15 Haverkate et al., 1997) showed baseline fibrinogen and C-reactive protein concentrations to be
16 highly correlated in angina patients and to be independently associated with increased risk of
17 myocardial infraction.

18 Support for a mechanistic hypothesis, relating to enhanced blood viscosity, was suggested
19 by an analysis of plasma viscosity data collected in a population of 3256 German adults in the
20 MONICA study (Peters et al., 1997a). Each subject provided one blood sample during October
21 1984 to June 1985. An episode of unusually high air pollution levels occurred during a 13 day
22 period while these measurements were being made. Among the 324 persons who provided
23 blood during the episode, there was a statistically significant elevation in plasma viscosity as
24 compared with 2932 persons studied at other times. The odds ratio for plasma viscosity
25 exceeding the 95th percentile was 3.6 (CI: 1.6, 8.1) among men and 2.3 (CI: 1.0, 5.3) among
26 women. Analysis of the distribution of blood viscosity data suggested that these findings were
27 driven by changes in the upper tail of the distribution rather than by a general shift in mean
28 viscosity, consistent with the likelihood of a susceptible subpopulation.

29 A prospective cohort study of a subset of male participants from the above-described
30 Augsburg, Germany MONICA study was reported by Peters et al. (2001b). Based on a survey
31 conducted in 1984/85, a sample of 631 randomly selected men (aged 45-64 yr and free of

1 cardiovascular disease at entry) were evaluated in a 3-yr follow-up that examined relationships
2 of air pollution to serum C-reactive protein concentrations. C-reactive protein is a sensitive
3 marker of inflammation, tissue damage, and infections, with acute and chronic infections being
4 related to coronary events. Inflammation is also related to systemic hypercoagulability and onset
5 of acute ischemic syndromes. During the 1985 air pollution episode affecting Augsburg and
6 other areas of Germany, the odds of abnormal increases in serum C-reactive protein (i.e.,
7 $\geq 90^{\text{th}}$ percentile of pre-episode levels = 5.7 mg/L) tripled; and associated increases in TSP levels
8 of $26 \mu\text{g}/\text{m}^3$ (5-day averages) were associated with an odds ratio of 1.37 (CI: 1.08, 1.73) for
9 C-reactive protein levels exceeding the 90^{th} percentile levels in two pollutant models that
10 included SO_2 levels. The estimated odds ratio for a $30 \mu\text{g}/\text{m}^3$ increase in the 5-day mean for SO_2
11 was 1.12 (CI: 0.92, 1.47).

12 Other studies have examined blood indices in relation to PM pollution in United Kingdom
13 cities. Seaton and colleagues (1999) collected sequential blood samples (up to 12) over an
14 18 month period in 112 subjects (all over age 60) in Belfast and Edinburgh, UK. Blood samples
15 were analyzed for hemoglobin, packed cell volumes, fibrinogen, blood counts, factor VII,
16 interleukin 6, and C-reactive protein. In a subset of 60 subjects, plasma albumin also was
17 measured. PM_{10} data monitored by TEOM were collected from ambient sites in each city.
18 Personal exposure estimates for three days preceding each blood draw were derived from
19 ambient PM data adjusted by time-activity patterns and I/O penetration factors. No co-pollutants
20 were analyzed. Data were analyzed by analysis of covariance, controlling for city, seasons,
21 temperature, and between-subject differences. In this relatively small panel study, significant
22 changes in several blood indices were associated with either ambient or estimated personal PM_{10}
23 levels; but all the associations were negative, except for C reactive protein in relation to ambient
24 PM_{10} .

25 Prescott et al. (2000) also investigated factors that might increase susceptibility to
26 PM-related cardiovascular events for a large cohort of 1,592 subjects aged 55-74 in Edinburgh,
27 UK. Baseline measurements of blood fibrinogen and blood and plasma viscosity were examined
28 as modifiers of PM effects (indexed by BS) on the incidence of fatal and non-fatal myocardial
29 infarction or stroke. All three blood indices were strong predictors of increased cardiac event
30 risk; but there was no clear evidence of either a main effect of BS, nor interactions between BS
31 and blood indices.

1 In another European study, Pekkanen and colleagues (2000) analyzed plasma fibrinogen
2 data from a cross-sectional survey of 4,982 male and 2,223 female office workers in relation to
3 same-day and previous three-day PM₁₀, BS, NO₂, CO, SO₂, and O₃ concentrations. In the full
4 analysis, NO₂ and CO were significantly associated with increased fibrinogen levels. When the
5 analysis was restricted to the summer season, PM₁₀ and BS, as well as NO₂ and CO showed
6 significant univariate associations.

7 Schwartz (2001) later reported even larger analyses for possible PM effects on factors
8 affecting blood coagulability among a subset of the NHANES III cohort. The NHANES III
9 cohort was comprised of a stratified random sample of the U.S. population, with oversampling of
10 minorities (Black and Mexican-Americans represented 30% of the cohort) and of the elderly
11 (20% of the cohort was ≥ 60 yr. old versus their being 16% of the U.S. population). The
12 NHANES III study included evaluations of numerous health and nutritional endpoints conducted
13 in two phases during 1989-1994, each phase sampling ~ 20,000 subjects in 44 communities and
14 including persons representative of the U.S. population. Analyzing data for first phase subjects
15 living in 30 urban areas having every-six-day PM₁₀ monitoring (no. of PM₁₀ observations =
16 1,373) by mixed models (PROC MIXED, SAS), Schwartz (2001) found not only significant
17 positive associations between PM₁₀ exposures and plasma fibrinogen levels in a subset of the
18 NHANES III cohort, but also PM₁₀ associations with platelet and white cell counts. The PM₁₀
19 associations were robust when O₃, NO₂, or SO₂ were included with PM₁₀ in two-pollutant
20 models. In univariate models, SO₂ was only significant for white cell counts and NO₂ with
21 platelet counts and fibrinogen but not O₃ with any of the three blood coagulability markers.
22 Given that CO data were not matched to specific subjects, no CO analyses were done.

23 Overall, the above findings add some limited support for hypotheses about possible
24 mechanisms by which PM exposure may be linked to adverse cardiac outcomes. They appear to
25 most clearly implicate ambient PM as likely contributing to increases in C-reactive protein (a
26 biological marker of inflammatory responses), blood fibrinogen levels, and blood viscosity, all
27 of which are thought to be predictive of increased risk for serious cardiac events.
28
29

1 **8.3.1.4 Issues in the Interpretation of Acute Cardiovascular Effects Studies**

2 *Susceptible subpopulations.* Because they lack extensive data on individual subject
3 characteristics, hospital admissions studies provide only limited information on susceptibility
4 factors based on stratified analyses. The relative effect sizes for PM-cardiovascular associations
5 (and respiratory) admissions reported in ecologic time-series studies are generally somewhat
6 higher than those for total admissions. This provides some limited support for hypothesizing
7 that acute PM effects operate via cardiopulmonary pathways or that persons with pre-existing
8 cardiopulmonary disease have greater susceptibility to PM, or both. Although there are some
9 data from ecologic time-series studies showing larger PM effects on cardiovascular admissions
10 in adults aged ≥ 65 yr versus younger populations, the differences are neither striking nor
11 consistent. One recent study reported larger CVD hospitalization among persons with current
12 respiratory infections. The other individual-level studies of cardiophysiological function assessed
13 above are suggestive, but do not yet fully confirm that elderly persons with pre-existing
14 cardiovascular or respiratory disease are susceptible to subtle changes in heart rate variability in
15 association with PM exposures. More data are needed before that conclusion can be drawn with
16 confidence. Because younger and healthier populations have not yet been much studied, it is not
17 yet possible to assess the extent to which ambient PM exposures may affect their cardiovascular
18 health status or whether they are at lower risk for PM-related CVD effects than are the elderly.

19
20 *Role of other environmental factors.* The time-series studies published since 1996 have
21 generally attempted to control for weather influences. In contrast, with one possible exception
22 (Pope et al., 1999a), the roles of meteorological factors have not been analyzed extensively as
23 yet in the individual-level studies of cardiac function. Thus, the possibility of weather-related
24 influences in such studies cannot yet be discounted. Also, various co-pollutants have been
25 analyzed extensively in many recent time-series studies of PM and hospital admissions. In some
26 studies, certain PM indices clearly have an independent association after controlling for gaseous
27 co-pollutants. In others, the PM effects are reduced once co-pollutants are added to the model;
28 but this may be in part due to collinearity between PM indices and co-pollutants and/or gaseous
29 pollutants (e.g., CO) having independent effects on cardiovascular function.

30

1 *Temporal patterns of responses following PM exposure.* The evidence from recent time-
2 series studies of CVD admissions suggests rather strongly that PM effects tend to be maximal at
3 lag 0, with some carryover to lag 1, with little evidence for important effects beyond lag 1.
4

5 *Relationship of CVD effects to PM size and chemical composition attributes.* Insufficient
6 data exist from the time-series CVD admissions studies or the emerging individual-level studies
7 to provide clear guidance as to which ambient PM components, defined on the basis of size or
8 composition, determine ambient PM CVD effect potency. The epidemiologic studies have been
9 constrained by limited availability of multiple PM metrics. Where multiple metrics exist, they
10 often are highly correlated or are of differential quality due to differences in numbers of
11 monitoring sites and monitoring frequency.
12

13 *PM effects on blood characteristics related to CVD events.* Interesting, though limited,
14 new evidence has also been derived which is highly suggestive of associations between ambient
15 PM indices and increased blood viscosity, increased serum C-reactive protein, and increased
16 blood fibrinogen (all biological markers related to increased risks of serious cardiac events).
17 However, much more research will be needed to order to both confirm such associations and to
18 better understand which specific ambient PM species may contribute to them.
19

20 **8.3.2 Effects of Short-Term Particulate Matter Exposure on the Incidence of** 21 **Respiratory-Related Hospital Admissions and Medical Visits**

22 **8.3.2.1 Introduction**

23 This section evaluates information on epidemiologic associations of ambient PM exposure
24 with both respiratory hospital admissions and medical visits. Although hospital admissions
25 represent one severe morbidity measure evaluated in regard to ambient PM exposures, hospital
26 emergency department (ED) visits are another notable related outcome. Doctors' visits also
27 represent yet another related health measure that, although less studied, is still very relevant to
28 assessing air pollution public health impacts. This category of pollution-affected persons can
29 represent a large population, one generally not evaluated due to the usual lack of centralized data
30 records for doctors' visits in the United States.

1 The section intercompares various studies examining size-related PM mass exposure
2 measures (e.g., for PM₁₀, PM_{2.5}, etc.) or various PM chemical components vis-à-vis their
3 associations with such health endpoints, and discusses their respective extents of coherence with
4 PM associations across related health effects measures. In the following discussion, the main
5 focus for quantitative intercomparisons is on U.S. and Canadian studies considering PM metrics
6 that measure mass or a specific mass constituent, i.e., PM₁₀, PM_{10-2.5}, PM_{2.5}, or sulfates (SO₄⁻²).
7 Study results for other related PM metrics (e.g., BS) are also considered, but mostly only
8 qualitatively, primarily with respect to their relative coherence with studies using mass or
9 composition metrics measured in North America. In order to consider potentially confounding
10 effects of other co-existing pollutants, study results for various PM metrics are presented both
11 for (1) when the PM metric is the only pollutant in the model and (2) the case where a second
12 pollutant (e.g., O₃) is also included. Results from models with more than two pollutants included
13 simultaneously, however, are not used here for quantitative estimates of effect size or statistical
14 strength, because of increased likelihood of bias and variance inflation due to multi-collinearity
15 of various pollutants (e.g., see Harris, 1975).

17 **8.3.2.2 Summary of Key Respiratory Hospital Admissions Findings from the 1996** 18 **Particulate Matter Air Quality Criteria Document**

19 In the 1996 PM AQCD, both COPD and pneumonia hospitalization studies were found to
20 show moderate, but statistically significant, relative risks in the range of 1.06 to 1.25 (or 6 to
21 25% excess risk increment) per 50 µg/m³ PM₁₀ increase or its equivalent. Whereas many
22 hospitalizations for respiratory illnesses occur in those > 65 years of age, there were also
23 increased hospitalizations for those < 65 years of age. Several hospitalization studies restricted
24 their analysis by age group, but did not explicitly examine younger age groups. One exception
25 noted was Pope (1991), who reported increased hospitalization for Utah Valley children (0 to
26 5 yrs) for monthly numbers of admissions in relation to PM₁₀ monthly averages, as opposed to
27 daily admissions in relation to daily PM levels used in other studies. Studies examining acute
28 associations between indicators of components of fine particles (e.g., BS; sulfates, SO₄⁼; and
29 acidic aerosols, H⁺) and hospital admissions were reported, too, as showing significant
30 relationships. While sulfates were especially predictive of respiratory health effects, it was not

1 clear whether the sulfate-related effects were attributable to their acidity, to the broader effects
2 of associated combustion-related fine particles, or to other factors.

3 4 **8.3.2.3 New Respiratory-Related Hospital Admissions Studies**

5 New studies appearing since the 1996 PM AQCD have examined various admissions
6 categories, including: total respiratory admissions for all ages and by age; asthma for all ages
7 and by age; chronic obstructive pulmonary disease (COPD) admissions (usually for patients
8 > 64 yrs.), and pneumonia admissions (for patients > 64 yrs.). Table 8B-2, Appendix 8B
9 summarizes salient details regarding the study area, study period, study population, PM indices
10 considered and their concentrations, methods employed, study results, and “bottom-line” PM
11 index percent excess risks per standard PM increment (e.g., 50 $\mu\text{g}/\text{m}^3$ for PM_{10}) for the newer
12 studies.

13 The percent excess risk (ER) estimates presented in Table 8B-2 are based upon the relative
14 risks (RR's) provided by the authors, but converted into percent increments per standardized
15 increments used by the U.S. EPA to facilitate direct intercomparisons of results across studies
16 (as discussed in Section 8.1). The ER's shown in the table are for the most positively significant
17 pollutant coefficient; and the maximum lag model is used to provide estimates of potential
18 pollutant-health effects associations.

19 Based on information from Dominici et al. (2002) indicating that the default convergence
20 criteria used in the S-Plus function GAM may not guarantee convergence to the best unbiased
21 estimate (as discussed earlier), only those studies that used other statistical algorithms or which
22 have reported reanalyzed S-Plus GAM results are assessed in the text below. However, given
23 the modest effects of such reanalyses on most study results (i.e., while effect estimates are
24 modified somewhat, the study conclusions remain largely unchanged), Table 8B-2 includes all
25 studies and notes those that originally used the S-Plus GAM algorithm as well as those studies
26 that have since been reanalyzed with more appropriate methods.

27 Of most pertinence here are those newly available studies that evaluate associations
28 between one or another ambient PM metric and respiratory hospital admissions in U.S. or
29 Canadian cities, such as those for PM_{10} mass concentrations summarized in Table 8-19.

30 Among numerous new epidemiologic studies of PM_{10} morbidity, many evaluated relatively
31 high PM_{10} levels. However, some did evaluate associations with PM_{10} concentrations ranging to

TABLE 8-19. SUMMARY OF UNITED STATES PM₁₀ RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels (ug/m ³)	Co-Pollutants Measured	Day Lag	Method	Effect Estimate (95% CL) (% increase per 50 ug/m ³)
Schwartz et al. (1996b)	Respiratory	PM ₁₀ = 43	SO ₃	—	Poisson GLM	5.8 (0.5, 11.4)
Samet et al. (2000a,b)* Reanalysis by Zanobetti and Schwartz (2003b)	COPD	PM ₁₀ = 33	SO ₂ , O ₃ , NO ₂ , CO	1	Default GAM	7.4 (5.1, 9.8)
					Default GAM	7.5 (5.3, 9.8)
				0-1	Default GAM	9.4 (5.9, 12.9)
				0-1	Strict GAM	8.8 (4.8, 13.0)
				0-1	NS GLM	6.8 (2.8, 10.8)
			0-1	PS GLM	8.0 (4.3, 11.9)	
Lippmann et al. (2000)* Reanalysis by Ito (2003)	COPD	PM ₁₀ = 45.4	SO ₂ , O ₃ , NO ₂ , CO, H ⁺	3798	Default GAM	No Co Poll: 9.6 (-5.3, 26.8)
				8	Default GAM	Co Poll: 1.0 (-15, 20)
				3	Default GAM	No Co Poll: 9.6 (-5.3, 26.8)
					Strict GAM	No Co Poll: 6.5 (-7.8, 23.0)
				NS GLM	No Co Poll: 4.6 (-9.4, 20.8)	
Moolgavkar (2000c)* Reanalysis by Moolgavkar (2003) Reanalysis by Moolgavkar (2003)	COPD (> 64 yrs) (median)	PM ₁₀ = 35, Chicago PM ₁₀ = 44, LA PM ₁₀ = 41, Phoenix PM ₁₀ = 44, LA	— — — CO	3799	Default GAM: 30df	2.4 (-0.2, 5.11)
				0	Default GAM: 30df	6.1 (1.1, 11.3)
					Default GAM: 30df	6.9 (-4.1, 19.3)
					Default GAM: 30df	0.6 (-5.1, 6.7)
						(two poll. model)
				0	Strict GAM: 100df	3.24 (.031, 6.24)
				3799	Strict GAM: 30df	7.78 (4.32-10.51)
0	Strict GAM: 100df	5.52 (2.53-8.59)				
	NS GLM: 100df	5.00 (1.22, 8.91)				
Samet et al. (2000a,b)* Reanalysis by Zanobetti and Schwartz (2003a)	Pneumonia	PM ₁₀ = 33	SO ₂ , O ₃ , NO ₂ , CO	1	Default GAM	8.1 (6.5, 9.7)
					Default GAM	6.7 (5.3, 8.2)
				0-1	Default GAM	9.9 (7.4, 12.4)
				0-1	Strict GAM	8.8 (5.9, 11.8)
				0-1	NS GLM	2.9 (0.2, 5.6)
			0-1	PS GLM	6.3 (2.5, 10.3)	
Lippmann et al. (2000) Reanalysis by Ito (2003)	Pneumonia	PM ₁₀ = 45.4	SO ₂ , O ₃ , NO ₂ , CO, H ⁺	3798	Default GAM	No Co Poll: 21.4 (8.2, 36.3)
				8	Default GAM	Co Poll: 24 (8.2, 43)
				3798	Default GAM	No Co Poll: 21.5 (8.3, 36)
	Strict GAM	No Co-Poll: 18.1 (5.3, 32.5)				
	NS GLM	No Co-Poll: 18.6 (5.6, 33.1)				
Jacobs et al. (1997)	Asthma	PM ₁₀ = 34	O ₃ , CO	—	Poisson GLM	6.11 (CI not reported)
Nauenberg and Basu (1999)	Asthma	PM ₁₀ = 45	O ₃	0	Poisson GLM	16.2 (2.0, 30)
Tolbert et al. (2000b)	Asthma	PM ₁₀ = 39	O ₃ , NO _x	1	GEE	13.2 (1.2, 26.7)
Sheppard et al. (1999)* Reanalysis by Sheppard (2003)	Asthma	PM ₁₀ = 31	CO, O ₃ , SO ₂	1	Default GAM	13.2 (5.5, 22.6)
					NS GLM	10.9 (2.8, 19.6)
					Strict GAM	8.1 (0.1, 16.7)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model

1 rather low levels. Of note is the fact that several investigators have reported associations
2 between acute PM₁₀ exposures and total respiratory-related hospital admissions for numerous
3 U.S. cities with annual mean PM₁₀ concentrations extending to below 50 µg/m³. On this
4 account, the results of the NMMAPS multi-city study (Samet et al., 2000a,b) of PM₁₀ levels and
5 hospital admissions by persons ≥ 65 in 14 U.S. cities are of particular interest. As noted in
6 Table 8-19, this study indicates PM₁₀ effects similar to other cities, but with narrower confidence
7 bands, due to its greater power derived by combining multiple cities in the same analysis. This
8 allows significant associations to be identified, despite the fact that many of the cities considered
9 have relatively small populations and that each had mean PM₁₀ below 50 µg/m³. The cities
10 considered and their respective annual mean/daily maximum PM₁₀ concentrations (in µg/m³) are
11 Birmingham (34.8/124.8); Boulder (24.4/125.0); Canton (28.4/94.8); Chicago (36.4/144.7);
12 Colorado Springs (26.9/147.2); Detroit (36.8/133.6); Minneapolis/St Paul (36.8/133.6);
13 Nashville (31.6/128.0); New Haven (29.3/95.4); Pittsburgh (36.0/139.3); Provo/Orem
14 (38.9/241.0); Seattle (31.0/145.9); Spokane (45.3/605.8); and Youngstown (33.1/104.0).

15 Table 8-20 also shows results of reanalyzing a number of the models considered in original
16 research with the use of models using more stringent convergence requirements than the original
17 default option. These reanalyses (Zanobetti and Schwartz, 2003a) show that the effect estimates
18 decline somewhat, but that the basic direction of effect and conclusions about the significance of
19 the PM effect on hospital admissions remained unchanged. In their reanalyses, Zanobetti and
20 Schwartz, (2003a) also considered spline models that are thought to better estimate confidence
21 intervals around pollutant effect estimates than the original GAM analyses. With the spline
22 models, confidence intervals usually increased over the original GAM model and the coefficients
23 also decreased somewhat (similar to GAM with more stringent convergence criteria). As for
24 possible co-pollutant confounding, it was reported that “In our previous studies we did not find
25 confounding due to other pollutants. These results are confirmed in this reanalysis by the meta-
26 regression analyses.” Overall, the authors concluded that “the general result is that the
27 association of PM₁₀ with hospital admissions remains and in most cases is little changed.”

28 Janssen et al. (2002) did further analyses for the Samet et al. (2000a,b) 14-city data set
29 examining associations for variable prevalence in air-conditioning (AC) and/or contributions of
30 different sources to total PM₁₀. For COPD and pneumonia, the associations were less
31 significant, but the pattern of association was similar to that for CVD. The Zanobetti and

TABLE 8-20. PERCENT INCREASE IN HOSPITAL ADMISSIONS PER 10- $\mu\text{g}/\text{m}^3$ INCREASE IN PM_{10} IN 14 U.S. CITIES (ORIGINAL AND REANALYZED RESULTS)

Constrained lag models (Fixed Effect Estimates)	% Increase	CVD (95% CI)	% Increase	COPD (95% CI)	% Increase	Pneumonia (95% CI)
Original One day mean (lag 0)	1.07	(0.93, 1.22)	1.44	(1.00, 1.89)	1.57	(1.27, 1.87)
Original Previous day mean	0.68	(0.54, 0.81)	1.46	(1.03, 1.88)	1.31	(1.03, 1.58)
Original Two day mean (for lag 0 and 1)	1.17	(1.01, 1.33)	1.98	(1.49, 2.47)	1.98	(1.65, 2.31)
Reanalyzed Two day mean (for lag 0 and 1)	0.99	(0.79, 1.19)	1.71	(0.95, 2.48)	1.98	(1.65, 2.31)
Original $\text{PM}_{10} < 50 \mu\text{g}/\text{m}^3$ (two day mean)	1.47	(1.18, 1.76)	2.63	(1.71, 3.55)	2.84	(2.21, 3.48)
Reanalyzed PM_{10} $< 50 \mu\text{g}/\text{m}^3$ (two day mean)	1.32	(0.77, 1.87)	2.21	(1.02, 3.41)	1.06	(0.06, 2.07)
Original Quadratic distributed lag	1.18	(0.96, 1.39)	2.49	(1.78, 3.20)	1.68	(1.25, 2.11)
Reanalyzed Quadratic distributed lag	1.09	(0.81, 1.38)	2.53	(1.20, 3.88)	1.47	(0.86, 2.09)
Unconstrained distributed lag						
Fixed effects estimate	1.19	(0.97, 1.41)	2.45	(1.75, 3.17)	1.9	(1.46, 2.34)
Original Random effects estimate	1.07	(0.67, 1.46)	2.88	(0.19, 5.64)	2.07	(0.94, 3.22)
Reanalyzed Random effects estimate	1.12	(0.84, 1.40)	2.53	(1.21, 3.87)	2.07	(0.94, 3.22)

Source: Samet et al. (2000a,b) and Zanobetti and Schwartz (2003a) reanalyses.

1 Schwartz (2003b) reanalyses also examined these results, and they stated that “We still found a
2 decreased PM_{10} effect with increasing percentage of home with central AC.”

3 Moolgavkar (2003) also reanalyzed his earlier GAM analyses of hospital admissions for
4 chronic obstructive pulmonary disease (Moolgavkar, 2000c) in Los Angeles (Los Angeles
5 County) and Chicago (Cook County). In his original publication, Moolgavkar found ~5.0%
6 excess risk for COPD hospital admissions among the elderly (64+ yr) in Los Angeles to be
7 significantly related to both $\text{PM}_{2.5}$ and $\text{PM}_{10-2.5}$ in one pollutant models; but the magnitudes of the
8 risk estimates dropped by more than half to non-statistically significant levels in two-pollutant

1 models including CO. However, unlike the meta-regression approach to the multiple pollutant
2 issue used by Zanobetti and Schwartz (2003a), simultaneous regression of moderately to highly
3 correlated pollutants can lead to biased pollutant coefficients and commonly results in
4 diminished effect estimates for some or all of the pollutants considered. In the same study,
5 similar magnitudes of excess risk (i.e., in the range of ca. 4 to 7%) were found in one-pollutant
6 models to be associated with PM_{2.5} or PM_{10-2.5} for other age groups (0-19 yr; 20-64 yr) in Los
7 Angeles, as well.

8 In his reanalyses of these GAM results using the more stringent convergence criteria,
9 Moolgavkar (2003) combined all three Los Angeles age groups into one analysis, providing
10 greater power, but also complicating before/after comparisons as to the actual effect of using the
11 more stringent convergence criteria on the results. In the Cook County analyses, the author
12 changed other model parameters (i.e., the number of degrees of freedom in the model smooths)
13 at the same time as implementing more stringent convergence criteria; so direct before/after
14 comparisons are not possible for Moolgavkar's (2003) Chicago analyses. Moolgavkar noted that
15 "changes in the convergence criteria and the use of GLM instead of GAM can, but does not
16 always, have substantial impact on the results of the analyses and their interpretation." He also
17 concluded: "Given that different analytic strategies can make substantial differences to the
18 estimates of effects of individual pollutants I do not believe that these numerical estimates are
19 too meaningful. Patterns of association appear to be robust, however. For example, in Los
20 Angeles, with the exception of COPD admissions with which NO₂ appears to show the most
21 robust association, it is clear that CO is the best single index of air pollution associations with
22 health end points, far better than the mass concentration of either PM₁₀ or of PM_{2.5}. In Cook
23 County the results are not so clear-cut, however, any one of the gases is at least as good an index
24 of air pollution effects on human health as is PM₁₀."

25 Tolbert et al. (2000b) used generalized estimating equations (GEE), logistic regression, and
26 Bayesian models to evaluate associations between emergency department visits for asthma (by
27 those < 17 yrs old) in Atlanta during the summers of 1993 – 1995 (~6000 visits for asthma out of
28 ~130,000 total visits) and several air pollution variables (PM₁₀, O₃, total oxides of nitrogen).
29 Logistic regression models controlling for temporal and demographic variables gave statistically
30 significant (p < 0.05) lag 1 day relative risk estimates of 1.04 per 15 µg/m³ 24-h PM₁₀ increment
31 and 1.04 per 20 ppb increase in maximum 8-h O₃ levels. In multipollutant models including

1 both PM₁₀ and O₃, the terms for each became non-significant due to high collinearity of the two
2 variables ($r^2 = 0.75$). The authors interpreted their findings as suggesting positive associations
3 between pediatric asthma visits and both PM₁₀ and O₃. The PM₁₀ effects appeared to be stronger
4 for concentrations $> 20 \mu\text{g}/\text{m}^3$ than below that 24-h value.

5 Other U.S. studies finding associations of respiratory-related hospital admissions or
6 medical visits with PM₁₀ levels extending below $50 \mu\text{g}/\text{m}^3$ include: Schwartz (1994) in
7 Minneapolis-St. Paul, Minnesota; Schwartz et al. (1996b) in Cleveland; Sheppard et al. (1999)
8 in Seattle; Linn et al. (2000) in Los Angeles; and Nauenberg and Basu (1999) in Los Angeles;
9 in Minneapolis-St. Paul, MN, but not in Birmingham, AL. The excess risk estimates most
10 consistently fall in the range of 5 to 25% per $50 \mu\text{g}/\text{m}^3$ PM₁₀ increment, with those for asthma
11 visits and hospital admissions often being higher than those for COPD and pneumonia
12 admissions.

13 Similar associations between increased respiratory related hospital admissions/medical
14 visits and low short-term PM₁₀ levels were also reported by various investigators for several
15 non-U.S. cities. Wordley et al. (1997), for example, reported positive and significant
16 associations between PM₁₀ (mean = $25.6 \mu\text{g}/\text{m}^3$, max. = $131 \mu\text{g}/\text{m}^3$) and respiratory admissions
17 in Birmingham, UK using multivariate linear regression methods; and Atkinson et al. (1999a),
18 using Poisson modeling, reported significant increases in hospital admissions for respiratory
19 disease to be associated with PM₁₀ (mean = $28.5 \mu\text{g}/\text{m}^3$) in London, UK. Hagen et al. (2000) and
20 Prescott et al. (1998) also found positive but non-significant associations of hospital admissions
21 and, PM₁₀ levels in Drammen, Norway (mean = $16.8 \mu\text{g}/\text{m}^3$) and Edinburgh, Scotland (mean =
22 $20.7 \mu\text{g}/\text{m}^3$). Admissions in Drammen considered relatively small populations, limiting
23 statistical power in this study. Petroeschovsky et al. (2001) examined associations between
24 outdoor air pollution and hospital admissions in Brisbane, Australia during 1987-1994 using a
25 light scattering index (BSP) for fine PM. The levels of PM are quite low in this city, relative to
26 most U.S. cities, but BSP was positively and significantly associated with total respiratory
27 admissions, but not for asthma.

8.3.2.3.1 *Particulate Matter Mass Fractions and Composition Comparisons*

While PM₁₀ mass has generally been the metric most often used as the particle pollution index in the U.S. and Canada, some new studies have examined the relative roles of various PM₁₀ mass fractions (e.g., PM_{2.5} and PM_{10-2.5}) and chemical constituents (such as SO₄⁻²) contributing to PM-respiratory hospital admissions associations. Several new studies (from among those summarized in Tables 8-21 and 8-22, respectively) report significant associations of increased respiratory-cause medical visits and/or hospital admissions with ambient PM_{2.5} and/or PM_{10-2.5} ranging to quite low concentrations. These include the Lippmann et al. (2000) study in Detroit, where all PM metrics (PM₁₀, PM_{2.5}, PM_{10-2.5}, H⁺) were positively related to pneumonia and COPD admissions among the elderly (aged 65+ yr) in single pollutant models, with their RR values for pneumonia generally remaining little changed (but with broader confidence intervals) in multipollutant models including one or more gaseous pollutant (e.g., CO, O₃, NO₂, SO₂). However, for COPD admissions, the effect estimates were reduced and became non-significant in multipollutant models including gaseous copollutants. Excess risks for pneumonia admissions in the one pollutant model using default GAM were 13% (CI: 3.7, 22) and 12% (CI: -0.6, 24) per 25 µg/m³ of PM_{2.5} and PM_{10-2.5}, respectively; those for COPD admissions were 5.5% (CI: -4.7, 17) and 9.3% (CI: -4.2, 25) per 25 µg/m³ PM_{2.5} and PM_{10-2.5}, respectively.

Lippmann et al. (2000) reported weaker associations with sulfate and acidic components of PM_{2.5} than with PM_{2.5} mass overall, but the acidity levels during this study were very low, being below detection on most study days. In contrast, past studies of sulfates and aerosol acidity associations with respiratory hospital admissions have found stronger sulfate associations when the acidity of those aerosols was higher (e.g., Thurston et al, 1994). As noted by Lippman et al.(2000), “a notable difference between the data of Thurston and colleagues from Toronto and our data is the H⁺ levels: the H⁺ levels in Toronto were 21.4, 12.6, and 52.3 nmol/m³ for the summers of 1986, 1987, and 1988, respectively, whereas in our study, the H⁺ level averaged only 8.8 nmol/m³.”

In order to evaluate the potential influence of the Generalized Additive Model (GAM) convergence specification on the results of the original Detroit data analysis, Ito (2003) re-examined associations between PM components and daily mortality/morbidity by using more stringent GAM convergence criteria and by applying Generalized Linear Models (GLM) that

TABLE 8-21. SUMMARY OF UNITED STATES PM_{2.5} RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels ug/m ³	Co-Pollutants Measured	Lag	Method	Effect Estimate (95% CL) (% increase per 25 ug/m ³)
Lippmann et al. (2000)	COPD	PM _{2.5} = 18	SO ₂ , O ₃ , NO ₂ , CO, H+	3 3	Default GAM Default GAM	No Co Poll: 5.5 (-4.7, 16.8) Co Poll: 2.8 (-9.2, 16)
Reanalysis by Ito (2003)	COPD				Default GAM Strict GAM NS GLM	No Co Poll: 5.5 (-4.7, 16.8) No Co Poll: 3.0(-6.9, 13.9) No Co Poll: 0.3(-9.3, 10.9)
Moolgavkar (2000c)*	COPD (> 64 yrs) (median)	PM _{2.5} = 22, LA PM _{2.5} = 22, LA	— CO	2 2	Default GAM Default GAM	5.1 (0.9, 9.4) 2.0 (-2.9, 7.1) Two poll. model
Reanalysis by Moolgavkar (2003)	COPD (all ages)			379 90	Strict GAM: 30df Strict GAM: 100df NS GLM: 100df	4.69 (2.06, 7.38) 2.87 (0.53, 5.27) 2.59 (-0.29, 5.56)
Lippmann et al. (2000)	Pneumonia	PM _{2.5} = 18	SO ₂ , O ₃ , NO ₂ , CO, H ⁺	11	Default GAM Default GAM	No Co-Poll: 12.5 (3.7, 22.1) Co Poll: 12 (1.7, 23)
Reanalysis by Ito (2003)	Pneumonia				Default GAM Strict GAM NS GLM	No Co-Poll: 12.5 (3.7, 22.1) No Co-Poll: 10.5 (1.8, 19.8) No Co-Poll: 10.1 (1.5, 19.5)
Sheppard et al. (1999)*	Asthma	PM _{2.5} = 16.7	CO, O ₃ , SO ₂	1	Default GAM	8.7 (3.3, 14.3)
Reanalysis by Sheppard (2003)			CO		Default GAM Strict GAM NS GLM Strict GAM NS GLM	No Co-Poll: 8.7 (3.3, 14.3) No Co-Poll: 8.7 (3.2,14.4) No Co-Poll: 6.5 (1.1,12.0) With Co-poll: 6.5 (2.1, 10.9) With Co-poll: 6.5 (2.1, 10.9)
Freidman et al. (2001)	Asthma	PM _{2.5} = 36.7-30.8	O ₃	3 d. cum	Poisson GEE	1.4 (0.80-2.48)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model.

1 approximated the original GAM models. The reanalysis of GAM Poisson models used more
2 stringent convergence criteria, as suggested by Dominici et al. (2002): the convergence
3 precision (epsilon) was set to 10-14, and the maximum iteration was set to 1000 for both the
4 local scoring and back-fitting algorithms. The GLM model specification approximated the
5 original GAM models. Natural splines were used for smoothing terms. To model time trend, the
6 same degrees of freedom as the smoothing splines in the GAM models were used, with the
7 default placement of knots. For weather models, to approximate LOESS smoothing with a span

TABLE 8-22. SUMMARY OF UNITED STATES PM_{10-2.5} RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels ug/m ³	Co-Pollutants Measured	Lag	Method	Effect Estimates (95% CL) (% increase per 25 ug/m ³)
Moolgavkar (2000c)*	COPD		—	3	Default GAM	5.1% (-0.4, 10.9)
Lippmann et al. (2000)*	COPD	PM _{10-2.5} = 12	SO ₂ , O ₃ , NO ₂ , CO, H ⁺	379 88	Default GAM Default GAM	No Co-Poll: 9.3 (-4.2, 24.7) Co-Poll: 0.3 (-14, 18)
Reanalysis by Ito (2003)					Default GAM Strict GAM NS GLM	No Co-Poll: 9.3 (-4.2, 24.7) No Co-Poll: 8.7 (-4.8, 24.0) No Co-Poll: 10.8 (-3.1, 26.5)
Lippmann et al. (2000)*	Pneumonia	PM _{10-2.5} = 12	SO ₂ , O ₃ , NO ₂ , CO, H ⁺	379 88	Default GAM Default GAM	No Co-Poll: 11.9 (-0.6, 24.4) Co-Poll: 13.9 (0.0, 29.6)
Reanalysis by Ito (2003)				379 88	Default GAM Strict GAM NS GLM	No Co-Poll: 11.9 (-0.6, 24.4) No Co-Poll: 9.9 (-0.1, 22.0) No Co-Poll: 11.2 (-0.02, 23.6)
Sheppard et al. (1999)*	Asthma	PM _{10-2.5} = 16.2	CO, O ₃ , SO ₂	1	Default GAM	11.1 (2.8, 20.1)
Reanalysis by Sheppard (2003)				379 88	Strict GAM NS GLM	5.5 (-2.7, 11.1) 5.5 (0, 14.0)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model.

1 of 0.5 in the GAM model, natural splines with degrees of freedom were used. Generally, the
2 GAM models with stringent convergence criteria and GLM models resulted in somewhat smaller
3 estimated relative risks than those reported in the original study, e.g., for pneumonia admissions
4 in Table 8-23. It was found that the reductions in the estimated relative risks were not different
5 across the PM indices. Thus, conclusions of the original study about the relative roles of PM
6 components by size and chemical characteristics remained unaffected.

7 Lumley and Heagerty (1999) illustrate the effect of reliable variance estimation on data
8 from hospital admissions for respiratory disease on King County, WA for eight years (1987-94),
9 together with air pollution and weather information, using estimating equations and weighted
10 empirical variance estimators. However, their weather controls were relatively crude (i.e.,
11 seasonal dummy variables and linear temperature terms). This study is notable for having
12 compared sub-micron PM (PM_{1.0}) versus coarse PM_{10-1.0} and for finding significant hospital
13 admission associations only with PM_{1.0}. This may suggest that the PM_{2.5} versus PM₁₀ separation

TABLE 8-23. INTERCOMPARISON OF DETROIT PNEUMONIA HOSPITAL ADMISSION RELATIVE RISKS (\pm 95% CI below) OF PM INDICES (per 5th-to-95th percentile pollutant increment) FOR VARIOUS MODEL SPECIFICATIONS.*

	Original GAM (default)	GAM (stringent)	GLM
PM _{2.5} (1)	1.185 (1.053, 1.332)	1.154 (1.027, 1.298)	1.149 (1.022, 1.292)
PM _{10-2.5} (1)	1.114 (1.006, 1.233)	1.095 (0.990, 1.211)	1.107 (1.00, 1.226)
PM ₁₀ (1)	1.219 (1.084, 1.372)	1.185 (1.054, 1.332)	1.190 (1.057, 1.338)
H ⁺ (3)	1.060 (1.005, 1.118)	1.049 (0.994, 1.107)	1.049 (0.994, 1.107)
SO ₄ ⁻ (1)	1.156 (1.050, 1.273)	1.128 (1.025, 1.242)	1.123 (1.020, 1.235)

*The selected lag is indicated in parenthesis next to the pollutant name.

Source: Ito (2003).

1 may not always be sufficient to differentiate submicron fine particle versus coarse-particle
2 toxicities.

3 Asthma hospital admission studies in various U.S. communities provide additional
4 important new data. Of particular note is a study by Sheppard et al. (1999) which evaluated
5 relationships between measured ambient pollutants (PM₁₀, PM_{2.5}, PM_{10-2.5}, SO₂, O₃, and CO) and
6 non-elderly adult (< 65 years of age) hospital admissions for asthma in Seattle, WA. PM and
7 CO were found to be jointly associated with asthma admissions. The authors noted “... we
8 observed unexpected associations for CO that dominated the PM effects. Nevertheless, although
9 there is substantial literature on the effects of CO on the cardiovascular system, there is no
10 evidence for an effect on the underlying physiology of asthma. CO may be an important
11 environmental indicator of incomplete combustion, particularly from mobile sources.”

12 An estimated 4 to 5% increase in the rate of asthma hospital admissions (lagged 1 day) was
13 reported to be associated with interquartile range changes in PM indices (19 $\mu\text{g}/\text{m}^3$ for PM₁₀,
14 11.8 $\mu\text{g}/\text{m}^3$ for PM_{2.5}, and 9.3 $\mu\text{g}/\text{m}^3$ for PM_{10-2.5}), equivalent to excess risk rates as follows: 13%
15 (CI: 0.5-23) per 50 $\mu\text{g}/\text{m}^3$ for PM₁₀; 9% (CI: 3-14) per 25 $\mu\text{g}/\text{m}^3$ PM_{2.5}; 11% (CI: 3-20) per

1 25 $\mu\text{g}/\text{m}^3$ $\text{PM}_{10-2.5}$. Also of note for the same region are analyses by the same research team
2 using similar methods (Norris et al., 1999) which showed associations of low levels of $\text{PM}_{2.5}$
3 (mean = 12 $\mu\text{g}/\text{m}^3$) with markedly increased asthma ED, i.e., excess risk = 44.5% (CI: 21.7-71.4)
4 per 25 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$.

5 Sheppard (2003) recently conducted a reanalysis of their nonelderly hospital admissions
6 data for asthma in Seattle, WA, to evaluate the effect of the fitting procedure on their previously
7 published analyses. As shown in Figure 8-11, the effect estimates were slightly smaller when
8 more stringent convergence criteria were used with GAM, and there was an additional small
9 reduction in the estimates when GLM with natural splines were used instead. The average
10 reduction in effect estimate between the default and stringent convergence criteria for $\text{PM}_{2.5}$,
11 PM_{10} , and $\text{PM}_{10-2.5}$ (coarse) mass averaged 10.7%. The coefficients remained statistically
12 significant for both $\text{PM}_{2.5}$ and PM_{10} but not for coarse mass. Confidence intervals were slightly
13 wider for the GLM model fit. Sheppard concluded that, "Overall the results did not change
14 meaningfully. There were small reductions in estimates using the alternate fitting procedures.
15 I also found that the effect of single imputation (i.e., not adjusting for replacing missing
16 exposure data with an estimate of its expected value) was to bias the effect estimates slightly
17 upward. In this data set this bias is of the same order as the bias from using too liberal
18 convergence criteria in the generalized additive model."

19 Moolgavkar (2003) also conducted reanalyses of respiratory-related hospital admissions,
20 but for COPD data for all ages in Los Angeles. Using GAM with strict convergence criteria and
21 30 degrees of freedom (df), an excess risk estimate of 4.7% (CI: 2.1, 7.4) was obtained per
22 25 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ increment. The notable effect of increasing degrees of freedom on modeling
23 results is well illustrated by the excess risk estimate dropping to 2.9% (CI: 0.5, 5.3) with strict
24 GAM and 100 df or 2.6% (CI: -0.3, 5.6) with NS GLM 100 df.

25 Burnett et al. (1997a) evaluated the role that the ambient air pollution mix, comprised of
26 gaseous pollutants and PM indexed by various physical and chemical measures, plays in
27 exacerbating daily admissions to hospitals for cardiac diseases and for respiratory diseases
28 (tracheobronchitis, chronic obstructive lung disease, asthma, and pneumonia). They employed
29 daily measures of $\text{PM}_{2.5}$ and $\text{PM}_{10-2.5}$, aerosol chemistry (sulfates and H^+), and gaseous pollutants
30 (O_3 , NO_2 , SO_2 , CO) collected in Toronto, Ontario, Canada, during the summers of 1992, 1993,
31 and 1994. Positive associations were observed for all ambient air pollutants for both respiratory

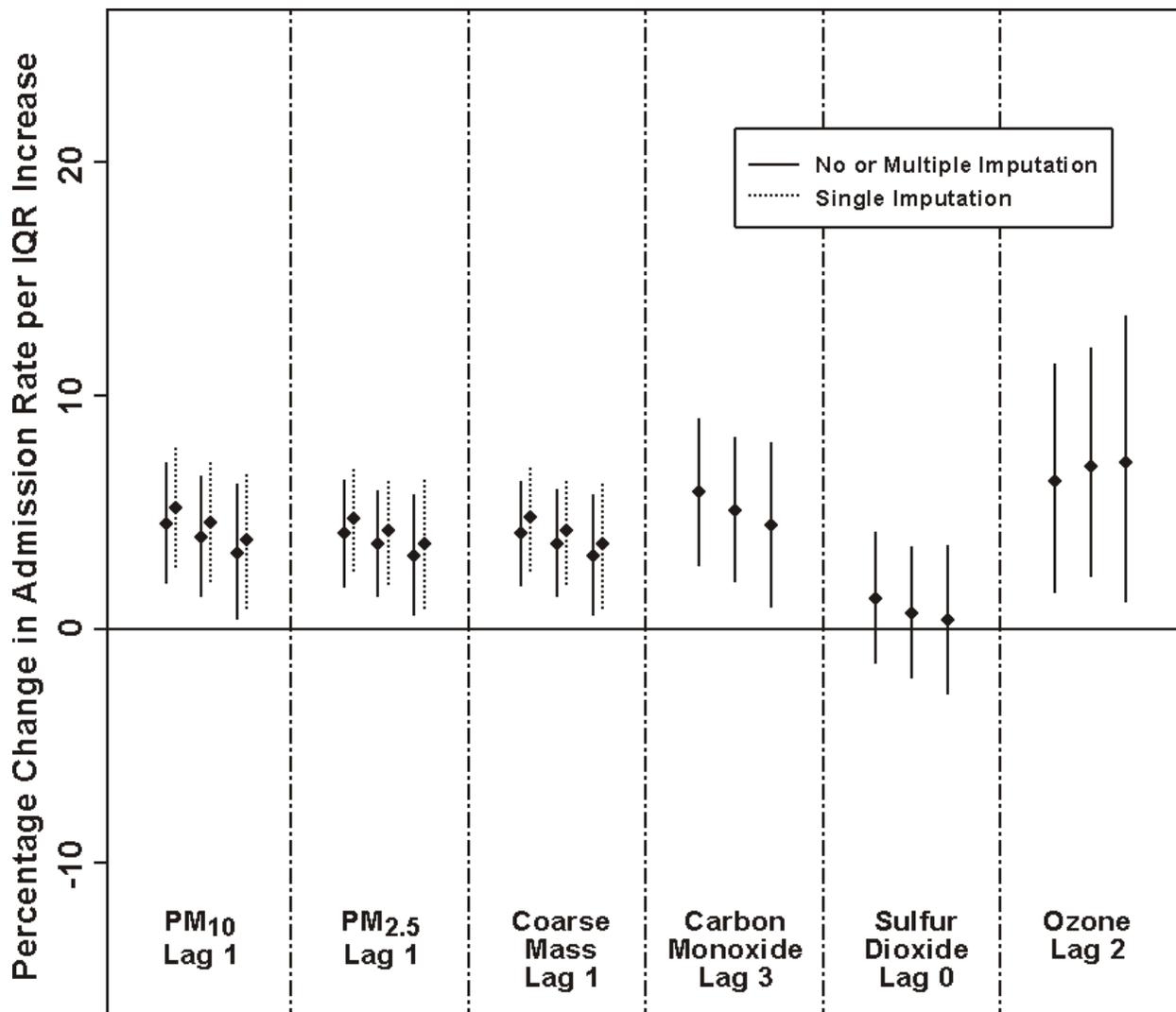


Figure 8-11. Percent change in hospital admission rates and 95% CIs for an IQR increase in pollutants from single-pollutant models for asthma. Poisson regression models are adjusted for time trends (64-df spline), day-of-week, and temperature (4-df spline). The IQR for each pollutant equals: 19 $\mu\text{g}/\text{m}^3$ for PM_{10} , 11.8 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 9.3 $\mu\text{g}/\text{m}^3$ for coarse PM, 20 ppb for O_3 , 4.9 ppb for SO_2 , and 924 ppb for CO. Triplets of estimates for each pollutant are for the original GAM analysis using smoothing splines, the revised GAM analysis with stricter convergence criteria, and the GLM analysis with natural splines. For pollutants that required imputation (i.e., estimation of missing value) estimates ignoring (single imputation) or adjusting for (multiple imputation) the imputation are shown.

Source: Sheppard (2003).

1 and cardiac diseases. Ozone was the most consistently significant pollutant and least sensitive to
2 adjustment for other gaseous and particulate measures. The PM associations with respiratory
3 hospital admissions were significant for: PM_{10} (RR = 1.11 for $50 \mu\text{g}/\text{m}^3$; CI: 1.05, 1.17); $PM_{2.5}$
4 (fine) mass (RR = 1.09 for $25 \mu\text{g}/\text{m}^3$; CI: 1.03, 1.14); $PM_{10-2.5}$ (coarse) mass (RR = 1.13 for
5 $25 \mu\text{g}/\text{m}^3$; CI: 1.05, 1.20); sulfate levels (RR = 1.11 for $155 \text{ nmoles}/\text{m}^3 = 15 \mu\text{g}/\text{m}^3$;
6 CI: 1.06, 1.17); and H^+ (RR = 1.40 for $75 \text{ nmoles}/\text{m}^3 = 3.6 \mu\text{g}/\text{m}^3$, as H_2SO_4 ; CI: 1.15, 1.70).
7 After inclusion of O_3 in the model, the associations with the respiratory hospital admissions
8 remained significant for: PM_{10} (RR = 1.10, CI: 1.04, 1.16); fine mass (RR = 1.06;
9 CI: 1.01, 1.12); coarse mass (RR = 1.11; CI: 1.04, 1.19); sulfate levels (RR = 1.06; CI: 1.0,
10 1.12); and H^+ (RR = 1.25; CI: 1.03, 1.53), using the same increments. Of the PM metrics
11 considered here, H^+ yielded the highest RR estimate. Regression models that included all
12 recorded pollutant simultaneously (with high intercorrelations among the pollutants) were also
13 presented.

14 A recent study by Lin et al. (2002) used both case-crossover and time-series analyses to
15 assess the associations between size-fractionated particulate matter and asthma hospitalization
16 among children 6-12 years old living in Toronto between 1981 and 1993. The authors used
17 exposures averaged over periods varying from 1 to 7 days to assess the effects of particulate
18 matter on asthma hospitalization. Estimates of the relative risk of asthma hospitalization were
19 adjusted for daily weather conditions (maximum and minimum temperatures, and average
20 relative humidity) for an incremental exposure corresponding to the interquartile range in
21 particulate matter. However, direct measurements of PM components were available only every
22 sixth day in this data set, and 5 out of every 6 PM data points in the analysis were based on
23 estimated $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10} data, weakening confidence in these input data. Time-series
24 plots of the $PM_{2.5-10}$ data showed much stronger seasonality in the estimated coarse PM data than
25 in the estimated fine PM mass data. Seasonality was controlled for in the time-series analyses
26 using a 3 month span smooth of the data, rather than the more commonly employed one month
27 or less span. Thus, residual seasonality may have been a factor in this study's $PM_{2.5-10}$ results.
28 Both bidirectional case-crossover and time-series analyses revealed that coarse particulate matter
29 ($PM_{10-2.5}$) averaged over 5-6 days was significantly associated with asthma hospitalization in
30 both males and females. The magnitude of this effect appeared to increase with increasing
31 number of days of exposure averaging for most models, with the relative risk estimates

1 stabilizing at about 6 days. Using a bidirectional case-crossover analysis, the estimated relative
2 risks were 1.14 (CI: 1.02, 1.28) for males and 1.18 (CI: 1.02, 1.36) for females, for an increment
3 of 8.4 $\mu\text{g}/\text{m}^3$ in 6-day averages of $\text{PM}_{10-2.5}$. The corresponding relative risk estimates were 1.10
4 and 1.18, respectively, from the time-series analysis. The effect of $\text{PM}_{10-2.5}$ remained positive
5 after adjustment for the effects of the gaseous pollutants carbon monoxide (CO), nitrogen
6 dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). They did not find significant effects of fine
7 particulate matter ($\text{PM}_{2.5}$) or of thoracic particulate matter (PM_{10}) on asthma hospitalizations,
8 except in the unidirectional case-cross-over analyses. Seasonal-specific results were not
9 presented. The paper's discussion ignores previous results by Thurston et al. (1994), which
10 provided results during summers in the same time range (1986-1988) that are in direct conflict
11 with respect to the significance of $\text{PM}_{2.5}$. That study used daily direct measurements of size
12 fractionated PM in their analysis of those three summers, finding significant effects for
13 summertime $\text{PM}_{2.5}$. Seasonality of data analysis may therefore be a factor in the differences
14 between these two Toronto hospital admissions studies regarding the adverse health effects of
15 fine PM. Overall, this new study suggests that coarse particle mass can also be a risk factor in
16 children's asthma hospital admissions.

17 There have also been numerous new time-series studies examining associations between
18 air pollution and respiratory-related hospital admissions in Europe, as summarized in
19 Appendix 8B, Table 8B-2, but most of these studies relied primarily on black smoke (BS) as
20 their PM metric. BS is a particle reflectance measure that provides an indicator of PM blackness
21 and is highly correlated with airborne carbonaceous particle concentrations (Bailey and Clayton,
22 1982). In the U.S., Coefficient of Haze (CoH) is a metric of particle transmittance that similarly
23 most directly represents a metric of particle blackness and ambient elemental carbon levels
24 (Wolff et al., 1983) and has been found to be highly correlated with BS ($r = 0.9$; Lee et al.,
25 1972). However, the relationship between airborne carbon and total mass of overall aerosol
26 (PM) composition varies over time and from locality to locality, so the BS-mass ratio is less
27 reliable than the BS-carbon relationship (Bailey and Clayton, 1982). This means that the BS-
28 mass relationship is likely to be very different between Europe and the U.S., largely due to
29 differences in local PM source characteristics (e.g., percentages of diesel powered motor
30 vehicles). Therefore, while these European BS-health effects studies may be of qualitative

1 interest for evaluating the PM-health effects associations, they are not as useful for quantitative
2 assessment of PM effects relevant to the U.S.

3 Probably the most extensive and useful recent European air pollution health effects
4 analyses have been conducted as part of the APHEA multi-city study, which evaluated
5 15 European cities from 10 different countries with a total population of over 25 million.
6 All studies used a standardized data collection and analysis approach, which included
7 consideration of the same suite of air pollutants (BS, SO₂, NO₂, SO₂, and O₃) and the use of time-
8 series regression addressing seasonal and other long-term patterns; influenza epidemics; day of
9 the week; holidays; weather; and autocorrelation (Katsouyanni et al., 1996). The general
10 coherence of the APHEA results with other results gained under different conditions strengthens
11 the argument for causality in the air pollution-health effects association. In earlier studies, the
12 general use of the less comparable suspended particle (SPM) measures and BS as PM indicators
13 in some of the APHEA locations and analyses lessens the quantitative usefulness of such
14 analyses in evaluating associations between PM and health effects most pertinent to the U.S.
15 situation. However, Atkinson et al. (2001) report results of PM₁₀ analyses in a study of eight
16 APHEA cities.

17 As for other single-city European studies of potential interest here, Hagan et al. (2000)
18 compared the association of PM₁₀ and co-pollutants with hospital admissions for respiratory
19 causes in Drammen, Norway during 1994-1997. Respiratory admissions averaged only 2.2 per
20 day; so, the power of this analysis is weaker than studies looking at larger populations and longer
21 time periods. The NMMAPS modeling approach was employed. While a significant association
22 was found for PM₁₀ as a single pollutant, it became non-significant in multiple pollutant models.
23 In two pollutant models, the associations and effect size of pollutants were generally diminished,
24 and when all eight pollutants were considered in the model, all pollutants became
25 non-significant. These results are typical of the problems of analyzing and interpreting the
26 coefficients of multiple pollutant models when the pollutants are even moderately inter-
27 correlated over time. A unique aspect of this work was that benzene was considered in this
28 community to be strongly affected by traffic pollution. In two pollutant models, benzene was
29 most consistently still associated. The authors conclude that PM is mainly an indicator of air
30 pollution in this city and emissions from vehicles seem most important for health effects.
31 Thompson et al. (2001) report a similar result in Belfast, Northern Ireland, where, after adjusting

1 for multiple pollutants, only the benzene level was independently associated with asthma
 2 emergency department (ED) admissions.

3
 4 **8.3.2.4 Key New Respiratory Medical Visits Studies**

5 As noted above, medical visits include both hospital ED and doctors' office visits. As in
 6 the past, most newly available morbidity studies in Table 8B-3, Appendix 8B and in Table 8-24
 7 below are of ED visits and their associations with air pollution. These studies collectively
 8 confirm the results provided in the 1996 PM AQCD, indicating a positive and generally
 9 statistically significant association between ambient PM levels and increased respiratory-related
 10 hospital visits.

11
 12
TABLE 8-24. SUMMARY OF UNITED STATES PM₁₀, PM_{2.5}, AND PM_{10-2.5} ASTHMA MEDICAL VISIT STUDIES

Reference	Outcome Measures	Mean Levels (µg/m ³)	Co-Pollutants Measured	Lag	Method	Effect Estimate* (95% CL)
<i>PM₁₀</i>						
Choudhury et al. (1997)	Asthma	41.5	Not considered	0	GLM	20.9 (11.8, 30.8)
Lipsett et al. (1997)	Asthma	61.2	NO ₂ , O ₃	2	GLM	34.7 (16, 56.5) at 20 °C
Tolbert et al. (2000b)	Asthma	38.9	O ₃	1	GEE	13.2 (1.2, 26.7)
Tolbert et al. (2000a)**	Asthma	29.1	NO ₂ , O ₃ , CO, SO ₂	0-2	GLM	8.8 (-8.7, 54.4)
<i>PM_{2.5}</i>						
Tolbert et al. (2000a)**	Asthma	19.4	NO ₂ , O ₃ , CO, SO ₂	0-2	GLM	2.3 (-14.8, 22.7)
<i>PM_{10-2.5}</i>						
Tolbert et al. (2000a)**	Asthma	9.39	NO ₂ , O ₃ , CO, SO ₂	0-2	GLM	21.1 (-18.2, 79.3)

* Effect estimates derived from single-pollutant models.

**Preliminary results based on emergency department visit data from 18 of 33 participating hospitals.

1 Of the medical visit and hospital admissions studies since the 1996 PM AQCD, among the
2 most informative are those that evaluate health effects at relatively low PM concentrations. As
3 for U.S. studies, Tolbert et al. (2000b) reported a significant PM₁₀ association with pediatric ED
4 visits in Atlanta where mean PM₁₀ = 39 µg/m³ and maximum PM₁₀ = 105 µg/m³. The Lipsett
5 et al. (1997) study of winter air pollution and asthma emergency visits in Santa Clara Co, CA,
6 may provide insight where one of the principal sources of PM₁₀ is residential wood combustion
7 (RWC). Their results demonstrate an association between PM₁₀ levels and asthma. Also of
8 interest, Delfino et al. (1997a) found significant PM₁₀ and PM_{2.5} associations for respiratory ED
9 visits among older adults in Montreal when mean PM₁₀ = 21.7 µg/m³ and mean PM_{2.5} =
10 12.2 µg/m³. Hajat et al. (1999) also reported significant PM₁₀ associations with asthma doctor's
11 visits for children and young adults in London when mean PM₁₀ = 28.2 µg/m³ and the PM₁₀ 90th
12 percentile was only 46.4 µg/m³. Overall, then, several new medical visits studies indicate
13 PM-health effects associations at lower PM_{2.5} and PM₁₀ levels than those from previous
14 publications.

15 16 **8.3.2.4.1 Scope of Medical Visit Morbidity Effects**

17 Several newer medical visit studies consider a new endpoint for comparison with ED
18 visits: visits in the primary care setting. In particular, key studies showing PM associations for
19 this health outcome include: the study by Hajat et al. (1999) that evaluated the relationship
20 between air pollution in London, UK; and daily General Practice (GP) doctor consultations for
21 asthma and other lower respiratory disease (LRD); the study by Choudhury et al. (1997) of
22 private asthma medical visits in Anchorage, Alaska; and the study by Ostro et al. (1999b) of
23 daily visits by young children to primary care health clinics in Santiago, Chile for upper or lower
24 respiratory symptoms.

25 While limited in number, the above studies collectively provide new insight into the fact
26 that there is a broader scope of morbidity associated with PM air pollution exposure than
27 previously documented. As the authors of the London study note: "There is less information
28 about the effects of air pollution in general practice consultations but, if they do exist, the public
29 health impact could be considerable because of their large numbers." Indeed, the London study
30 of doctors' GP office visits indicates that the effects of air pollution, including PM, can affect
31 many more people than indicated by hospital admissions alone.

1 These new studies also provide indications as to the quantitative nature of medical visits
2 effects, relative to those for hospital admissions. In the London case, comparing the number of
3 admissions from the authors' earlier study (Anderson et al., 1996) with those for GP visits in the
4 1999 study (Hajat et al., 1999) indicates that there are ~24 asthma GP visits for every asthma
5 hospital admission in that city. Also, comparing the PM₁₀ coefficients indicates that the all-ages
6 asthma effect size for the GP visits (although not statistically different) was about 30% larger
7 than that for hospital admissions. Thus, these new studies suggest that looking at only hospital
8 admissions and emergency hospital visit effects may greatly underestimate the overall numbers
9 of respiratory morbidity events due to acute ambient PM exposure.

11 **8.3.2.4.2 Factors Potentially Affecting Respiratory Medical Visit Study Outcomes**

12 Some newly available studies have examined certain factors that might extraneously affect
13 the outcomes of PM-medical visit studies. Stieb et al. (1998a) examined the occurrence of bias
14 and random variability in diagnostic classification of air pollution and daily cardiac or
15 respiratory ED visits, such as for asthma, COPD, respiratory infection, etc. They concluded that
16 there was no evidence of diagnostic bias in relation to daily air pollution levels. Also, Stieb et al.
17 (1998b) reported that for a population of adults visiting an emergency department with
18 cardiorespiratory disease, fixed site sulfate monitors appear to accurately reflect daily variability
19 in average personal exposure to particulate sulfate, whereas acid exposure was not as well
20 represented by fixed site monitors. Another study investigated possible confounding of
21 respiratory visit effects due to pollens and mold spores (Steib et al, 2000). Aeroallergen levels
22 did not influence the results, similar to asthma panel studies described below in Section 8.3.3.
23 In London, Atkinson et al. (1999a) studied the association between the number of daily ED visit
24 for respiratory complaints and measures of outdoor air pollution for PM₁₀, NO₂, SO₂ and CO.
25 They examined different age groups and reported strongest associations for children for visits for
26 asthma, but were unable to separate PM₁₀ and SO₂ effects.

28 **8.3.2.5 Identification of Potential Susceptible Subpopulations**

29 Associations between ambient PM measures and respiratory admissions have been found
30 for all age groups, but older adults and children generally have been indicated by hospital
31 admissions studies to exhibit the most consistent PM-health effects associations. As reported in

1 previous PM AQCDs, numerous studies of older adults (e.g., those 65+ years of age) have
2 related acute PM exposure with an increased incidence of hospital admissions (e.g., see
3 Anderson et al, 1998). However, only a limited number have specifically studied children as a
4 subgroup. Burnett et al. (1994) examined the differences in air pollution-hospital admissions
5 associations as a function of age in Ontario, reporting that the largest percentage increase in
6 admissions was found among infants (neonatal and post-neonatal, one year or less in age).

7 Further efforts have aimed at identifying and quantifying air pollution effects among
8 potentially especially susceptible subpopulations of the general public. Some new studies have
9 further investigated the hypothesis that the elderly are especially affected by air pollution.
10 Zanobetti et al. (2000a) examined PM₁₀ associations with hospital admissions for heart and lung
11 disease in ten U.S. cities, finding an overall association for COPD, pneumonia, and CVD. They
12 found that these results were not significantly modified by poverty rate or minority status in this
13 population of Medicare patients. Ye et al. (2001) examined emergency transports to the hospital.
14 Both PM₁₀ and NO₂ levels were significantly associated with daily hospital transports for angina,
15 cardiac insufficiency, myocardial infarction, acute and chronic bronchitis, and pneumonia. The
16 pollutant effect sizes were generally found to be greater in men than in women, except those for
17 angina and acute bronchitis, which were the same across genders. Thus, in these various studies,
18 cardiopulmonary hospital visits and admissions among the elderly were seen to be consistently
19 associated with PM levels across numerous locales in the U.S. and abroad, generally without
20 regard to race or income; but sex was sometimes an effect modifier.

21 Several new studies of children's morbidity also support the indication of air pollution
22 effects among children. Pless-Mulloli et al. (2000) evaluated children's respiratory health and
23 air pollution near opencast coal mining sites in a cohort of nearly 5,000 children aged 1-11 in
24 England. Mean PM levels were not high (mean < 20 µg/m³ PM₁₀), but statistically significant
25 PM₁₀ associations were found with respiratory symptoms. A roughly 5 percent increase of
26 General Practitioner medical visits was also noted, but was not significant. Ilabaca et al. (1999)
27 also found an association between levels of fine PM and ED visits for pneumonia and other
28 respiratory illnesses among children < 15 years in Santiago, Chile, where the levels of PM_{2.5}
29 were very high (mean = 71.3 µg/m³) during 1995-1996. The authors found it difficult to separate
30 out the effects of various pollutants, but concluded that PM (especially the fine component) is
31 associated with the risk of these respiratory illnesses. Overall, these new studies support past

1 assertions that children, and especially neo-natal infants, are especially susceptible to the health
2 effects of air pollution.

3 The respiratory-related hospital admissions studies summarized in Appendix 8B reveal that
4 the PM RR's for all children (e.g., 0-18) are not often notably larger than those for adults, but
5 such comparisons of RR's must adjust for differences in baseline risks for each group. For
6 example, if hospital admissions per 100,000 per day for young children are double the rate for
7 adults, then they will have a pollution relative risk (RR) per $\mu\text{g}/\text{m}^3$ that is half that of the adults
8 given the exact same impact on admissions/100,000/ $\mu\text{g}/\text{m}^3/\text{day}$. Thus, it is important to adjust
9 RR's or Excess Risks (ER's) for each different age groups' baseline, but this information is
10 usually not available (especially regarding the population catchment for each age group in each
11 study). One of the few indications that is notable when comparing children with other age group
12 effect estimates in Table 8B-2 is the higher excess risk estimate for infants (i.e., the group < 1 yr.
13 of age) in the Gouveia and Fletcher (2000) study, an age group that has estimated risk estimate
14 roughly twice as large as for other children or adults.

15 16 **8.3.2.6 Summary of Salient Findings on Acute Particulate Matter Exposure and** 17 **Respiratory-Related Hospital Admissions and Medical Visits**

18 The results of new studies discussed above are generally consistent with and supportive of
19 findings presented in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a),
20 with regard to ambient PM associations of short-term exposures with respiratory-related hospital
21 admissions/medical visits. Figure 8-12 summarizes results for maximum excess risk of
22 respiratory-related hospital admission and visits per $50 \mu\text{g}/\text{m}^3 \text{PM}_{10}$ based on single-pollutant
23 models for selected U.S. cities. The excess risk estimates fall most consistently in the range of
24 5 to 20% per $50 \mu\text{g}/\text{m}^3 \text{PM}_{10}$ increments, with those for asthma visits and hospital admissions
25 generally somewhat higher than for COPD and pneumonia hospital admissions. More limited
26 new evidence both (a) substantiates increased risk of respiratory-related hospital admissions due
27 to ambient fine particles ($\text{PM}_{2.5}$, $\text{PM}_{1.0}$, etc.) and also (b) points towards such admissions being
28 associated with ambient coarse particles ($\text{PM}_{10-2.5}$). Excess risk estimates tend to fall in the range
29 of ca. 5.0 to 15.0% per $25 \mu\text{g}/\text{m}^3 \text{PM}_{2.5}$ or $\text{PM}_{10-2.5}$ for overall respiratory admissions or for COPD
30 admissions, whereas larger estimates are found for asthma admissions.

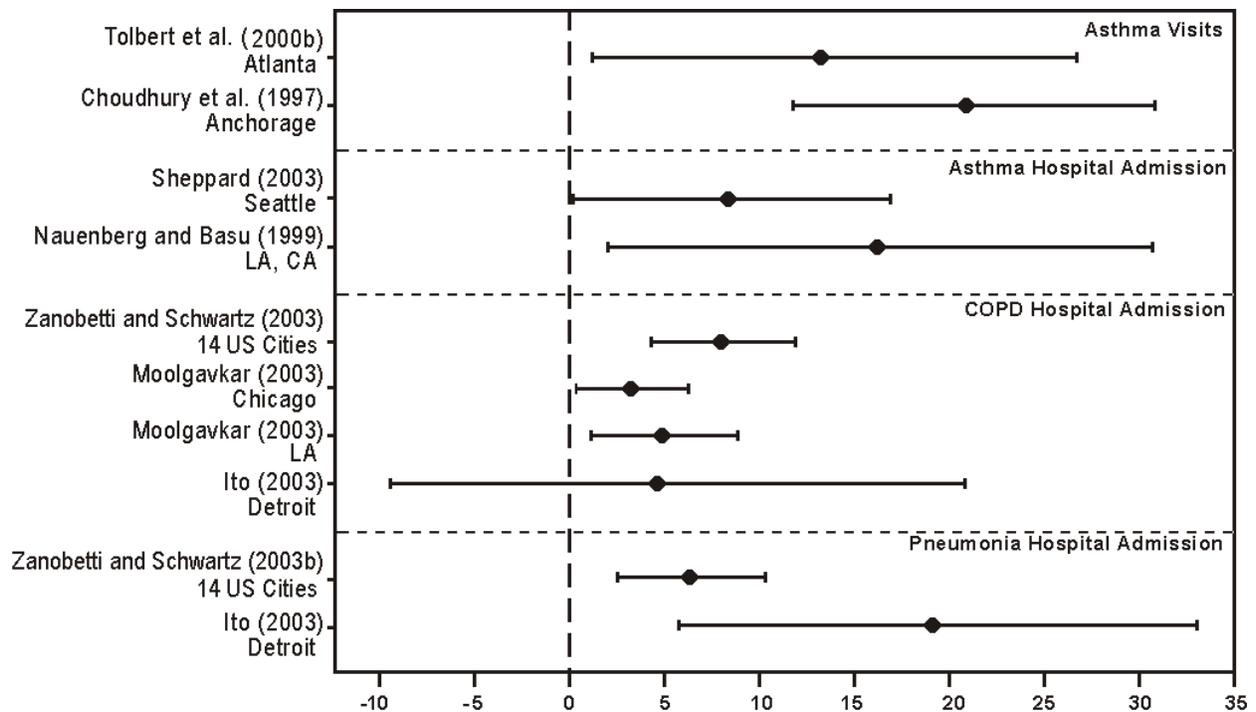


Figure 8-12. Maximum excess risk of respiratory-related hospital admissions and visits per 50 µg/m³ PM₁₀ increment in studies of U.S. cities based on single-pollutant models.

1 Various new medical visits studies (including non-hospital physician visits) indicate that
 2 the use of hospital admissions alone can greatly understate the total clinical morbidity effects of
 3 air pollution. Thus, these results support the hypothesis that considering only hospital
 4 admissions and ED visit effects may greatly underestimate the numbers of medical visits
 5 occurring in a population as a result of acute ambient PM exposure. Those groups identified in
 6 these morbidity studies as most strongly affected by PM air pollution are older adults and the
 7 very young.

8.3.3 Effects of Particulate Matter Exposure on Lung Function and Respiratory Symptoms

11 In the 1996 PM AQCD, the available respiratory studies used a wide variety of designs
 12 examining pulmonary function and respiratory symptoms in relation to ambient concentrations
 13 of PM₁₀. The populations studied included several different subgroups (e.g., children, asthmatics,

1 etc.); and the models used for analysis varied, but did not include GAM use. The pulmonary
2 function studies were suggestive of short-term effects resulting from ambient PM exposure.
3 Peak expiratory flow rates showed decreases in the range of 2 to 5 l/min per 50 $\mu\text{g}/\text{m}^3$ increase in
4 24-h PM_{10} or its equivalent, with somewhat larger effects in symptomatic groups, e.g.,
5 asthmatics. Studies using FEV_1 or FVC as endpoints showed less consistent effects. The
6 chronic pulmonary function studies, less numerous than the acute studies, had inconclusive
7 results.

8 9 **8.3.3.1 Effects of Short-Term Particulate Matter Exposure on Lung Function and** 10 **Respiratory Symptoms**

11 The available acute respiratory symptom studies discussed in the 1996 PM AQCD included
12 several different endpoints, but typically presented results for upper respiratory symptoms, lower
13 respiratory symptoms, or cough. These respiratory symptom endpoints had similar general
14 patterns of results. The odds ratios were generally positive, the 95% confidence intervals for
15 about half of the studies being statistically significant (i.e., the lower bound exceeded 1.0).

16 The earlier studies of morbidity health outcomes of PM exposure on asthmatics were
17 limited in terms of conclusions that could be drawn because of the few available studies on
18 asthmatic subjects. Lebowitz et al. (1987) reported a relationship with TSP exposure and
19 productive cough in a panel of 22 asthmatics but not for peak flow or wheeze. Pope et al. (1991)
20 reported on respiratory symptoms in two panels of Utah Valley asthmatics. The 34 asthmatic
21 school children panel yielded estimated odd ratios of 1.28 (1.06, 1.56) for lower respiratory
22 illness (LRI) and the second panel of 21 subjects aged 8 to 72 for LRI of 1.01 (0.81, 1.27) for
23 exposure to PM_{10} . Ostro et al. (1991) reported no association for $\text{PM}_{2.5}$ exposure in a panel of
24 207 adult asthmatics in Denver; but, for a panel of 83 asthmatic children age 7 to 12 in central
25 Los Angeles, found a relationship of shortness of breath to O_3 and PM_{10} , but could not separate
26 effects of the two pollutants (Ostro et al., 1995). These few studies did not indicate a consistent
27 relationship for PM_{10} exposure and health outcome in asthmatics.

28 Numerous new studies of short-term PM exposure effects on lung function and respiratory
29 symptoms published since 1996 were identified by an ongoing Medline search. Most of these
30 followed a panel of subjects over one or more time periods and evaluated daily lung function
31 and/or respiratory symptom in relation to changes in ambient PM_{10} , $\text{PM}_{10-2.5}$, and/or $\text{PM}_{2.5}$. Some

1 used other measures of airborne particles, e.g. ultrafine PM, TSP, BS, and sulfate fraction of
2 ambient PM. Lung function was usually measured daily, with most studies including forced
3 expiratory volume (FEV), forced vital capacity (FVC) and peak expiratory flow rate (PEF),
4 measured both in the morning and afternoon. Various respiratory symptoms were measured,
5 e.g., cough, phlegm, difficulty breathing, wheeze, and bronchodilator use. Detailed summaries
6 of these studies are presented in Appendix 8B. Data on physical and chemical aspects of
7 ambient PM levels (especially for PM₁₀, PM_{10-2.5}, PM_{2.5}, and smaller size fractions) are of
8 particular interest, as are new studies examining health outcome effects and/or exposure
9 measures not much studied in the past.

10 Specific studies were selected for summarization based on the following criteria:

- 11 • Peak flow was used as the primary lung function measurement of interest.
- 12 • Cough, phlegm, difficulty breathing, wheeze, and bronchodilator use were summarized as
measures of respiratory symptoms when available.
- 13 • Quantitative relationships were estimated using PM₁₀, PM_{2.5}, PM_{10-2.5}, and/or smaller PM as
independent variables.
- 14 • Analyses used in the study were done such that each individual served as their own control.

15 16 ***8.3.3.1.1 Lung Function and Respiratory Symptom Effects in Asthmatic Subjects***

17 Appendix B Tables 8B-4 and 8B-5 summarize salient features of new studies of short-term
18 PM exposure effects on lung function and respiratory symptoms, respectively, in asthmatic
19 subjects; and key quantitative results are summarized in Table 8-25 for PM₁₀ and Table 8-26 for
20 PM_{2.5}. The peak flow analyses results for asthmatics tend to show small decrements for PM₁₀
21 and PM_{2.5} as seen in studies by Gielen et al. (1997), Peters et al. (1997c), Romieu et al. (1997),
22 and Pekkanen et al. (1997).

23 For PM₁₀, the available point estimates for morning PEF lagged one day showed decreases,
24 but the majority of the studies were not statistically significant (as per Table 8-25 and as shown
25 in Figure 8-13 as an example of PEF outcomes). Lag 1 may be more relevant for morning
26 measurement of asthma outcome from the previous day. The figure presents studies which
27 provided such data. The results were consistent for both AM and PM peak flow analyses.
28 Effects using two- to five-day lags averaged about the same as did the zero to one-day lags, but

TABLE 8-25. SUMMARY OF QUANTITATIVE PFT CHANGES IN ASTHMATICS PER 50 µg/m³ PM₁₀ INCREMENT

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m ³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/m ³ PM ₁₀
Asthma Studies					
Pekkanen et al. (1997)	Morning PEFr	14 (10, 23)	NO ₂	0 day	-2.71 (-6.57, 1.15)
Gielen et al. (1997)	Morning PEFr	30.5 (16, 60)	Ozone	1 day	1.39 (-0.57, 3.35)
Romieu et al. (1996)	Morning PEFr	166.8 (29, 363)	Ozone	1 day	-4.70 (-7.65, -1.70)
Romieu et al. (1997)	Morning PEFr	(12, 126)	Ozone	1 day	-0.65 (-5.32, 3.97)
Peters et al. (1997a)	Morning PEFr	47 (29, 73)	SO ₂ , sulfate, H ⁺	1 day	-0.84 (-1.62, -0.06)
Peters et al. (1997b)	Morning PEFr	55 (?, 71)	SO ₂ , sulfate, H ⁺	1 day	-1.30 (-2.36, -0.24)
Gielen et al. (1997)	Morning PEFr	30.5 (16, 60)	Ozone	2 day	0.34 (-1.78, 2.46)
Romieu et al. (1996)	Morning PEFr	166.8 (29, 363)	Ozone	2 day	-4.90 (-8.40, -1.50)
Romieu et al. (1997)	Morning PEFr	(12, 126)	Ozone	2 day	2.47 (-1.75, 6.75)
Gielen et al. (1997)	Evening PEFr	30.5 (16, 60)	Ozone	0 day	-0.30 (-2.24, 1.64)
Romieu et al. (1996)	Evening PEFr	166.8 (29, 363)	Ozone	0 day	-4.80 (-8.00, -1.70)
Romieu et al. (1997)	Evening PEFr	(12, 126)	Ozone	0 day	-1.32 (-6.82, 4.17)
Pekkanen et al. (1997)	Evening PEFr	14 (10, 23)	NO ₂	0 day	-0.35 (-4.31, 3.61)
Peters et al. (1996)	Evening PEFr	112	SO ₂ , sulfate, PSA	0 day	-1.03 (-1.98, -0.08)
Peters et al. (1997a)	Evening PEFr	47 (29, 73)	SO ₂ , sulfate, H ⁺	0 day	-0.92 (-1.96, 0.12)
Peters et al. (1997b)	Evening PEFr	55 (?, 71)	SO ₂ , sulfate, H ⁺	0 day	-0.37 (-1.82, 1.08)
Timonen & Pekkanen (1997) Urban	Evening PEFr	18 (?, 60)	NO ₂ , SO ₂	0 day	-1.10 (-5.20, 3.00)
Timonen & Pekkanen (1997) Suburban	Evening PEFr	13 (?, 37)	NO ₂ , SO ₂	0 day	-1.66 (-8.26, 4.94)
Gielen et al. (1997)	Evening PEFr	30.5 (16, 60)	Ozone	2 day	-2.32 (-5.36, 0.72)
Romieu et al. (1996)	Evening PEFr	166.8 (29, 363)	Ozone	2 day	-3.65 (-7.20, 0.03)
Romieu et al. (1997)	Evening PEFr	(12, 126)	Ozone	2 day	-0.04 (-4.29, 4.21)
Segala et al. (1998)	Morning PEFr	34.2 (9, 95)	SO ₂ , NO ₂	2 day	-0.62 (-1.52, 0.28)
Pekkanen et al. (1997)	Evening PEFr	14 (10, 23)	NO ₂	2 day	0.14 (-6.97, 7.25)

**TABLE 8-25 (cont'd). SUMMARY OF QUANTITATIVE PFT CHANGES IN ASTHMATICS
PER 50 µg/m³ PM₁₀ INCREMENT**

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m ³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/m ³ PM ₁₀
Asthma Studies (cont'd)					
Peters et al. (1997b)	Evening PEFR	55 (? , 71)	SO ₂ , sulfate, H ⁺	2 day	-2.31 (-4.53, -0.10)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (? , 60)	NO ₂ , SO ₂	2 day	-1.13 (-4.75, 2.52)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (? , 37)	NO ₂ , SO ₂	2 day	0.38 (-6.37, 7.13)
Peters et al. (1996)	Evening PEFR	112	SO ₂ , sulfate, PSA	5 day	-1.12 (-2.13, -0.10)
Peters et al. (1997a)	Evening PEFR	47 (29, 73)	SO ₂ , sulfate, H ⁺	1-5 day	-1.34 (-2.83, 0.15)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (? , 60)	NO ₂ , SO ₂	1-4 day	-0.73 (-7.90, 6.44)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (? , 37)	NO ₂ , SO ₂	1-4 day	-4.18 (-20.94, 12.58)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO ₂ , SO ₂	1 day	-0.90 (-3.84, 2.04)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO ₂ , SO ₂	2 day	-0.50 (-4.22, 3.22)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO ₂ , SO ₂	1-7 day	-2.20 (-10.43, 6.03)
Vedal et al. (1998)	Ave. AM & PM	19.1 (1, 159)	None	1-4 day	-1.35 (-2.70, -.05)

TABLE 8-26. SUMMARY OF PFT CHANGES IN ASTHMATICS PER 25 µg/m³ PM_{2.5} INCREMENT

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m ³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 µg/m ³ PM _{2.5}
Romieu et al. (1996)	Morning PEFR	85.7 (23, 177)	Ozone	1 day	-3.65 (-8.25, 1.90)
Peters et al. (1997b)	Morning PEFR	50.8 (9, 347)	SO ₂ , sulfate, H ⁺	1 day	-0.71 (-1.30, 0.12)
Romieu et al. (1996)	Morning PEFR	85.7 (23, 177)	Ozone	2 day	-3.68 (-9.37, 2.00)
Peters et al. (1997c)	Morning PEFR	50.8 (9, 347)	SO ₂ , sulfate, H ⁺	1-5 day	-1.19 (-1.18, 0.57)
Romieu et al. (1996)	Evening PEFR	85.7 (23, 177)	Ozone	0 day	-4.27 (-7.12, -0.85)
Peters et al. (1997b)	Evening PEFR	50.8 (9, 347)	SO ₂ , sulfate, H ⁺	0 day	-0.75 (-1.66, 0.17)
Romieu et al. (1996)	Evening PEFR	85.7 (23, 177)	Ozone	2 day	-2.55 (-7.84, 2.740)
Peters et al. (1997b)	Evening PEFR	50.8 (9, 347)	SO ₂ , sulfate, H ⁺	1-5 day	-1.79 (-2.64, -0.95)

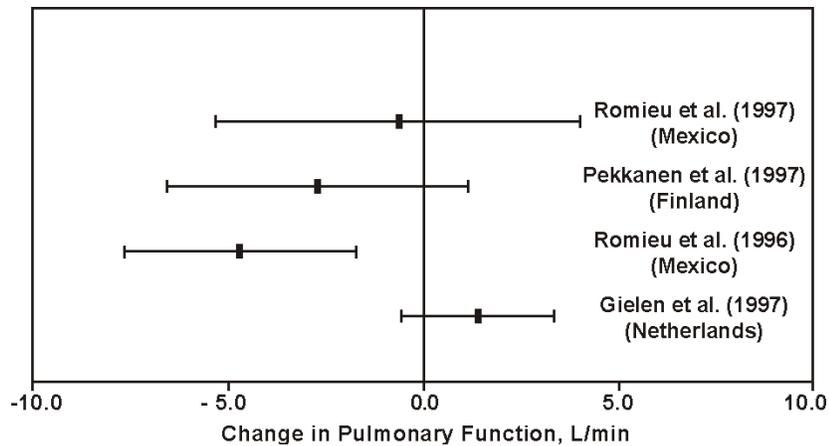


Figure 8-13. Illustrative acute pulmonary function change studies of asthmatic children. Effect of $50 \mu\text{g}/\text{m}^3$ PM_{10} on morning peak flow lagged one-day.

1 had wider confidence limits. Similar results were found for the fewer $\text{PM}_{2.5}$ studies. Of these,
 2 Pekkanen et al. (1997) and Romieu et al. (1996) found similar results for $\text{PM}_{2.5}$ and PM_{10} , while
 3 the study of Peters et al. (1997b) found slightly larger effects for $\text{PM}_{2.5}$.

4 Pekkanen et al. (1997) also reported changes in peak flow to be related to several sizes of
 5 PM. The authors reported morning PEF changes of -0.970 ($\text{SE} = 0.502$) l/cm^3 for particle
 6 number count (0.032 - 0.10 in size), -0.901 (0.536) for $\text{PM}_{1.0-3.2}$, and -1.13 ($\text{SE} = 0.478$) for
 7 PM_{10} . Peters et al. (1997c) report that the strongest effects on peak flow were found with
 8 ultrafine particles: $\text{PM}_{\text{MC}0.01-0.1}$: -1.21 ($-2.13, -0.30$); $\text{PM}_{\text{MC}0.01-2.5}$: -1.01 ($-1.92, -0.11$); and
 9 PM_{10} : -1.30 ($-2.36, -0.24$). Penttinen et al. (2001) using biweekly spirometry over 6 months on
 10 a group of 54 adult asthmatics found that FVC, FEV_1 , and spirometric PEF were inversely, but
 11 mostly nonsignificantly-associated with ultrafine particle concentrations. Compared to the effect
 12 estimates for self-monitored PEF, the effect estimates for spirometric PEF tended to be
 13 larger. The strongest associations were observed in the size range of 0.1 to $1 \mu\text{m}$. In a further
 14 study, von Klot et al. (2002) evaluated 53 adult asthmatics in Erfurt, Germany in the winter of
 15 1996-1997. Relationships were estimated from generalized estimating equations, adjusting for
 16 autocorrelation. Asthma symptoms were related to small particles ($\text{PM}_{\text{MC}0.1-0.5}$, $\text{PM}_{\text{MC}0.01-2.5}$) and
 17 $\text{PM}_{2.5-10}$. The strongest relations were for 14 day mean PM levels, especially for the smaller
 18 particles ($\text{PM}_{\text{MC}0.01-2.5}$).

1 Overall, then, PM₁₀ and PM_{2.5} both appear to affect lung function in asthmatics, but there is
2 only limited evidence for a stronger effect of fine versus coarse fraction particles; nor do
3 ultrafine particles appear to have any notably stronger effect than other larger-diameter fine
4 particles. Also, of the studies provided, few if any analyses were able to clearly separate out the
5 effects of PM₁₀ and PM_{2.5} from other pollutants.

6 The effects of PM₁₀ on respiratory symptoms in asthmatics tended to be positive, although
7 they are somewhat less consistent than PM₁₀ effects on lung function. Most studies showed
8 increases in cough, phlegm, difficulty breathing, and bronchodilator use, although these
9 increases were generally not statistically significant for PM₁₀ (see Tables 8-27, 8-28, 8-29, and
10 8-30; and, for cough as an example, see Figure 8-14). Vedal et al. (1998) reported that
11 (a) increases in PM₁₀ were associated with increased reporting of cough, phlegm production, and
12 sore throat and (b) children with diagnosed asthma are more susceptible to the effects than are
13 other children. Similarly, in the Gielen et al. (1997) study of a panel of children, most of whom
14 had asthma, low levels of PM increased symptoms and medication use. The Peters et al. (1997b)
15 study of asthmatics examined particle effects by size and found that fine particles were
16 associated with increases in cough, of which MC 0.01-2.5 was the best predictor.

17 Delfino et al. (1998a) used an asthma symptom score to evaluate the effects of acute air
18 pollutant exposures. The 1- and 8-hr PM₁₀ maximum concentrations had larger effects than the
19 24-hr mean. Subgroup analyses showed effects of current day PM maxima to be strongest in the
20 10 more frequently symptomatic children; the odds ratios for symptoms were 2.24 (1.46, 3.46)
21 for 47 µg/m³ 1-hr PM₁₀; 1.82 (1.18, 2.8) for 36 µg/m³ 8-hr PM₁₀, and 1.50 (0.80-2.80) for
22 25 µg/m³ 24-hr PM₁₀. Analyses suggested that effects of O₃ and PM₁₀ were largely independent.
23 Delfino et al. (2002) also studied 22 asthmatic children aged 9-19 years in March and April
24 1996. Associations were evaluated by generalized estimating equations, adjusting for
25 autocorrelation. The endpoint was symptoms interfering with daily activities. This endpoint
26 was associated with PM₁₀, NO₂, and ozone and there was a positive interaction effect of PM₁₀
27 and NO₂ jointly. Both of these studies also reported significant associations with fungal spores,
28 but not pollens; no significant interactions were found between aeroallergens and air pollutants.

29 Romieu et al. (1996) found children with mild asthma to be more strongly affected by high
30 ambient levels of PM (mean PM₁₀ = 166.8 µg/m³) observed in northern Mexico City than in a
31 study (Romieu et al., 1997) conducted in a nearby area with lower PM₁₀ levels (mean

TABLE 8-27. SUMMARY OF ASTHMA PM₁₀ COUGH STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu\text{g}/\text{m}^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to $50 \mu\text{g}/\text{m}^3$ PM ₁₀
Asthma Studies					
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	0 day	1.40 (1.04, 1.88)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	0 day	2.19 (0.77, 6.20)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO ₂ , SO ₂	0 day	0.93 (0.83, 1.04)
Peters et al. (1997b)	OR cough	55 (?, 71)	SO ₂ , sulfate, H ⁺	0 day	1.32 (1.16, 1.50)
Peters et al. (1997c)	OR cough	47 (29, 73)	SO ₂ , sulfate, H ⁺	0 day	1.01 (0.97, 1.07)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	0 day	1.21 (1.10, 1.33)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	0 day	1.27 (1.16, 1.42)
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	2 day	1.40 (1.13, 1.73)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	2 day	2.19 (0.47, 10.24)
Segala et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO ₂ , NO ₂	2 day	(values not given because not significant)
Neukirch et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO ₂ , NO ₂	3 day	(values not given because not significant)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	2 day	1.27 (1.07, 1.50)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	2 day	1.00 (0.92, 1.10)
Ostro et al. (2001)	OR cough	47 (11, 119) 24 hr	Ozone, NO ₂	3 day	1.32 (1.12, 1.55)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO ₂ , SO ₂	1-7 day	0.94 (0.82, 1.08)
Peters et al. (1997b)	OR cough	55 (?, 71)	SO ₂ , sulfate, H ⁺	1-5 day	1.30 (1.09, 1.55)
Peters et al. (1997c)	OR cough	47 (29, 73)	SO ₂ , sulfate, H ⁺	1-5 day	1.10 (1.04, 1.17)
Ostro et al. (2001)	OR cough	102 (47, 360) 1 hr max	ozone, NO ₂	3 day	1.05 (1.02, 1.18)

TABLE 8-28. SUMMARY OF ASTHMA PM₁₀ PHLEGM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu\text{g}/\text{m}^3$	Co-Pollutants Measured	Lag Structure	Effect measures standardized to 50 $\mu\text{g}/\text{m}^3$ PM ₁₀
Vedal et al. (1998)	OR phlegm	19.1 (1, 159)	None	0 day	1.28 (0.86, 1.89)
Peters et al. (1997c)	OR phlegm	47 (29, 73)	SO ₂ , sulfate, H ⁺	0 day	1.13 (1.04, 1.23)
Romieu et al. (1997)	OR phlegm	(12, 126)	Ozone	0 day	1.05 (0.83, 1.36)
Romieu et al. (1996)	OR phlegm	166.8 (29, 363)	Ozone	0 day	1.21 (1.00, 1.48)
Vedal et al. (1998)	OR phlegm	19.1 (1, 159)	None	2 day	1.40 (1.03, 1.90)
Romieu et al. (1997)	OR phlegm	(12, 126)	Ozone	2 day	1.00 (0.86, 1.16)
Romieu et al. (1996)	OR phlegm	166.8 (29, 363)	Ozone	2 day	1.16 (0.91, 1.49)
Peters et al. (1997c)	OR phlegm	47 (29, 73)	SO ₂ , sulfate, H ⁺	1-5 day	1.17 (1.09, 1.27)

TABLE 8-29. SUMMARY OF ASTHMA PM₁₀ LOWER RESPIRATORY ILLNESS (LRI) STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range)	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 $\mu\text{g}/\text{m}^3$ PM ₁₀
Vedal et al. (1998)	LRI	19.1 (1, 159)	None	0 day	1.10 (0.82, 1.48)
Gielen et al. (1997)	LRI	30.5 (16, 60)	Ozone	0 day	1.26 (0.94, 1.68)
Romieu et al. (1997)	LRI	(12, 126)	Ozone	0 day	1.00 (0.95, 1.05)
Romieu et al. (1996)	LRI	166.8 (29, 363)	Ozone	0 day	1.21 (1.10, 1.42)
Vedal et al. (1998)	LRI	19.1 (1, 159)	None	2 day	1.16 (1.00, 1.34)
Gielen et al. (1997)	LRI	30.5 (16, 60)	Ozone	2 day	1.05 (0.74, 1.48)
Segala et al. (1998)	LRI	34.2 (9, 95)	SO ₂ , NO ₂	2 day	1.66 (0.84, 3.30)
Romieu et al. (1997)	LRI	(12, 126)	Ozone	2 day	1.00 (0.93, 1.08)
Romieu et al. (1996)	LRI	166.8 (29, 363)	Ozone	2 day	1.10 (0.98, 1.24)
Delfino et al. (1998)	LRI	24 h 26 (6, 51)	Ozone	0 day	1.47 (0.90 - 2.39)
		8-h 43 (23-73)	Ozone	0 day	2.17 (1.33 - 3.58)
		1-h 57 (30-108)	Ozone	0 day	1.78 (1.25 - 2.53)

TABLE 8-30. SUMMARY OF ASTHMA PM₁₀ BRONCHODILATOR USE STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu\text{g}/\text{m}^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 $\mu\text{g}/\text{m}^3$ PM ₁₀
Gielen et al. (1997)	OR bronchodilator use	30.5 (16, 60)	Ozone	0 day	0.94 (0.59, 1.50)
Hiltermann et al. (1998)	OR bronchodilator use	39.7 (16, 98)	Ozone, NO ₂ , SO ₂	0 day	1.03 (0.93, 1.15)
Peters et al. (1997c)	OR bronchodilator use	47 (29, 73)	SO ₂ , sulfate, H ⁺	0 day	1.06 (0.88, 1.27)
Gielen et al. (1997)	OR bronchodilator use	30.5 (16, 60)	Ozone	2 day	2.90 (1.81, 4.66)
Hiltermann et al. (1998)	OR bronchodilator use	39.7 (16, 98)	Ozone, NO ₂ , SO ₂	1-7 day	1.12 (1.00, 1.25)
Peters et al. (1997c)	OR bronchodilator use	47 (29, 73)	SO ₂ , sulfate, H ⁺	1-5 day	1.23 (0.96, 1.58)

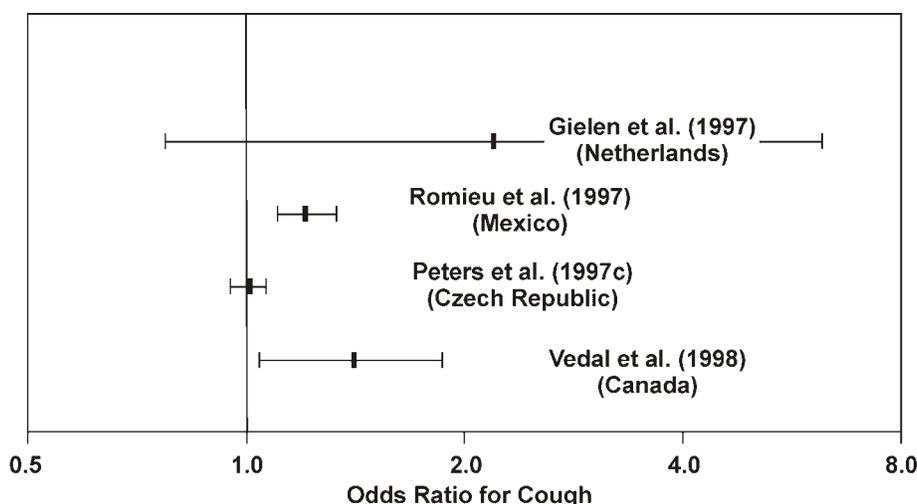


Figure 8-14. Odds ratios with 95% confidence interval for cough per 50- $\mu\text{g}/\text{m}^3$ increase in PM_{10} for illustrative asthmatic children studies at lag 0.

1 $\text{PM}_{10} = 54.2 \mu\text{g}/\text{m}^3$). Yu et al. (2000) reported estimates of odds ratios for asthma symptoms and
 2 $10 \mu\text{g}/\text{m}^3$ increments in PM_{10} and $\text{PM}_{1.0}$ values of 1.18 (1.05, 1.33) and 1.09 (1.01, 1.18),
 3 respectively. Multipollutant models with CO and SO_2 yielded 1.06 (0.95, 1.19) for PM_{10} , and
 4 1.11 (0.98, 1.26) for $\text{PM}_{1.0}$, thus showing a lower value for PM_{10} and a loss of significance for
 5 both PM_{10} and $\text{PM}_{1.0}$. The correlation between CO and $\text{PM}_{1.0}$ and PM_{10} was 0.82 and 0.86. Ostro
 6 et al. (2001) studied a panel of inner-city African American children using a GEE model with
 7 several measures of PM, including PM_{10} (both 24-hour average and 1-hour max.) and $\text{PM}_{2.5}$,
 8 demonstrating positive associations with daily probability of shortness of breath, wheeze, and
 9 cough.

10 Desqueyroux et al. (2002) studied 60 adult severe asthmatics from November 1995 to
 11 November 1996. Relationships were estimated from generalized estimating equations adjusting
 12 for autocorrelation. Each asthma exacerbation was confirmed by a physician, and each of the
 13 cases were followed for a sufficient length of time to allow investigations of any lagged
 14 associations with air pollution. Statistical analysis that accounted for temporal, meteorological,
 15 and aerobiological variables and some individual characteristics revealed significant associations
 16 between PM_{10} , O_3 , and incident asthma attacks. Odds Ratio (OR) for an increase of $10 \mu\text{g}/\text{m}^3$ of
 17 PM_{10} was 1.41 (CI: 1.16, 1.71). PM_{10} was not related to incident asthma attacks using lags of

1 1 or 2 days; but PM₁₀ associations for 3, 4, and 5 day lags were significant. PM₁₀ remained
2 significant even after adjusting for other pollutants including O₃, SO₂, and NO₂.

3 Just et al. (2002) also studied 82 asthmatic children for 3 months during spring and early
4 summer in Paris. Relationships were estimated from generalized estimating equations adjusting
5 for autocorrelation. No significant relationships were found between PM₁₃ and lung function or
6 respiratory symptoms. For PM_{2.5} results, see Table 8-31. All showed positive associations
7 (several being clearly significant at p < 0.05) between PM_{2.5} and increased cough, phlegm, or
8 LRI.

9 Of studies that included two indicators for PM (PM₁₀, PM_{2.5}) in their analyses, the study of
10 Peters et al. (1997b) found similar effects for the two PM measures, whereas the Romieu et al.
11 (1996) study found slightly larger effects for PM_{2.5}.

12 Two asthma studies, both in the United States, examined PM indicators by 1 hr averages as
13 well as by 24 hr averages. The PM₁₀ 1 hr outcome was larger than the 24 hr outcome for lower
14 respiratory illness in one study (Delfino et al., 1998a) but was lower for cough in the other study
15 (Ostro et al., 2001).

16 Several of the studies reviewed above (Delfino et al., 1998a, 2002; Ostro et al., 2001;
17 Yu et al., 2000; Mortimer et al., 2002; Vedal et al., 1998) that were conducted in the
18 United States and Canada found positive associations between various health endpoints for
19 asthmatics and ambient PM exposure (indexed by PM₁₀, PM_{2.5}, or PM_{10-2.5}). The endpoints
20 included PEF decrements, various individual respiratory symptoms, and combinations of
21 respiratory symptoms. The various endpoints each represent effects on respiratory health.

22 23 **8.3.3.1.2 Lung Function and Respiratory Symptom Effects in Nonasthmatic Subjects**

24 Results for PM₁₀ peak flow analyses in non-asthmatic studies (summarized in Appendix 8B
25 Table 8B-6) were inconsistent, with fewer studies reporting results in the same manner as for the
26 asthmatic studies. Many of the point estimates showed increases rather than decreases (see
27 Table 8-32). The effects on respiratory symptoms in non-asthmatics (see Appendix 8B
28 Table 8B-7) were similar to those in asthmatics. Most studies showed that PM₁₀ increases
29 cough, phlegm, difficulty breathing, and bronchodilator use, although these were generally not
30 statistically significant (Table 8-33). Vedal et al. (1998) reported no consistent evidence for
31 adverse health effects in a nonasthmatic control group.

TABLE 8-31. SUMMARY OF ASTHMA PM_{2.5} RESPIRATORY SYMPTOM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 µg/m³ PM_{2.5}
Peters et al. (1997c)	OR cough	50.8 (9, 347)	SO ₂ , sulfate, H ⁺	0 day	1.22 (1.08, 1.38)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	0 day	1.27 (1.08, 1.42)
Tiittanen et al. (1999)	OR cough	15 (3, 55)	NO ₂ , SO ₂ , CO, ozone	0 day	1.04 (0.86, 1.20)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	2 day	1.16 (0.98, 1.33)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO ₂ , SO ₂ , CO, ozone	2 day	1.24 (1.02, 1.51)
Ostro et al. (2001)	OR cough	40.8 (4, 208)	Ozone, NO ₂	3 day	1.02 (0.98, 1.06)
Peters et al. (1997c)	OR cough	50.8 (9, 347)	SO ₂ , sulfate, H ⁺	1-5 day	1.02 (0.90, 1.17)
Romieu et al. (1996)	OR Phlegm	85.7 (23, 177)	Ozone	0 day	1.21 (0.98, 1.48)
Romieu et al. (1996)	OR Phlegm	85.7 (23, 177)	Ozone	2 day	1.16 (0.99, 1.39)
Romieu et al. (1996)	OR LRI	85.7 (23, 177)	Ozone	0 day	1.21 (1.05, 1.42)
Romieu et al. (1996)	OR LRI	85.7 (23, 177)	Ozone	2 day	1.16 (1.05, 1.42)

TABLE 8-32. SUMMARY OF NON-ASTHMA PM₁₀ PFT STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu\text{g}/\text{m}^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to $50 \mu\text{g}/\text{m}^3$ PM ₁₀
Gold et al. (1999)	Morning PEFR	51 (23, 878)	Ozone	1 day	-0.20 (-0.47, 0.07)
Tiittanen et al. (1999)	Morning PEFR	28 (5, 122)	NO ₂ , SO ₂ , CO, ozone	0 day	1.21 (-0.43, 2.85)
Neas et al. (1999)	Morning PEFR	32	Ozone	1-5 day	2.64 (-6.56, 11.83)
Tiittanen et al. (1999)	Morning PEFR	28 (5, 122)	NO ₂ , SO ₂ , CO, ozone	1-4 day	-1.26 (-5.86, 3.33)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO ₂ , SO ₂	1 day	1.04 (0.95, 1.13)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO ₂ , SO ₂	2 day	1.02 (0.93, 1.11)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO ₂ , SO ₂	1-5 day	1.05 (0.91, 1.21)
Neas et al. (1999)	Morning PEFR	32	Ozone	0 day	-8.16 (-14.81, -1.55)
Harré et al. (1997)	% change in morning PEFR	(not given)	NO ₂ , SO ₂ , CO	1 day	0.07 (-0.50, 0.63)
Neas et al. (1999)	Evening PEFR	32	Ozone	0 day	-1.44 (-7.33, 4.44)
Schwartz & Neas (2000) Uniontown	Evening PEFR	(not given)	Sulfate fraction	0 day	-1.52 (-2.80, -0.24)
Schwartz & Neas (2000) State College	Evening PEFR	(not given)	Sulfate fraction	0 day	-0.93 (-1.88, 0.01)
Tiittanen et al. (1999)	Evening PEFR	28 (5, 122)	NO ₂ , SO ₂ , CO, ozone	0 day	0.72 (-0.63, 1.26)
Tiittanen et al. (1999)	Evening PEFR	28 (5, 122)	NO ₂ , SO ₂ , CO, ozone	0 day	2.33 (-2.62, 7.28)
Gold et al. (1999)	Evening PEFR	51 (23, 878)	Ozone	0 day	-0.14 (-0.45, 0.17)
Neas et al. (1999)	Evening PEFR	32	Ozone	1-5 day	1.47 (-7.31, 10.22)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO ₂ , SO ₂	0 day	1.17 (1.08, 1.28)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO ₂ , SO ₂	2 day	1.08 (0.99, 1.17)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO ₂ , SO ₂	1-5 day	1.16 (1.02, 1.33)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO ₂ , SO ₂ , sulfate	0 day	1.44 (1.02, 2.03)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO ₂ , SO ₂ , sulfate	2 day	1.14 (0.83, 1.58)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO ₂ , SO ₂ , sulfate	1-5 day	1.16 (0.64, 2.10)
Harré et al. (1997)	% change in evening PEFR	(not given)	NO ₂ , SO ₂ , CO	1 day	-0.22 (-0.57, 0.16)

TABLE 8-33. SUMMARY OF NON-ASTHMA PM₁₀ RESPIRATORY SYMPTOM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu\text{g}/\text{m}^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 mg/m^3 PM ₁₀
Schwartz & Neas (2000)	OR cough – no other symptoms	(not given)	Sulfate fraction	0 day	1.20 (1.07, 1.35)
Boezen et al. (1998)	OR cough	42 (5, 146)	NO ₂ , SO ₂	0 day	1.06 (0.93, 1.21)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO ₂ , SO ₂ , sulfate	0 day	1.04 (0.95, 1.14)
Tiittanen et al. (1999)	OR cough	28 (5, 122)	NO ₂ , SO ₂ , CO, ozone	0 day	1.00 (0.87, 1.16)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO ₂ , SO ₂ , sulfate	2 day	0.94 (0.89, 1.06)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO ₂ , SO ₂ , sulfate	1-5 day	0.95 (0.80, 1.13)
Tiittanen et al. (1999)	OR cough	28 (5, 122)	NO ₂ , SO ₂ , CO, ozone	1-4 day	1.58 (0.87, 2.83)
Boezen et al. (1998)	OR phlegm	42 (5, 146)	NO ₂ , SO ₂	0 day	1.11 (0.91, 1.36)
Tiittanen et al. (1999)	OR phlegm	28 (5, 122)	NO ₂ , SO ₂ , CO, ozone	2 day	Positive but not significant
Schwartz & Neas (2000)	LRI	(not given)	Sulfate fraction	0 day	
Van der Zee et al. (1999) Urban areas	LRI	34 (?, 106)	NO ₂ , SO ₂ , sulfate	0 day	0.98 (0.89, 1.08)
Van der Zee et al. (1999) Urban areas	LRI	34 (?, 106)	NO ₂ , SO ₂ , sulfate	2 day	1.01 (0.93, 1.10)

1 Results of the PM_{2.5} peak flow and symptom analyses in non-asthmatic studies (see
2 Appendix 8B Table 8B-8, Table 8-34) were similar to PM₁₀ results discussed above.

3 Three authors, Schwartz and Neas (2000), Tiittanen et al. (1999) and Neas et al. (1999),
4 used PM_{10-2.5} as a coarse fraction particulate measure (Table 8-35). Schwartz and Neas (2000)
5 found that PM_{10-2.5} was significantly related to cough. Tiittanen found that one day lag of
6 PM_{10-2.5} was related to morning PEF, but there was no effect on evening PEF. Neas et al. found
7 no effects of PM_{10-2.5} on PEF.

8 The Schwartz and Neas (2000) reanalyses allows comparison of fine and coarse particle
9 effects on healthy school children using two pollutant models of fine and coarse PM. CM was
10 estimated by subtracting PM_{2.1} from PM₁₀ data. For reanalysis of the Harvard Six City Diary
11 Study in the two PM pollutant model, they report for cough a PM_{2.5} OR of 1.07 (0.90, 1.26; per
12 15 µg/m³ increment) and a PM_{10-2.5} OR of 1.18 (1.04, 1.34; per 8 µg/m³ increment) in contrast to
13 lower respiratory symptom results of a PM_{2.5} OR of 1.29 (1.06, 1.57) and a PM_{10-2.5} OR of
14 1.05 (0.9, 1.23). In the Uniontown reanalysis, peak flow for PM_{2.1} (for a 14 µg/m³ increment)
15 was -0.91 l/m (-1.14, -1.68) and for PM_{10-2.1} (for a 15 µg/m³ increment) was +1.04 l/m
16 (-1.32, +3.4). For State College, peak flow for PM_{2.1} was -0.56 (-1.13, +0.01), and for PM_{10-2.1}
17 it was -0.17 (-2.07, +1.72).

18 Coull et al. (2001) reanalyzed data from the Pope et al. (1991) study of PM effects on
19 pulmonary function of children in the Utah Valley, using additive mixed models which allow for
20 assessment of heterogeneity of response or the source of heterogeneity. These additive models
21 describe complex covariate effects on each child's peak expiratory flow while allowing for
22 unexplained population heterogeneity and serial correlation among repeated measurements. The
23 analyses indicate heterogeneity among that population with regard to PM₁₀ (i.e., specifically that
24 there are three subjects in the Utah Valley study who exhibited a particularly acute response to
25 PM₁₀). However the limited demographic data available in the Utah Valley Study does not
26 explain the heterogeneity in PM sensitivity among the school children population.

27 Two studies examined multipollutant models. The Jalaludin et al. (2000) analyses used a
28 multipollutant model that evaluated PM₁₀, O₃, and NO₂. They found in metropolitan Sydney that
29 ambient PM₁₀ and O₃ concentrations are poorly correlated (r = 0.13). For PEF the β (SE) for
30 PM₁₀ only was 0.0045 (0.0125), p = 0.72; and for PM₁₀ and O₃, 0.0051 (0.0124), p = 0.68.
31 Ozone was also unchanged in the one- and two-pollutant models. Gold et al. (1999) attempted to

TABLE 8-34. SUMMARY OF NON-ASTHMA PM_{2.5} RESPIRATORY OUTCOME STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu\text{g}/\text{m}^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 $\mu\text{g}/\text{m}^3$ PM _{2.5}
Gold et al. (1999)	Morning PEFR	30.3 (9, 69)	Ozone	1 day	-0.22 (-0.46, 0.01)
Tiittanen et al. (1999)	Morning PEFR		NO ₂ , SO ₂ , CO, ozone	0 day	1.11 (-0.64, 2.86)
Tiittanen et al. (1999)	Morning PEFR		NO ₂ , SO ₂ , CO, ozone	1-4 day	-1.93 (-7.00, 3.15)
Neas et al. (1999)	Morning PEFR	24.5 (?, 88)	Ozone	1-5 day	2.64 (-6.56, 11.83)
Schwartz & Neas (2000) Uniontown	Evening PEFR	(not given)	Sulfate fraction	0 day	-1.52 (-2.80, -0.24)
Schwartz & Neas (2000) State College	Evening PEFR	(not given)	Sulfate fraction	0 day	-0.93 (-1.88, 0.01)
Tiittanen et al. (1999)	Evening PEFR		NO ₂ , SO ₂ , CO, ozone	0 day	0.70 (-0.81, 2.20)
Tiittanen et al. (1999)	Evening PEFR		NO ₂ , SO ₂ , CO, ozone	0 day	1.52 (-3.91, 6.94)
Gold et al. (1999)	Evening PEFR	30.3 (9, 69)	Ozone	0 day	-0.10 (-0.43, 0.22)
Neas et al. (1999)	Evening PEFR	24.5 (?, 88)	Ozone	1-5 day	1.47 (-7.31, 10.22)
Tiittanen et al. (1999)	OR cough	15 (3, 55)	NO ₂ , SO ₂ , CO, ozone	0 day	1.04 (0.86, 1.20)
Tiittanen et al. (1999)	OR cough	15 (3, 55)	NO ₂ , SO ₂ , CO, ozone	2 day	1.24 (1.02, 1.51)
Schwartz & Neas (2000)	OR LRS	(not given)	Sulfate fraction	0 day	1.61 (1.19, 2.14)

TABLE 8-35. SUMMARY OF NON-ASTHMA COARSE FRACTION STUDIES OF RESPIRATORY ENDPOINTS

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu\text{g}/\text{m}^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to $25 \mu\text{g}/\text{m}^3 \text{PM}_{10-2.5}$
Tiittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	1 day	-1.26 (-2.71, 0.18)
Neas et al. (1999)	Morning PEFR	8.3	Ozone	1 day	-4.31 (-11.43, 2.75)
Tiittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	2 day	0.51 (-0.77, 2.16)
Tiittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	1-4 day	-0.57 (-1.96, 0.81)
Neas et al. (1999)	Morning PEFR	8.3	Ozone	1-5 day	-6.37 (-21.19, 8.44)
Tiittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	0 day	0.66 (-0.33, 1.81)
Neas et al. (1999)	Evening PEFR	8.3	Ozone	1 day	1.88 (-4.75, 8.44)
Tiittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	2 day	0.03 (-1.41, 1.47)
Tiittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	1-4 day	2.37 (-1.69, 4.96)
Neas et al. (1999)	Evening PEFR	8.3	Ozone	1-5 day	5.94(-7.00, 18.94)
Tiittanen et al. (1999)	OR cough	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	0 day	0.99 (0.87, 1.12)
Tiittanen et al. (1999)	OR cough	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	2 day	1.23 (1.06, 1.42)
Tiittanen et al. (1999)	OR cough	8 (.2, 67)	NO ₂ , SO ₂ , CO, ozone	1-4 day	1.31 (0.81, 2.11)
Schwartz & Neas (2000)	OR cough without other symptoms	(not given)	Sulfate fraction	0 day	1.77 (1.24, 2.55)
Schwartz & Neas (2000)	OR LRS	(not given)	Sulfate fraction	0 day	1.51 (0.94, 4.87)

1 study the interaction of $PM_{2.5}$ and O_3 on PEF in Mexico City children (age = 8 to 12 yrs). The
2 authors found independent effects of the two pollutants, but the joint effect was slightly less than
3 the sum of the independent effects.

4 5 **8.3.3.2 Long-Term Particulate Matter Exposure Effects on Lung Function and** 6 **Respiratory Symptoms**

7 *8.3.3.2.1 Summary of 1996 Particulate Matter Air Quality Criteria Document Key Findings*

8 In the 1996 PM AQCD, the available long-term PM exposure-respiratory disease studies
9 were limited in terms of conclusions that could be drawn. At that time, three studies based on a
10 similar type of respiratory symptom questionnaire administered at three different times as part of
11 the Harvard Six-City and 24-City Studies provided data on the relationship of chronic respiratory
12 disease to PM. All three studies suggest a long-term PM exposure effect on chronic respiratory
13 disease. The analysis of chronic cough, chest illness and bronchitis tended to be significantly
14 positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using
15 a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include
16 24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio
17 = 1.66) in the community with the highest particle strong acidity when compared with the least
18 polluted community. Fine particulate sulfate was also associated with higher reporting of
19 bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

20 Interpretation of such studies requires caution in light of the usual difficulties ascribed to
21 cross-sectional studies. That is, evaluation of PM effects is based on variations in exposure
22 determined by a different number of locations. In the first two studies, there were six locations
23 and, in the third, twenty-four. The results seen in all studies were consistent with a PM gradient,
24 but it was not readily possible to separate out clear effects of PM from other factors or pollutants
25 having the same gradient.

26 Chronic pulmonary function studies by Ware et al. (1986), Dockery et al. (1989), and Neas
27 et al. (1994) had good monitoring data and well-conducted standardized pulmonary function
28 testing over many years, but showed no effect for children from airborne particle pollution
29 indexed by TSP, PM_{15} , $PM_{2.5}$ or sulfates. In contrast, the Raizenne et al. (1996) study of U.S.
30 and Canadian children found significant associations between FEV_1 and FVC and acidic
31 particles (H^+). Overall, the available studies provided only limited evidence suggestive of

1 pulmonary lung function decrements being associated with chronic exposure to PM indexed by
2 various measures (TSP, PM₁₀, sulfates, etc.). However, it was noted that cross-sectional studies
3 require very large sample sizes to detect differences because they cannot eliminate person to
4 person variation, which is much larger than the within person variation. There may be so much
5 noise in the large variability that one cannot observe the exposure - effect signal.

7 ***8.3.3.2.2 New Studies of Respiratory Effects of Long-Term Particulate Matter Exposure***

8 Several studies published since 1996 evaluated effects of long-term PM exposure on lung
9 function and respiratory illness (see Appendix 8B, Table 8B-8). The new studies examining
10 PM₁₀ and PM_{2.5} in the United States include McConnell et al. (1999), Abbey et al. (1998),
11 Berglund et al. (1999), Peters et al. (1999a,b), and Avol et al. (2001), all of which examined
12 effects in California cohorts but produced variable results. McConnell et al. (1999) noted that,
13 as PM₁₀ increased across communities, the bronchitis risk per interquartile range also increased,
14 results consistent with those reported by Dockery et al. (1996). However, the high correlation of
15 PM₁₀, acid, and NO₂ precludes clear attribution of the McConnell et al. bronchitis effects
16 specifically to PM alone. Avol et al. (2001) reported that, for 110 children who moved to other
17 locations, those subjects who moved to areas of lower PM₁₀ showed increased growth in lung
18 function and subjects who moved to communities with higher PM₁₀ showed slowed lung
19 function growth.

20 Gauderman et al. (2000, 2002) presented results from a study that is both a cohort and a
21 cross-sectional study. This unique design followed two cohorts of southern California children
22 who were fourth graders in 1993 and 1996 respectively. The cohorts, located in 12 communities,
23 were followed for 4 years. A three stage model which allowed for individual slopes, within
24 community covariates, and community-wide air pollution averages, was fitted using SAS Proc
25 MIXED. Pulmonary function measurements included FVC, FEV₁, MMEF, and PEF_R, all of
26 which gave similar results for both PM_{2.5} and PM₁₀. In the first cohort, PM₁₀ showed a
27 significant 1.3% decrease in annual growth rates for a 51.5 µg/m³ difference in PM₁₀. This
28 difference was only 0.4% in the second cohort; however, the two were not significantly different
29 from each other. The effect for PM_{2.5} was slightly less for a difference of 22.2 µg/m³. In an
30 earlier cross-sectional analysis, Peters et al. (1999b) studied the prevalence of respiratory
31 symptoms in 12 southern California communities in 1993. To estimate the relationship between

1 symptoms and pollutants a two-stage regression approach was used. The first stage estimated
2 community-specific rates adjusted for individual covariates. The second stage regressed these
3 rates on pollutant averages from 1986 to 1990, finding no significant relationships between
4 respiratory symptoms and average PM₁₀ levels.

5 In a non-U.S. PM₁₀ study, Horak et al. (2002) conducted a combined cohort and cross-
6 sectional study similar in design to that of Gauderman et al. (2000). The cohorts were taken
7 from 975 school children in 8 communities in lower Austria between 1994-1997. Relationships
8 were estimated from generalized estimating equations adjusting for autocorrelation.
9 Adjustments were made for sex, atopy, ETS, baseline lung function, height, and site. Growth in
10 FVC and MEF were significantly related to winter PM₁₀ levels.

11 Gehring et al. (2002) enrolled 1,756 newborn children in the Munich area. Individual
12 PM_{2.5} and NO₂ levels were estimated from actual measurements at 40 sites combined with a GIS
13 predictor model. PM_{2.5} levels ranged from 11.9 to 21.9 µg/m³. The incidence (in the first two
14 years of life) of cough without infection and dry cough at night were related to PM_{2.5} levels.
15 Wheeze, bronchitis, respiratory infections, and runny nose were not related to PM_{2.5} levels.

16 Other non-U.S. studies examined PM measures such as TSP and BS in European countries.
17 In Germany, Heinrich et al. (2000) reported a cross-sectional survey of children, conducted
18 twice (with the same 971 children included in both surveys). TSP levels decreased between
19 surveys, as did the prevalence of all respiratory symptoms (including bronchitis). Also, Krämer
20 et al. (1999) reported a study in six East and West Germany communities, which found
21 decreasing yearly TSP levels to be related to ever-diagnosed bronchitis from 1991-1995. Lastly,
22 Jedrychowski et al. (1999) reported an association between both BS and SO₂ levels in various
23 areas of Krakow, Poland, and slowed lung function growth (FVC and FEV₁).

24 Leonardi et al. (2000) studied a different health outcome measure as part of the Central
25 European Air Quality and Respiratory Health (CESAR) study. Blood and serum samples were
26 collected from school children ages 9-11 yrs. in each of 17 communities in Central Europe
27 (N = 10 to 61 per city). Numbers of lymphocytes increased as PM concentrations increased
28 across the cities. Regression slopes, adjusted for confounder effects, were larger and statistically
29 significant for PM_{2.5}, but small and non-significant for PM_{10-2.5}. A similar positive relationship
30 was found between IgG concentration in serum and PM_{2.5} gradient, but not for PM₁₀ or PM_{10-2.5}.

8.3.3.2.3 *Summary of Long-Term Particulate Matter Exposure Respiratory Effects*

The methodology used in the long-term studies varies much more than the methodology in the short-term studies. Some studies reported highly significant results (related to one or another ambient PM indicator), whereas others reported no significant results. The cross-sectional studies are often confounded, in part, by unexplained differences between geographic regions. The studies that looked for a time trend are also confounded by other conditions that were changing over time. The newer cohort studies provide the best evidence bearing on chronic PM exposure effects. The Gauderman et al. (2000, 2002) cohort studies found significant decreases in lung function growth among So. California school children to be related to PM₁₀ levels, but the Peters et al. (1999b) cross-sectional study of the children in the Gauderman et al. cohorts found no relationship between respiratory symptoms and annual average PM₁₀ levels in 12 southern California communities. In addition, the well-conducted cross-sectional studies by Dockery et al. (1996) and Raizenne et al. (1996), assessed earlier in the 1996 PM AQCD, found differences in peak flow and bronchitis rates associated with fine particle sulfate and acidity, and they remain among the more credible available studies of long-term PM exposure effects on respiratory function symptoms.

8.3.4 **Ambient PM Impacts on Fetal and/or Early Postnatal Development/Mortality**

Some older cross-sectional mortality studies reviewed in the 1996 PM AQCD suggested that the young may represent a susceptible subpopulation for PM-related mortality. Lave and Seskin (1977), for example, found significant associations of TSP mortality among those 0-14 years of age. Also, Bobak and Leon (1992) studied neonatal (ages < 1 mo) and post-neonatal mortality (ages 1-12 mo) in the Czech Republic and reported significant associations between PM₁₀ and post-neonatal mortality, even after considering other pollutants. Post-neonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM₁₀ remained significant in multi-pollutant models. The exposure duration was longer than a few days, but shorter than in adult chronic PM exposure prospective cohort studies. Thus, the few available studies reviewed in the 1996 PM AQCD suggested an association between ambient PM concentrations and infant mortality, especially among post-

1 neonatal infants. More recent studies have focused on ambient PM relationships (a) with
2 intrauterine mortality and morbidity and (b) with early post neonatal infant mortality.

3 4 **8.3.4.1 PM Effects on Intrauterine Fetal Morbidity / Mortality**

5 During the past decade or so, increasing attention has begun to be focused on the
6 evaluation of possible effects or prenatal exposures to ambient PM and other “criteria air
7 pollutants” on fetal growth and development. Concerns about these possible air pollution
8 impacts, as indexed by measures such as low birth weight (LBW) or preterm births, are
9 prompted by studies indicating that both preterm births and low birth weights are important
10 predictors of infant mortality, childhood morbidity, and perhaps even adult morbidity (Barker
11 et al., 1993; Spinello et al., 1995; Joseph and Kramer, 1996). In evaluating possible pollutant
12 effects, a number of variables with well-established links to fetal growth and development must
13 be taken into account, e.g., maternal and paternal weight and height, gestational weight gain,
14 maternal smoking and alcohol consumption, the infant’s sex and racial/ethnic background, etc.
15 (Kramer, 1987; Berkowitz and Papiernik, 1993; Divon et al., 1994).

16 In one large-scale U.S. study, Ritz et al (2000) evaluated the effects of ambient PM₁₀, CO,
17 NO₂, SO₂, and O₃ exposures during pregnancy on the occurrence of preterm births among a
18 cohort of 97,518 neonates born in the South Coast Air Basin (SoCARB) of California. Pollutant
19 values measured at the closest of 17 air-monitoring stations (within 2 mi. radius of residential zip
20 code on birth certificate) were averaged over the entire pregnancy or distinct periods during
21 pregnancy for each birth in nondesert portions of Los Angeles, San Bernardino, Riverside, and
22 Orange Counties (which comprise the SoCARB district) during 1989 - 1993. Adjusting for
23 various factors known to be related to occurrence of premature births (e.g., maternal age, race,
24 smoking during pregnancy, etc.), the effects of the different air pollutants on preterm birth risk
25 were analyzed by means of both single-pollutant and multiple pollutant logistic regression
26 models. A 16% increase in preterm birth risk was estimated per 50 µg/m³ increment in PM₁₀
27 concentrations averaged over the first month of pregnancy (RR=1.20; CI 1.06, 1.26) and a 20%
28 increase per 50 µg/m³ PM₁₀ averaged over 6 weeks prior to birth. The effects sizes varied only
29 slightly between single and multiple pollutant models or with adjustments for other risk factors.
30 Significant associations were also found for CO, but inclusion of other pollutants or covariates in

1 the model caused CO effect estimates to fluctuate. For both PM₁₀ and CO, the most precise
2 effects estimates (with narrowest CI) were found for exposures averaged over 6 weeks prebirth.

3 In another large U.S. study, Maisonet et al. (2001) evaluated associations between low
4 birth weight (LBW, $\leq 2,500$ g at birth) and daily average PM₁₀, SO₂, and CO levels, based on
5 every 6th day ambient 24 hr PM₁₀ monitor readings and 24 hr averages of hourly SO₂ and CO
6 readings at community monitoring stations in six Northeastern U.S. cities (Boston, MA;
7 Hartford, CT; Philadelphia, PA; Pittsburgh, PA; Springfield, MA; Washington, DC). Using air
8 pollution data from U.S. EPA, average trimester exposures were estimated for PM₁₀, SO₂, and
9 CO based on 3 to 4 PM₁₀, 1 to 4 SO₂, and 2 to 4 CO monitors per city. Based on NCHS data
10 sets, information on numerous covariates (e.g., gestational age, gender, maternal age, maternal
11 race/ethnicity, maternal prenatal smoking, alcohol consumption, etc.) was included in a logistic
12 regression model to generate adjusted odds ratios (AOR) and 95% CI for LBW, and then linear
13 regression models were used to assess reductions in birth weight (in grams) in relation to each
14 air pollution variable. Ranges of exposure categories were defined for each air pollutant as
15 percentiles of the exposure distribution ($< 25^{\text{th}}$ percentile; 25 to 50th; 50th to 75th; 75th to 95th; and
16 $\geq 95^{\text{th}}$). Of 130,465 live singleton births during 1994 to 1996, after exclusions for several
17 reasons, 89,557 (68.6%) of infants were included in the final analyses. There were no
18 statistically significant ($p < 0.05$) associations between LBW and PM₁₀ percentile groups
19 $\geq 25^{\text{th}}$ versus $< 25^{\text{th}}$ percentile or for continuous ($10 \mu\text{g}/\text{m}^3$) PM₁₀ and LBW during any of the
20 prenatal trimesters among white or African-American infants. However, first trimester ambient
21 PM₁₀ levels were associated with increased risk for full-term LBW among Hispanics (AOR 1.36;
22 CI 1.06, 1.75). Much more consistent increases in AOR for LBW were found for various
23 trimesters of CO and/or SO₂ exposure. The authors concluded that, overall, LWB was not
24 associated with PM₁₀ exposure during pregnancy.

25 Rogers et al. (2000) reported results of another, much smaller, population-based case-
26 control study of possible associations between exposures to ambient TSP and SO₂ (using a
27 combined TSP SO₂ index) and risk of having a very low birth weight (VLBW) baby (i.e.,
28 weighing $< 1,500$ g at birth) among women residing in Atlanta, Savannah, or other areas in
29 Georgia Health Care District 9 in 1986-88. Environmental transport models were used to
30 estimate TSP SO₂ exposures at the birth homes of study subjects, and exposures $\leq 9.94 \mu\text{g}/\text{m}^3$,
31 the median of TSP and SO₂ exposures for the control subjects were used as referent exposures.

1 The controls included 202 mothers of babies weighing 1,500 g or more at birth for comparison
2 versus 143 mothers of VLBW babies. A distinct trend suggesting a relationship between
3 TSP/SO₂ exposure and increased risk for VLBW was reported. However, the results, while
4 suggestive of possible ambient TSP and/or SO₂ effects on VLBW at high exposure levels
5 (frequency distributions for cases and controls began to separate at ~55 µg/m³ TSP SO₂), are not
6 based on direct TSP or SO₂ monitoring data and should not be accorded much weight unless
7 confirmed by other studies using better more directly measured air pollution exposure indices.

8 With regard to new non-U.S. studies of prenatal PM exposure effects on intrauterine
9 morbidity / mortality, Dejmek et al. (1999) evaluated possible impacts of ambient PM₁₀ and
10 PM_{2.5} exposure (monitored by EPA-developed VAPS methods) during pregnancy on risk for
11 intrauterine growth retardation (IUGR) in the highly polluted Teplice District of Northern
12 Bohemia in the Czech Republic during 1993-1996. Mean levels of pollutants (PM, NO₂, SO₂)
13 were calculated for each month of gestation and three concentration intervals (low, medium,
14 high) were derived for each pollutant. Preliminary analyses found significant associations of
15 IUGR with PM₁₀ and SO₂ early in pregnancy but not with NO₂. Odds ratios for IUGR for PM₁₀
16 and PM_{2.5} levels were determined by logistic regressions for each month during gestation, after
17 adjusting for potential confounding factors (e.g., maternal smoking, alcohol consumption during
18 pregnancy, etc.). Definition of an IUGR birth was any one for which the birth weight fell below
19 the 10th percentile by gender and age for live births in the Czech Republic (1992-93). The ORs
20 for IUGR were significantly related to PM₁₀ during the first month of gestation: that is, as
21 compared to low PM₁₀, the medium level PM₁₀ OR = 1.47 (CI: 0.99, 2.16) and the high level
22 PM₁₀ OR = 1.85 (CI: 1.29, 2.66). PM_{2.5} levels were highly correlated with PM₁₀ (r = 0.98) and
23 manifested similar patterns (OR = 1.16, CI: 0.08, 0.69 for medium PM_{2.5} level; OR = 1.68,
24 CI: 1.18, 2.40 for high PM_{2.5} level). These results suggest effects of PM exposures (probably
25 including fine particles such as sulfates, acid aerosols, and PAHs in the Teplice ambient mix)
26 early in pregnancy (circa embryo implantation) on fetal growth and development.

27 In broader further analyses of the same data set from which the above Czech study results
28 were derived, Dejmek et al. (2000) evaluated relationships between IUGR and exposures to
29 PM₁₀, PM_{2.5} and PAHs during early pregnancy among women residing in the highly polluted
30 Teplice area or in Prachatice (an area with similarly high PAH but low particle concentrations).
31 Mean PM₁₀, PM_{2.5} and c-PAH exposures during 9 gestation months (GM) were estimated for

1 each mother and regressed (controlling for several potential covariates, e.g., maternal age,
2 smoking, alcohol consumption, parental education, etc.) in logistic regression models against
3 data for all European-origin live births during 1993 to 1998 in Teplice (n = 3,378) and Prachatice
4 (n = 1,505). The adjusted odds ratio (AOR) for IURG confirmed the previously published
5 findings noted above for increased risk of IURG being associated with ambient particle
6 exposures in Teplice during the first GM, but not in Prachatice (the lower particle area).
7 Adjusted odds ratios calculated for low, medium, and high c-PAH levels (L = < 15, M = 15-30,
8 M ≥ 30 ng/m³) for fetuses from Teplice during the first GM were 1.60 (CI: 1.06, 2.15) and
9 2.15 (CI: 2.7, 3.6), respectively, for medium and high c-PAHs versus the low c-PAH exposure
10 group. Similar associations were reported for the medium and high PAH exposures (during first
11 GM) in Prachatice even in the presence of low overall particle levels, prompting the authors to
12 hypothesize a likely important role for PAHs.

13 14 **8.3.4.2 PM Effects on Post-Neonatal Infant Mortality**

15 Results suggestive of possible early postnatal PM exposure effects on neonatal infant
16 mortality have also emerged from some new studies. Woodruff et al. (1997), for example, used
17 cross-sectional methods to evaluate possible associations between post-neonatal infant mortality
18 and ambient PM₁₀ pollution in U.S. urban areas. This study involved an analysis of a cohort of
19 ~4 million infants born during 1989-1991 in 86 U.S. metropolitan statistical areas (MSAs). Data
20 from the National Center for Health Statistics-linked birth/infant death records were combined at
21 the MSA level with PM₁₀ data from EPA's Aerometric database. Infants were categorized as
22 having low, medium, or high exposures based on tertiles of PM₁₀ averaged over the first
23 2 postnatal months. Relationships between this early neonatal PM₁₀ exposure and total and
24 cause-specific post-neonatal mortality rates (from 1 mo to 1 y of age) were examined using
25 logistic regression analyses, adjusting for demographic and environmental factors. Overall post-
26 neonatal mortality rates per 1,000 live births were 3.1 among infants in areas with low PM₁₀
27 exposures, 3.5 among infants with medium PM₁₀ exposures, and 3.7 among high PM₁₀ exposed
28 infants. After adjustment for covariates, the OR and 95% confidence intervals for total post-
29 neonatal mortality for the high versus the low exposure group was 1.10 (CI: 1.04, 1.16). For
30 normal birth weight infants, high PM₁₀ exposure was associated with mortality for respiratory
31 causes (OR = 1.40, CI: 1.05, 1.85) and sudden infant death syndrome (OR = 1.26, CI: 1.14,

1 1.39). Among low birth weight babies, high PM₁₀ exposure was positively (but not significantly)
2 associated with mortality from respiratory causes (OR = 1.18, CI: 0.86, 1.61). However, other
3 pollutants (e.g., CO) were not considered as possible confounders, and this lack of consideration
4 of other air pollutants as potential confounders in this new study introduces uncertainty in
5 attribution of observed effects to PM.

6 Lipfert et al. (2000c) used a modeling approach similar to that of Woodruff et al. (1997),
7 but used annual-average PM₁₀ air quality data for one year (1990) instead of PM₁₀ averaged over
8 the first two postnatal months during 1989-1991. The quantitative relationship between the
9 individual risk of infant mortality did not differ among infant categories (by age, by birthweight,
10 or by cause), but PM₁₀ risks for SIDS deaths were higher for babies of smoking mothers. SO₄⁻²
11 was a strong negative predictor of SIDS mortality for all age and birth weight categories. The
12 authors (a) noted difficulties in ascribing the reported PM₁₀ and SO₄⁻² associations to effects of
13 the PM pollutants per se versus the results possibly reflecting interrelationships between the air
14 pollution indices, a strong well-established East-West gradient in U.S. SIDS cases, and/or
15 underlying sociodemographic factors (e.g., the socioeconomic or education level of parents) and
16 (b) hypothesized that a parallel gradient in use of wood burning in fireplaces or woodstoves and
17 consequent indoor wood smoke exposure might explain the observed cross-sectional study
18 results. Lipfert et al. (2000c) also raised questions as to whether the findings of Woodruff et al.
19 (1977) could be due to confounding factors.

20 The study by Loomis et al. (1999) of infant mortality in Mexico City during 1993-1995
21 provides interesting information pointing towards possible fine particle effects on infant
22 mortality. That is, in Mexico City (where mean 24-h PM_{2.5} = 27.4 µg/m³), infant mortality was
23 found to be associated with PM_{2.5}, NO₂, and O₃ in single pollutant GAM Poisson models, but
24 much less consistently with NO₂ and O₃ than PM_{2.5} in multipollutant models. The estimated
25 excess risk for PM_{2.5}-related infant mortality lagged 3-5 days was 18.2% (CI = 6.4, 30.7) per
26 25 µg/m³ PM_{2.5}. The extent to which such a notable increased risk for infant mortality might be
27 extrapolated to U.S. situations is not clear, however, due to possible differences in prenatal
28 maternal or early postnatal infant nutritional status.

29 Bobak and Leon (1999) conducted a matched population-based case-control study covering
30 all births registered in the Czech Republic from 1989 to 1991 that were linked to death records.
31 They used conditional logistic regression to estimate the effects of suspended particles and

1 nitrogen oxides on risk of death in the neonatal and early post-neonatal period, controlling for
2 maternal socioeconomic status and birth weight, birth length, and gestational age. The effects of
3 all pollutants were strongest in the post-neonatal period and specific for respiratory causes. Only
4 PM showed a consistent association when all pollutants were entered in one model. Thus, in this
5 study, long-term exposure to PM was the air pollutant metric most strongly associated with
6 excess post-neonatal deaths.

8 **8.3.4.3 Summary of Salient Points on PM Effects on Fetal and/or Early Postnatal** 9 **Development/Mortality**

10 A few older cross-sectional studies reviewed in the 1996 PM AQCD reported findings
11 suggestive of (a) possible TSP relationship to increased postnatal mortality among U.S. infants,
12 children, and adolescents (aged 0-14 yrs.) and (b) possible associations between early postnatal
13 mortality among Czech infants (1-12 mo). Several more recent studies conducted in the U.S.
14 have focused on the possible effects of air pollution exposures during pregnancy on the
15 occurrence of preterm or low birth weight births, both of these being risk factors for a myriad of
16 later health problems (childhood morbidity/mortality; possible adult morbidity). One study
17 found results suggestive of prenatal PM₁₀ exposures during the 1st month of pregnancy or
18 averaged over 6 weeks prior to birth being associated with increased risk of preterm birth, even
19 in multi pollutant models. However, another large scale U.S. study found little evidence
20 indicative of prenatal PM₁₀ exposures being related to increased risk of low birth weight,
21 whereas a new Czech study did find evidence indicative of interuterine growth retardation
22 (leading to low birth weight) being related to PM_{2.5} exposures during the first gestational month.
23 Similarly, analogously mixed results were reported for some new studies that evaluated ambient
24 PM relationships to early postnatal mortality among U.S., Czech, and Mexican infants. These
25 results, overall, highlight the need for more research to elucidate potential ambient PM effects on
26 fetal development/mortality and for postnatal morbidity/mortality.

1 **8.4 INTERPRETIVE ASSESSMENT OF THE EPIDEMIOLOGIC** 2 **EVIDENCE**

3 **8.4.1 Introduction**

4 Numerous PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient
5 PM as a likely contributor to mortality and morbidity effects associated with ambient air
6 pollution exposures. Since preparation of the 1996 PM AQCD, the epidemiologic evidence
7 concerning ambient PM-related health effects has vastly expanded. Past regulatory decisions
8 have been important in the selection of PM indices and evolution of PM epidemiologic literature.
9 That is, the adoption of PM₁₀ standards in 1987 and of PM_{2.5} standards in 1997 have generated
10 ambient air concentration databases that have made it possible for research to address many
11 previously unresolved issues regarding potential linkages between airborne PM and human
12 health; and the newly authorized nationwide network of speciation samplers holds promise for
13 further advances regarding identification of the most influential specific components of the
14 ambient air pollution mixture and their sources.

15 As was discussed in Sections 8.2 and 8.3, numerous new PM epidemiology studies have
16 evaluated health effects associated with short or long-term ambient PM exposure. Most have
17 found positive associations (many being statistically significant) between (a) excess risks for
18 various mortality and/or morbidity endpoints in many U.S. cities and elsewhere and (b) ambient
19 PM indexed by a variety of ambient community monitoring methods. Some other new studies
20 have found positive, but non-significant associations with PM, and a few have reported negative
21 (usually non-significant) associations with ambient PM and/or more robust gaseous co-pollutant
22 effects. Several issues and attendant uncertainties continue to be important in assessing and
23 interpreting the overall PM epidemiology database and its implications for estimating risks
24 associated with exposure to ambient PM concentrations in the United States. These include
25 issues concerning: (1) approaches to model specification to take into account important effect
26 modifiers (such as weather) and to control for potential confounding of PM effects by co-
27 pollutants (especially major gaseous pollutants such as O₃, CO, NO₂, SO₂); (2) temporal
28 relationships between exposure and effect (lags); (3) potential consequences of measurement
29 error; (4) attribution of various types of health effects to specific PM components (e.g., PM₁₀,
30 PM_{10-2.5}, PM_{2.5}, ultrafines, sulfates, metals, etc.) or to source-oriented indicators (motor vehicle
31 emissions, vegetative burning, etc.); (5) the general shape of exposure-response relationship(s)

1 between PM and/or other pollutants and observed health effects (e.g., potential indications of
2 thresholds); (6) geographic homogeneity / heterogeneity of PM exposure-health risk
3 relationships; and (7) implications of PM-related mortality effects (e.g. mortality displacement;
4 life shortening). All of these issues are of much importance for characterizing and interpreting
5 ambient PM-health effects associations.

6 Assessing the above uncertainties in relation to the PM epidemiology data base remains a
7 challenge. The basic issue is that there are an extremely large number of possible models, any of
8 which may turn out to give the best statistical “fit” of a given set of data, and only some of which
9 can be dismissed *a priori* as biologically or physically illogical or impossible, except that
10 putative cause clearly cannot follow effect in time. Most of the models for daily time-series
11 studies are fitted by adjusting for changes over long time intervals and across season, by day of
12 week, weather, and climate. Many of the temporal and weather variable models have been fitted
13 to data using semi-parametric methods such as spline functions or local regression smoothers
14 (LOESS). The goodness of fit of these base models has been evaluated by criteria suitable for
15 generalized linear models (GLM) with Poisson or hyper-Poisson responses (number of events)
16 with a log link function, particularly the Akaike Information Criterion (AIC) and the more
17 conservative Bayes information criterion (BIC), which adjust for the number of parameters
18 estimated from the data. The Poisson over-dispersion index and the auto-correlation of residuals
19 are also often used. However, if high correlations between PM and one or more gaseous
20 pollutants emitted from a common source (e.g., motor vehicles) exist in a given area, then
21 disentangling their relative individual partial contributions to observed health effects
22 associations becomes very difficult.

23 An informed modeling strategy can yield a useful set of models as one type of sensitivity
24 analysis. To illustrate, a systemic evaluation of model choice has been carried out by Clyde
25 et al. (2000), using Bayesian Model Averaging for the same Birmingham, AL, data as analyzed
26 by Smith et al. (2000). Several different calibrated information criterion priors were tried in
27 which models with large numbers of parameters are penalized to various degrees. After taking
28 out a baseline trend (estimated using a GLM estimate with a 30-knot thin-plate smoothing
29 spline), 7,860 models were selected for use in model averaging. These included lags 0-3 days of
30 a daily monitor PM_{10} , an area-wide average PM_{10} value with the same lags, temperature (daily
31 extremes and average) lagged 0-2 days, humidity (dewpoint, relative humidity min and max,

1 average specific humidity) lagged 0-2 days, and atmospheric pressure, lagged 0-2 days. The
2 model choice is sensitive to the specification of calibrated information criterion priors, in
3 particular disagreeing as to whether different PM₁₀ variables should be included or not.
4 For example, one or another PM₁₀ variable is included in all the top 25 Akaike Information
5 Criterion (AIC) models, but only in about 1/3 of the top Bayes Information Criterion (BIC)
6 models. Both approaches give a relative risk estimate of about 1.05, with credibility intervals of
7 (0.94, 1.17) for the AIC prior and (0.99, 1.11) for the BIC prior. A validation study in which
8 randomly selected data were predicted using the different priors favored Bayesian model
9 averaging with BIC prior over model selection (picking the best model) with BIC or any
10 approach with AIC. This type of modeling may represent another type of multi-pollutant
11 modeling approach in addition to more typical hypotheses-driven model construction and
12 interpretation that draws more on external information (e.g., exposure, dosimetric, toxicologic
13 relationships) in specifying models and interpreting their results.

14 In most of this document, confidence intervals, or credible intervals for Bayesian analyses,
15 are reported in order to emphasize that the effect size is not known with certainty, but some
16 values are more nearly consistent with the data than effect size values outside the interval.
17 P-values or t-values are implicitly associated with a null hypothesis of no effect. A nominal
18 significance level of $p \leq 0.05$ or 5% (i.e., a 95% confidence interval) is usually used as a guide
19 for the reader, but P-values should not be used as a rigid decision-making tool. If the observed
20 confidence intervals were arrived at by a number of prior model specification searches,
21 eliminating some worse fitting models, the true interval may well be wider.

22 Given the now extremely large number of published epidemiologic studies of ambient PM
23 associations with health effects in human populations and the considerably wide diversity in
24 applications of even similar statistical approaches (e.g., “time-series analyses” for short-term PM
25 exposure effects), it is neither feasible nor useful here to try to evaluate the methodological
26 soundness of every individual study. Rather, a four-pronged approach is likely to yield useful
27 evaluative information: (1) an overall characterization of evident general commonalities (and/or
28 notable marked differences) among findings from across the body of studies dealing with
29 particular PM exposure indices and types of health outcomes, looking for convergence (and/or
30 divergence) of evidence regarding types of effects and effect-sizes attributable to ambient PM
31 indices across various geographic locations based on various methodologically acceptable

1 analyses; (2) thorough, critical assessment of newly published multi-city analyses of PM effects,
2 assuming that greater scientific weight is generally ascribable to their results than those of
3 smaller-sized studies (often of individual cities) yielding presumably less precise effect size
4 estimates; (3) evaluation of, albeit at times less precise, single city results; and (4) evaluation of
5 coherence of the findings with other types of pertinent biological information (e.g., exposure,
6 dosimetry, toxicity, etc.).

7 In the sections that follow, issues noted above are critically discussed. First follows a
8 discussion of the GAM issue and a summary of some key findings emerging from the short
9 communications and peer-review commentary published by HEI (2003b).

11 **8.4.2 GAM Issue and Reanalyses Studies**

12 As discussed earlier, Dominici et al. (2002) reported that the default convergence criteria
13 used in the S-Plus function GAM may not guarantee convergence to the best unbiased estimate
14 in all cases. The actual importance of this effect has begun to be quantified, with the results of
15 the reanalyses of a number of important studies described in short communications published in
16 the HEI (2003c) Special Report being especially helpful in this regard. As for the net outcome
17 of these reanalyses efforts, HEI (2003c) summarizes it well, as follows:

18
19 Overall, the revised analyses using GAM with more stringent convergence criteria and
20 iterations and GLM-natural splines resulted in lower estimates, but largely confirmed the
21 effect of exposure to particulate matter on mortality (Burnett and Goldberg, 2003; Dominici
22 et al., 2003; Katsouyanni et al., 2003; Samoli et al., 2003; Schwartz, 2003b; Zanobetti and
23 Schwartz, 2003b) and morbidity, especially for hospitalizations for cardiovascular and
24 respiratory diseases (Atkinson et al., 2003; Fairley, 2003; Gold et al., 2003; Hoek, 2003; Ito,
25 2003; Le Tertre et al., 2003; Ostro et al., 2003; Schwartz, 2003a; Sheppard, 2003; Zanobetti
26 and Schwartz, 2003a). As in earlier analyses, the effect was more pronounced among
27 individuals 65 years of age and older (Fairley; Gold et al.; Goldberg and Burnett; Ito; Le
28 Tertre et al.; Mar et al.; Moolgavkar; Schwartz a). The impact of various sensitivity analyses,
29 when these were performed, differed across the studies. No significant impacts were seen in
30 some (Ostro et al.), whereas in others, alternative modeling of time (Klemm and Mason;
31 Moolgavkar) and weather factors (Goldberg and Burnett; Ito) resulted in substantial changes.

1 The following discussion elaborates in more detail the nature and extent of potential
2 problems in various studies that have used the GAM default algorithm, but which have also had
3 their analyses redone using alternative methods in order to address this convergence issue.
4

5 **8.4.2.1 Impact of Using the More Stringent GAM Model on PM Effect Estimates** 6 **for Mortality**

7 Many of the reanalysis studies analyzed associations between PM_{10} and mortality, allowing
8 evaluation of the impact of the GAM convergence problem on this PM index. Table 8-36 and
9 Figure 8-15 show the percent excess total non-accidental mortality (unless noted otherwise) risk
10 estimates per $50 \mu\text{g}/\text{m}^3$ increase in PM_{10} derived from the reanalysis studies for (1) GAM with
11 default convergence criteria; (2) GAM with stringent convergence criteria; and, (3) GLM with
12 natural splines that approximate the original GAM model. The table and figure show results
13 only from the studies that used all of the three alternative models for PM_{10} . It can be seen that
14 most, but not all, reanalyses resulted in reductions in PM_{10} risk estimates when more stringent
15 convergence criteria were used in GAM models. Using GLM with natural splines resulted in
16 additional reduction in PM_{10} risk estimates for most, but not all, cases. The extent of reduction
17 in PM_{10} risk estimates seen with use of GAM with more stringent convergence criteria or GLM
18 with natural splines was generally proportionally greater for the larger-scale multi-city studies
19 than for the single-city analyses. The decreases in PM_{10} effect size estimates for the multi-city
20 studies can be seen in Table 8-36 to fall rather evenly across the range of -3 to -33% for the
21 GAM-stringent and from -18 to -52% for the GLM reanalyses values. In contrast, the single-
22 city reanalyses yielded PM_{10} effect size estimates that were generally little changed from the
23 original estimates (varying by $\pm 10\%$ for 7 of 9 GAM-stringent and for 6 of 9 GLM reanalyses,
24 with the others decreasing by 17 to 59%). The relative percent reduction is greater for the
25 studies that had smaller PM_{10} risk estimates in the original analyses (e.g., NMMAPS U.S.
26 90 cities analyses). It can also be seen in Figure 8-15 that the extent of reduction in PM_{10} risk
27 estimates is smaller than the variability of PM_{10} risk estimates across the studies. Thus, the
28 effect of the GAM convergence problem does not appear, in most cases, to be substantial.
29 Several of the reanalysis reports also analyzed $PM_{2.5}$ and $PM_{10-2.5}$. Generally, the pattern and
30 extent of reductions in mortality risk estimates were similar to those for PM_{10} . The results for
31 $PM_{2.5}$ and $PM_{10-2.5}$ mortality risk estimates are compared in a later section.

TABLE 8-36. PM₁₀ EXCESS RISK ESTIMATES FROM REANALYSIS STUDIES FOR TOTAL NON-ACCIDENTAL MORTALITY PER 50 µg/m³ INCREASE IN PM₁₀

Study	GAM-default	GAM-stringent	GLM
<i>Multi-Cities Analyses</i>			
NMMAPS 90-cities; Dominici et al. (2002)	2.1 (1.6, 2.6)	1.4 (0.9, 1.9)	1.1 (0.5, 1.7)
Harvard 6-cities; Klemm and Mason (2003)	4.1 (2.8, 5.4)	3.6 (2.1, 5.0)	2.0 (0.3, 3.8)
US 10 cities; Schwartz (2003b)	3.4 (2.7, 4.1)	3.3 (2.6, 4.1)	2.8 (2.0, 3.6)
8 Canadian cities; Burnett and Goldberg (2003)	4.5 (2.2, 6.7)	3.6 (1.4, 5.8)	2.7 (-0.1, 5.5)
APHEA2; Katsouyanni et al. (2003)	3.5 (2.9, 4.1)	3.3 (2.8, 3.9)	2.1 (1.5, 2.8)
<i>Single-Cities Analyses</i>			
Santa Clara Co.; Fairley (2003)	8.0**	7.8 (2.8, 13.1)	8.3 (2.9, 13.9)
Coachella Valley; Ostro et al. (2003)*	5.6 (1.7, 9.6)	5.5 (1.6, 9.5)	5.1 (1.2, 9.1)
Los Angeles Co.; Moolgavkar (2003)	2.4 (0.5, 4.4)	2.4 (0.5, 4.3)	2.3 (0.1, 4.5)
Cook Co.; Moolgavkar (2003)	2.4 (1.3, 3.5)	2.6 (1.6, 3.6)	2.6 (1.5, 3.7)
Phoenix, AZ; Mar et al. (2003)*	9.9 (1.9, 18.4)	9.7 (1.7, 18.3)	9.5 (0.6, 19.3)
Detroit, '85-'90; Ito (2003)	1.7 (0.2, 3.2)	0.9 (-0.5, 2.4)	0.7 (-0.8, 2.1)
Detroit, '92-'94; Ito (2003)	4.4 (-1.0, 10.1)	3.3 (-2.0, 8.9)	3.1 (-2.2, 8.7)
The Netherlands; Hoek (2003)	0.9 (0.1, 1.7)	0.9 (0.2, 1.7)	0.9 (0.1, 1.7)
Erfurt, Germany; Stolzel et al. (2003)	6.4 (0.3, 12.9)	6.2 (0.1, 12.7)	5.3 (-1.8, 12.9)

*Cardiovascular Mortality

**No CI interval given

1 Dominici et al. (2002) also illustrated that GAM models, even with stringent convergence
2 criteria, still result in biased (downward) standard errors of regression coefficients. This was the
3 main reason for the use of GLM with natural splines in the reanalysis studies. As can be seen
4 from Figure 8-15, the 95% confidence bands are somewhat wider for GLM results than for GAM
5 results in some, but not all cases. However, the extent of wider confidence bands is not
6 substantial in most cases (the bias ranged from a few percent to ~15% in most cases). It should
7 be noted that, while a GLM model with natural splines provides correct standard error of
8 regression coefficient, it is not equivalently as flexible as LOESS or smoothing splines. Unlike

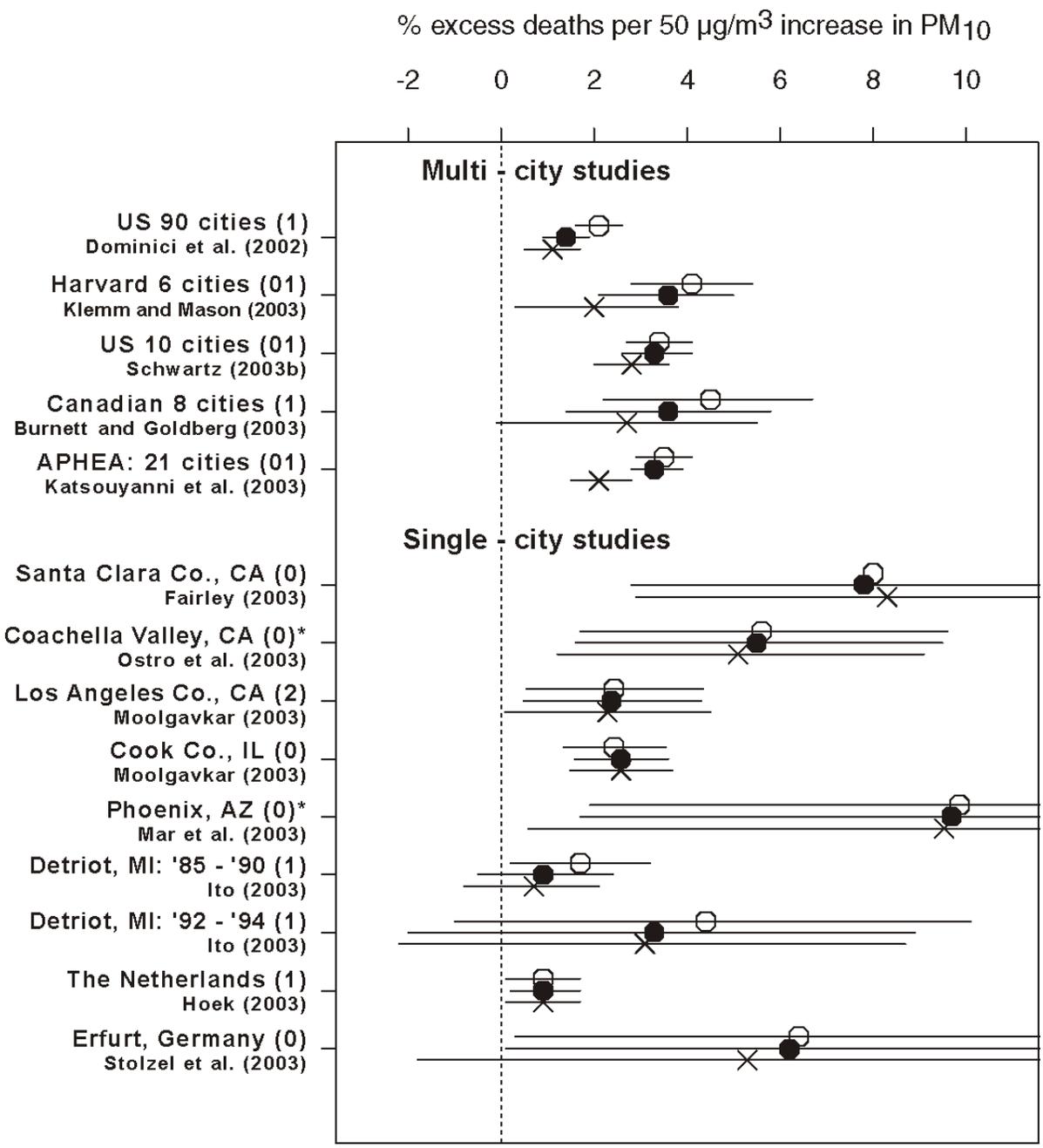


Figure 8-15. PM_{10} excess risk estimates for total non-accidental mortality for numerous locations (and for cardiovascular mortality[*] for Coachella Valley, CA and Phoenix, AZ), using: (1) GAM with default convergence criteria (white circle); (2) GAM with stringent convergence criteria (black circle); and, (3) GLM/natural splines (x) that approximate the original GAM model from the GAM reanalysis studies. The numbers in parenthesis indicate lag days used (“01” is average of 0 and 1 day lags).

1 LOESS or smoothing splines, natural splines fit linearly at both ends of the data span. Natural
2 splines therefore may not be an ideal model option for temperature effects, for which the slopes
3 are likely non-linear (especially at the higher end). Goldberg and Burnett (2003), in their
4 reanalysis of Montreal data, discussed related issues. In their reanalysis, the originally reported
5 risk estimates of PM indices (CoH, extinction coefficient, predicted PM_{2.5}, and sulfate) were
6 greatly attenuated in the GLM model with natural splines. One of the alternative explanations
7 for these results was that the natural spline does not fit the possibly non-linear (threshold) effect
8 of temperature as well as non-parametric smoothers. Hoek (2003), in his reanalysis of the
9 Netherlands data, also showed that, compared to GAM models, GLM/natural spline models
10 resulted in larger deviance, indicating poorer fits. Thus, there are remaining issues regarding the
11 trade-off between GAM/non-parametric smoothers and GLM/parametric smoothers. The
12 GLM/natural splines may produce correct standard errors but cannot guarantee “correct” model
13 specifications. More recently, Domimici et al. (2003) developed and published a GAM routine
14 for SPlus that gives correct standard errors, but it was not developed in time to be used for the
15 GAM reanalysis effects reported on in HEI (2003c).

16 Three reanalysis reports applied alternative smoothing approaches (e.g., penalized splines)
17 that, as with GLM/natural splines, did not have the problem of biased standard error. These
18 studies were: reanalyses of Harvard six cities data by Schwartz (2003a); reanalysis of 10 U.S.
19 cities data by Schwartz (2003b); and reanalysis of APHEA2 by Katsouyanni et al. (2003).
20 Generally, as with GLM/natural splines, the use of alternative smoothing approaches resulted in
21 smaller PM risk estimates than GAM with stringent convergence criteria. In the reanalysis of
22 APHEA2 study, the PM₁₀ risk estimates from penalized splines were smaller than those from
23 GAM, but larger than those from natural splines. Three alternative smoothing approaches (B-
24 splines, penalized splines, and thin-plate splines) used in the reanalysis of Harvard six cities
25 PM_{2.5} data resulted in generally smaller risk estimates than those from natural splines. As was
26 expected, all of these alternative smoothing approaches resulted in standard errors that were
27 comparable to those from natural splines but larger than those from GAM models.

28 Several of the GAM reanalysis reports included additional sensitivity analyses which
29 provided useful information. These sensitivity analyses included examinations of the effect of
30 changing degrees of freedom for smoothing of temporal trends and weather variables (Dominici
31 et al. [2002]; Ito [2003]; Klemm and Mason [2003]; Moolgavkar [2003]; and Burnett and

1 Goldberg [2003]). In these analyses, changing the degrees of freedom for smoothing of
2 temporal trends or weather effects often resulted in change of PM coefficients to a similar or
3 even greater extent than those caused by the GAM convergence problem. A distinctly less well
4 investigated issue is the effect of the use of different weather model specifications (i.e., how
5 many and which weather variables and their lags are included). In a limited examination of this
6 issue in the reanalysis of Detroit data (Ito, 2003), a weather model specification similar to that
7 used in the NMMAPS U.S. 90 cities study consistently yielded smaller PM₁₀ risk estimates than
8 a weather model similar to that used in the Harvard six cities study.

9 In summary, the results from the GAM reanalysis studies indicate that PM risk estimates
10 from GAM models were often, but not always, reduced when more stringent convergence
11 criteria were used. However, the extent of the reduction was not substantial in most cases. The
12 variability of PM risk estimates due to the model specification, including the number of weather
13 terms and extent of smoothing, is likely larger than the effect of the GAM convergence problem.
14 The extent of downward bias in standard errors reported for these data (a few percent to ~15%)
15 also appears not to be very substantial, especially when compared to the range of standard errors
16 across studies due to differences in population size and numbers of days available. Nevertheless,
17 this chapter mainly considers results of the reanalyzed studies or of other originally published
18 studies that did not use GAM with default convergence criteria, because the extent of the effect
19 of this problem is not generally predictable in each individual study.

21 **8.4.2.2 Impact of Using the More Stringent GAM Model on PM Effect Estimates for** 22 **Respiratory Hospital Admissions**

23 The NMMAPS multi-city study (Samet et al., 2000a,b) of PM₁₀ concentrations and hospital
24 admissions used the default GAM model specification with multiple smooths. The changes
25 derived from use of the more stringent GAM convergence criteria are illustrated by the results of
26 reanalyses by Zanobetti and Schwartz (2003a). Their results indicate that there was only about a
27 14% decline in the effect estimates associated with use of the more appropriate stringent
28 convergence requirement. The two estimates were well within the 95% confidence interval of
29 each other. Also, in comparing the difference in the estimates between each of the six pairs of
30 estimates by a two-sided z-statistic, all the p-values are greater than 0.5 indicating that the two
31 convergence requirements gave insignificant differences in estimates.

1 To examine the potential influence of the GAM convergence specification on the results of
2 the original Detroit data analysis by Lippmann et al. (2000), the associations between PM
3 components and daily mortality/morbidity were re-examined by Ito (2003) using more stringent
4 convergence criteria, as well as by applying a GLM that approximated the original GAM
5 models. Generally, the GAM models with stringent convergence criteria and GLM models
6 resulted in somewhat smaller estimated relative risks than those reported in the original study,
7 averaging 17% less for the stringent GAM case versus the default case. For COPD, the decrease
8 associated with the more stringent convergence criteria was larger (averaging 30%). Overall, for
9 all types of hospital admissions (including pneumonia, COPD and ischemic heart disease) the
10 change to the more stringent GAM convergence criteria gave an average decrease of 20 percent,
11 while a switch to the GLM model specification gave an average 29% decrease in estimated PM
12 effect size.

13 As discussed earlier, Sheppard (2003) recently conducted a reanalysis of their non-elderly
14 hospital admissions data for asthma in Seattle, WA, in order to evaluate the effect of the fitting
15 procedure on their previously published analyses. A lag of 1 day was used for all PM models.
16 As shown in Table 8-37, the results were provided in the manuscript to only one significant
17 figure (to the nearest whole percent), making the calculation of percent changes between models
18 problematic, since the rounding of the effect estimates are nearly on the order of the size of the
19 effect estimate changes. However, it can be seen that the pattern of changes in effects estimates
20 and 95% CI values is very similar to that seen in other studies.

21 Further evidence of the relatively small effect of the default convergence criteria issue in
22 most applications is the recent work by Moolgavkar (2003), in which he reanalyzed his earlier
23 GAM analyses of hospital admissions for COPD (Moolgavkar, 2000c) for the cities of
24 Los Angeles (Los Angeles County) and Chicago (Cook County). In his original publication,
25 Moolgavkar found ~5.0% excess risk for COPD hospital admissions among the elderly (64+ yr)
26 in Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10-2.5}$ in one pollutant models.
27 In the same study, similar magnitudes of excess risk (i.e., in the range of ~4 to 7%) were found
28 in one-pollutant models to be associated with $PM_{2.5}$ or $PM_{10-2.5}$ for other age groups (0-19 yr;
29 20-64 yr) in Los Angeles, as well. In his reanalyses of these GAM results using the more
30 stringent convergence criteria, however, Moolgavkar (2003) combined all three Los Angeles
31 age groups into one analysis, providing greater power, but also complicating before/after

TABLE 8-37. COMPARISON OF MAXIMUM SINGLE DAY LAG EFFECT ESTIMATES FOR PM_{2.5}, PM_{2.5-10}, and PM₁₀ FOR SEATTLE ASTHMA HOSPITAL ADMISSIONS BASED ON ORIGINAL GAM ANALYSES USING DEFAULT CONVERGENCE CRITERIA VERSUS REANALYSES USING GAM WITH MORE STRINGENT CONVERGENCE CRITERIA AND GLM

	Original Default GAM Model* % Increase/IQR (95% CI)	Reanalysis Stringent GAM % Increase/IQR (95% CI)	Reanalysis GLM (Natural Spline) % Increase/IQR (95% CI)
PM _{2.5}	4 (2, 7)	4 (1, 6)	3 (1, 6)
PM _{2.5-10}	4 (1, 7)	2 (0, 5)	2 (-1, 4)
PM ₁₀	5 (2, 8)	4 (1, 7)	3 (0, 6)

*PM_{2.5} IQR=11.8 ug/m³; PM_{2.5-10} IQR = 9.3 ug/m³; PM₁₀ IQR = 19 ug/m³.

Source: Derived from Sheppard (2003).

1 comparisons as to the actual effect on the results of using the more stringent convergence
 2 criteria. In the case of the Cook County analyses, the author changed other model parameters
 3 (i.e., the number of degrees of freedom in the model smooths) at the same time as implementing
 4 the more stringent convergence criteria, so direct before/after comparisons were not possible for
 5 Moolgavkar's Chicago reanalyses.

6 Therefore, in order to provide a one-to-one comparison for Los Angeles, the original age-
 7 specific GAM analyses have been pooled using inverse variance weighting and are presented
 8 along with Moolgavkar's (2003) reanalyses results (in terms of a % increase per 10 µg/m³ mass
 9 increase for both PM_{2.5} and PM₁₀) in Table 8-38. As shown in that table, the Moolgavkar
 10 Los Angeles results for all-age COPD admissions for the original and the more stringent
 11 convergence criteria GAM cases (using the same degrees of freedom) are very similar, with the
 12 effects estimate either decreasing (for PM_{2.5}) or increasing (for PM₁₀) very slightly. In those
 13 cases where a much larger number of degrees of freedom were used with either the more
 14 stringent GAM model or a natural spline GLM model, larger reductions in effects estimates were
 15 seen as compared to the original GAM model. For the same number of degrees of freedom, the
 16 natural spline model gave either a slightly larger (for PM_{2.5}) or a slightly smaller (for PM₁₀)
 17 effects estimate than the stringent GAM model. Thus, the reanalyses indicate that use of more

**TABLE 8-38. COMPARISON OF LOS ANGELES COPD HOSPITAL ADMISSIONS
 MAXIMUM SINGLE DAY LAG EFFECT ESTIMATES FOR PM_{2.5} and PM₁₀
 FROM THE ORIGINAL GAM ANALYSES USING DEFAULT CONVERGENCE
 CRITERIA VERSUS EFFECT ESTIMATES DERIVED FROM REANALYSES USING
 MORE STRINGENT CONVERGENCE CRITERIA AND FOR MODELS SMOOTHED
 WITH MORE DEGREES OF FREEDOM**

	Original Default GAM Model* (30df) % Increase/10 ug/m ³ (95% CI)	Reanalysis Stringent GAM (30df) % Increase/10 ug/m ³ (95% CI)	Reanalysis Stringent GAM (100df) % Increase/10 ug/m ³ (95% CI)	Reanalysis Natural Spline (100df) % Increase/10 ug/m ³ (95% CI)
PM _{2.5}	1.90 (0.97-2.84)**	1.85 (0.82-2.89)**	1.38(0.51-2.25)***	1.49(0.41-2.58)***
PM ₁₀	1.43 (0.85-2.02)**	1.51 (0.85-2.18)**	1.08 (0.50-1.66)**	0.98 (0.24-1.72)**

*Original GAM estimates derived for “all ages” from original analyses by age subgroups using inverse variance weights.

**For (maximum) lag case = 2 days.

***For (maximum) lag case = 0 days.

Source: Derived from Moolgavkar (2000c) and Moolgavkar (2003).

1 stringent GAM convergence criteria results in minimal changes in PM effect size estimates in
 2 this case, as compared to those obtained using the default GAM model; whereas the number of
 3 degrees of freedom used with either GAM or GLM models can result in much larger changes in
 4 the PM effect size estimates and broader confidence intervals.

5 These various reanalyses results therefore confirm that the PM effect estimates generally
 6 do decline somewhat when using the more stringent convergence criteria, as compared to the
 7 default GAM, with the new estimates being well within the confidence intervals of the original
 8 estimates. However, the effect of using more stringent convergence criteria was seen to have
 9 less influence on the effect estimate than investigator-to-investigator variations in model
 10 specifications (e.g., the extent of smoothing). Overall, then the absolute impact was relatively
 11 small and the basic direction of effect and conclusions regarding the significance of the PM
 12 effect on hospital admissions remained unchanged in these analyses when more stringent GAM
 13 convergence criteria were used.

14

15

1 **8.4.2.3 HEI Commentaries**

2 The HEI Special Report (2003a,c) presents the HEI Special Panel’s reviews of both the
3 Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study (NMMAPS),
4 Part II and the Revised Analyses of Selected Time-Series Studies, which includes short
5 communication reports presenting results from other revised analyses of original articles and
6 reports. Beyond looking at the results of reanalyses designed specifically to address problems
7 associated with the use of default convergence criteria in the S-Plus GAM function, the reviews
8 also identified issues associated with the sensitivity of study findings to the use of alternative
9 modeling approaches that some investigators employed in their reanalyses. In general, the
10 Special Panel concluded that the original PM effects estimates were more sensitive to the
11 modeling approach used to account for temporal effects and weather variables than to the
12 convergence criteria used in the GAM model.

13 A modeling issue of particular importance highlighted by HEI (2003c) is the sensitivity of
14 all models (e.g., GAM, GLM-natural splines, GLM-penalized splines) to the degrees of freedom
15 allotted to potentially confounding weather variables and time. The commentary discusses the
16 trade-off involved in selecting the number of degrees of freedom for time and weather variables,
17 while recognizing that there remains no altogether satisfactory way to choose the most
18 appropriate degrees of freedom. For example, in considering the effect of temperature, if the
19 degrees of freedom in the smoothing function for temperature are overly restricted, some actual
20 nonlinear effects of temperature would be falsely ascribed to the pollution variable. To avoid
21 this, the analyst is tempted to afford many degrees of freedom to temperature or other potentially
22 confounding variables. However, if more degrees of freedom are allotted than needed, such that
23 the temperature smooth function is more “wiggly” than the true dose response function, then the
24 result will be a much less efficient estimate of the pollutant effect. This would have the effect of
25 incorrectly ascribing part of the true pollution effect to the temperature variable, which would
26 compromise our ability to detect a true but small pollution effect. The commentary notes that
27 the empirical data cannot determine the optimal trade-off between these conflicting needs, and it
28 is difficult to use an a priori biological or meteorologic knowledge to determine the optimal
29 trade-off. Thus, the Special Panel generally recommended further exploration of the sensitivity
30 of these studies both to a wider range of alternative degrees of smoothing and to alternative
31 specifications of weather variables in time-series models.

1 More specifically, the HEI Special Panel offered the conclusions and recommendations for
2 NMMAPS and other revised analyses highlighted below:

3
4 ***NMMAPS Revised Analyses***

5 Dominici et al. (2002) conducted a range of revised analyses, applying alternative methods
6 to correct shortcomings in the S-Plus GAM programming. HEI's Special Panel review (HEI,
7 2003a) of this revised analyses yielded the following conclusions:

- 8 • While estimates of effect are quantitatively smaller than those in the original studies, a statistically significant overall effect of PM₁₀ on mortality remains, and the qualitative conclusions that were initially drawn from NMMAPS remain unchanged.
- 9 • While the alternative approaches used to model temporal effects in the revised NMMAPS analyses addressed the problems of obtaining incorrect effect estimates and standard errors when using the preprogrammed GAMs software, no models can be recommended at this time as being strongly preferred over another for use in this context.
- 10 • While formal tests of PM effect across cities did not indicate evidence of heterogeneity because of the generally large individual-city effect standard errors, the power to assess the presence of heterogeneity was low. The possibility of heterogeneity still exists.
- 11 • The appropriate degree of control for time in these time-series analyses has not been determined. Thus, the impact of more aggressive control for time should continue to be explored and studies to evaluate bias related to the analytic approach to smoothing and the degree of smoothing should be encouraged.
- 12 • Weather continues to be a potential confounder of concern, such that further work should be done on modeling weather-related factors.

13
14 ***Revised Analyses for Other Short Communications***

15 Based on its review, the HEI Special Panel (HEI, 2003c) reached the following
16 conclusions:

- 17 • As was the case with the findings of the original studies, the revised findings will continue to help inform regulatory decisions regarding PM.
- 18 • The PM effect persisted in the majority of studies; however, the number of studies showing an adverse effect of PM was slightly smaller.
- 19 • In some of the large number of studies in which the PM effect persisted, the estimates of PM effect were substantially reduced.

- 1 • In the few studies in which further sensitivity analyses were performed, some showed marked sensitivity of the PM effect estimate to the degree of smoothing and/or the specification of weather.
- 2 • The use of more appropriate convergence criteria on the estimates of PM effect in the revised analyses produced varied effects across the studies. In some studies, stricter convergence criteria had little impact, and in a few the impact was substantial. No study's conclusions changed in a meaningful way by the use of stricter criteria compared to the original analyses.
- 3 • In most studies, parametric smoothing approaches used to obtain correct standard errors of the PM effect estimates produced slightly larger standard errors than the GAM. However, the impact of these larger standard errors on level of statistical significance of the PM effect was minor.
- 4 • For the most part, the original PM effect estimates were more sensitive to the method used to account for temporal effects than to changing the convergence criteria.
- 5 • Even though the alternative approaches used to model temporal effects in the revised analyses addressed the problems of obtaining incorrect effect estimates and standard errors when using the GAMs software, none can be recommended at this time as being strongly preferred over another for use in this context.
- 6 • Neither the appropriate degree of control for time nor the appropriate specification of the effects of weather in these time-series analyses has been determined. This awareness introduces a degree of uncertainty that has not been widely appreciated previously, such that the sensitivity of these studies to a wider range of alternative degrees of smoothing and alternative specifications of weather variables in time-series models should continue to be explored.

7 8 **8.4.3 Assessment of Confounding by Co-Pollutants and Adjustments for** 9 **Meteorological Variables**

10 **8.4.3.1 Introduction to Assessment of Confounding by Co-Pollutants**

11 Airborne particles are found among a complex mixture of atmospheric pollutants, some of
12 which are widely measured (such as gaseous criteria co-pollutants O₃, CO, NO₂, SO₂) and others
13 which are not routinely measured. Determining the extent to which observed ambient PM-health
14 effects associations can be attributed to airborne particles acting alone or in combination with
15 other air pollutants or may be due to confounding by other pollutants is one of the more difficult
16 issues encountered in assessing PM-related epidemiologic evidence. Because (a) many of the
17 pollutants are closely correlated due to emissions by common sources and dispersion by

1 common meteorological factors and (b) some are in the pathway of formation of other pollutants
2 (e.g., $\text{NO} \rightarrow \text{NO}_2 \rightarrow \text{NO}_3^- \rightarrow \text{Particle Mass}$), it may be difficult to disentangle their effects (as
3 noted in Section 8.1.1).

4 It is widely accepted that some PM metrics are associated with health effects, and that PM
5 has effects independent of the gaseous co-pollutants. The extent to which ambient gaseous
6 co-pollutants have health effects independent of PM is important in considering the extent to
7 which health effects attributed to PM may actually be due in part to co-pollutants or to some
8 other environmental factors, and vice versa. EPA produces Air Quality Criteria Documents for
9 four gaseous pollutants: CO, NO₂, SO₂, and O₃ (U.S. Environmental Protection Agency, 1982,
10 1993, 1996b, 2000b). Health effects of the gaseous pollutants exerted independently from PM,
11 and in some cases jointly with PM, are discussed in those documents. They are also considered
12 to some extent in this section and elsewhere in this document because they may affect
13 quantitative assessments of the effects of various PM metrics when these other pollutants are
14 also present in the atmosphere. The gaseous pollutants may also be of interest as PM effect
15 modifiers or through interactions with PM.

16 Co-pollutant models have received a great deal of attention in the last several years
17 because there exist improved statistical methods for estimating PM effects by analyses of daily
18 time-series of mortality (Schwartz and Marcus, 1990; Schwartz, 1991) or hospital admissions
19 (Schwartz, 1994) and/or in prospective cohort studies (Dockery et al., 1993). A number of
20 studies using such methods have not only found significant positive relationships between
21 mortality and one or more PM indicators, but also with one or another of the four gaseous
22 criteria pollutants (O₃, NO₂, CO, SO₂) in daily time-series studies, and between SO₂ and
23 mortality in the reanalyses of two large prospective cohort studies (Krewski et al., 2000). In the
24 daily time-series studies, the estimated PM effect is relatively stable when the co-pollutant is
25 included in the model in some cities, whereas the estimated PM effect in other cities changes
26 substantially when certain co-pollutants are included. In interpreting the results of any of these
27 studies, it is reasonable to consider the biological plausibility of a given pollutant being likely to
28 affect the particular health endpoint.

29 Some gaseous co-pollutants (e.g., CO, SO₂ and NO₂) may be acting as indicators of distinct
30 emission sources and/or as indicators of PM from these sources. Concentrations of such gaseous
31 co-pollutants may therefore be correlated with total PM mass or even more strongly correlated

1 with specific PM constituents (due to their emission from a common source). Thus, one or
2 another specific gaseous co-pollutant may serve as an indicator of the day-to-day variation in the
3 contribution of a distinct emission source and to the varying concentrations of airborne PM. In a
4 model with total PM mass, then, a gaseous co-pollutant may well actually be serving as a
5 surrogate for the source-apportioned contribution to ambient air PM. Or, PM could also act as
6 an indicator for emission sources or gaseous co-pollutants. It would be interesting to evaluate
7 models that include both source-relevant particle components and gaseous pollutants derived
8 from common sources (e.g., those attributable to motor vehicles, coal combustion, oil
9 combustion, etc.). The closest approach thus far has been Model II in Burnett et al. (2000), a
10 default GAM analysis.

11 The role of gaseous pollutants as surrogates for source-apportioned PM may be distinct
12 from confounding. The true health effect may be independently associated with a particular
13 ambient PM constituent that may be more or less toxic than the particle mix as a whole. Thus,
14 a gaseous co-pollutant may give rise to the appearance of confounding in a regression model.
15 If it were to serve as an indicator of the more toxic particles, the gaseous co-pollutant could
16 greatly diminish the coefficient for total particle mass. In such a model, the coefficient for total
17 particle mass would most properly be interpreted as an indicator of the other, less-toxic particles.

18 19 **8.4.3.2 Statistical Issues in the Use of Multi-Pollutant Models**

20 Multi-pollutant models may be useful tools for assessing whether the gaseous co-pollutants
21 may be *potential* confounders of PM effects, but cannot determine if in fact they are. Variance
22 inflation and effect size instability can occur in non-confounded multipollutant models as well as
23 in confounded models. Our usual regression diagnostic tools can only determine whether there
24 is a potential for confounding. In PM epidemiology studies, the gaseous pollutants, except O₃,
25 frequently have a high degree of positive linear correlation with PM metrics, a condition known
26 as multi-collinearity; therefore, although multi-collinearity leading to effect size estimate
27 instability and variance inflation are necessary conditions for confounding, they are not
28 sufficient in and of themselves to determine whether confounding exists.

29 The most commonly used methods include multi-pollutant models in which both the
30 putative causal agent (PM) and one or more putative co-pollutants are used to estimate the health
31 effect of interest. If the effect size estimate for PM is “stable,” then it is often assumed that the

1 effects of confounding are minimal. “Stable” is usually interpreted as meaning that the
2 magnitude of the estimated effect is similar in models with PM alone and in models with PM and
3 one or more co-pollutants, and the statistical significance or width of the confidence interval for
4 the PM effect is similar for all models, with or without co-pollutants. These criteria (usually
5 unquantified) diagnose confounding in a narrow sense, interpreted as synonymous with multi-
6 collinearity, not as a failure of the study design or other forms of model mis-specification.

7 Beyond the conceptual issues discussed above that arise in assessing confounding,
8 a number of technical issues arise in the use of statistical models, as discussed below.

9
10 (a) Model mis-specification assumes many forms. The omission of predictive regressors
11 (“underfitting”, defined by Chen et al., 2000) may produce biased estimates of the effects of
12 truly predictive regressors that are included in the model. Inclusion of unnecessary or
13 non-predictive regressors along with all truly predictive regressors (“over-fitting”) will produce
14 unbiased estimates of effect, but may increase the estimated standard error of the estimated
15 effect if it is correlated with other predictors. Omitting a truly predictive regressor while
16 including a correlated but non-causal variable (“mis-fitting”) will attribute the effect of the
17 causal regressor to the non-causal regressor. Interaction terms are candidates for omitted
18 regressor variables. It is important to avoid the “mis-fitting” scenario. Assuming that there is a
19 linear relationship when the true concentration-response function is non-linear will produce a
20 biased estimate of the effect size, high or low, at different concentrations. One of the most
21 common forms of model mis-specification is to use the wrong set of multi-day lags, which could
22 produce any of the consequences described as “under-fitting” (e.g., using single-day lags when a
23 multi-day or distributed lag model is needed), “over-fitting” (e.g., including a longer span of
24 days than is needed), or “mis-fitting” (e.g., using a limited set of lags while the effects are in fact
25 associated with different set of lags). Different PM metrics and gaseous pollutants may have
26 different lag structures, so that in a multi-pollutant model, forcing both PM and gases to have the
27 same lag structure is likely to yield “mis-fitting.” Finally, classical exposure measurement errors
28 (from use of proxy variables) attenuates (biases) effect size estimates under most assumptions
29 about correlations among regressors and among their measurement errors (Zeger et al., 2000).

1 (b) Bias: All of the mis-specifications listed in (a) can bias the effect size estimate except
2 for “over-fitting” and measurement error of Berkson type. The estimates of the standard error of
3 the effect size estimate under “over-fitting” or Berkson error cases are inflated, however; and
4 result in broader confidence intervals than would otherwise occur with a more appropriately
5 specified model and/or one with less Berkson type measurement error.

6
7 (c) Effect size standard error estimates are usually sensitive to model mis-specification.
8 When all truly predictive regressors are added to an “underfit” model, the reduction in
9 uncertainty is almost always sufficient to be reflected by the standard errors of estimated effect
10 size being reduced (“variance deflation”). On the other hand, adding correlated non-causal
11 variables to “over-fitted” or “mis-fitted” models further increases estimated standard errors
12 (“variance inflation”). Variance inflation can occur whenever a covariate is highly correlated
13 with the regressor variable that is presumably the surrogate for the exposure of interest.
14 Confounding with the regressor variable can occur only when the covariate is correlated (a) with
15 the regressor variable proxy for the exposure of interest and (b) with the outcome of interest in
16 the absence of the exposure of interest.

17
18 (d) Mis-specification errors may compound each other. If the underlying concentration-
19 response function is nonlinear but there is measurement error in the exposure metrics used, then
20 different subpopulations may actually have greater or smaller risk than assigned by a linear
21 model. Consider the hypothetical case of a “hockey-stick” model with a threshold. If there was
22 no exposure measurement error, then those in the population with measured concentrations
23 above the threshold would have excess risk, whereas those below would not. However, if
24 exposures were measured with error, even if the measured concentration were above the
25 threshold, some people could experience actual exposures that are, in fact, below the threshold
26 and, therefore, pose no excess risk. Conversely, if the measured (with error) concentration fell
27 below the threshold, some people could actually experience concentrations above the threshold
28 and could be at excess risk. The flattening of a non-linear concentration-response curve by
29 measurement error is a well known phenomenon detectable by standard methods (Cakmak et al.,
30 1999).

1 (e) Whether effect size estimates and their standard errors are really significantly different
2 among models is a question not usually addressed quantitatively. Some authors report various
3 goodness-of-fit criteria such as AIC, BIC, deviance, or over-dispersion index (e.g., Chock et al.,
4 2000; Clyde et al., 2000), but this is not yet so wide-spread as to assist in analyses of secondary
5 data for use in this document. Variance inflation may also happen with a correctly specified
6 model when both pollutants are causal and highly correlated, compared to a model in which only
7 one pollutant is causal and the non-causal pollutant is omitted. The situation where the variance
8 or standard error decreases when an additional variable is added (variance deflation) suggests
9 that the model with the covariate is more nearly correct and that the standard errors of all
10 covariates may decrease. Statistical significance is a concept of limited usefulness in assessing
11 or comparing results of many models from the same data set. Still, it is a familiar criterion, and
12 one addressed here by using a nominal two-sided 5% significance level for all tests and 95%
13 confidence intervals for all estimates, acknowledging their limitations. There is at present no
14 consensus on what clearly constitutes “stability” of a model estimate effect size, e.g., effect sizes
15 that differ by no more than 20% (or some other arbitrary number) from the single-pollutant
16 models. Simple comparison of the overlap of the confidence intervals of the models is not used
17 because the model estimates use the same data, and the confidence intervals for effect size in
18 different models are more-or-less correlated. In analyses with missing days of data for different
19 pollutants, comparisons must also incorporate differences in sample size or degrees of freedom.

20 In any case, statistical comparisons alone cannot fully resolve questions about either
21 conceptual or statistical issues in confounding via considerations about statistical significance.
22 If the model is mis-specified in any of the numerous ways described above, then effect size
23 estimates and/or their estimated standard errors are likely biased.

24 The most commonly used approach to diagnose potential confounding is fitting multi-
25 pollutant models and evaluating the stability of the estimated particle effect sizes against
26 inclusion of co-pollutants. If an additional covariate is added to a baseline model (e.g., with PM
27 alone) and the model predicts the outcome better with the covariate, then the reduction in
28 variance (or deviance for generalized linear or additive models [GLM or GAM]) outweighs the
29 loss of degrees of freedom for variability. Although not always true, it is reasonable to expect a
30 decrease in the estimated asymptotic standard error of the effect size estimate (“variance
31 deflation”), but improved goodness-of-fit may not reduce the standard errors of all parameters in

1 equal proportion because introducing the new covariate modifies the covariate variance-
2 covariance matrix. The weighted inverse covariance matrix provides an exact estimate for
3 standard errors in ordinary linear regression models, and approximately so in GLM or GAM.
4 The effects on other parameter estimates are rarely reported.

5 “Variance inflation” may occur under several circumstances, including “under-fitting” and
6 “mis-fitting” in which a truly predictive covariate is omitted or replaced by a correlated proxy,
7 and “over-fitting” in which a non-predictive covariate correlated with the PM metric is also
8 included in the model. The potential for over-fitting can be diagnosed by evaluating the
9 eigenvalues of the correlation matrix of the predictors, with very small values identifying near-
10 collinearity. However, the complete covariate correlation matrix is almost never reported,
11 including all weather variables and nonlinear functions entered separately as covariates.
12 Nonetheless, even a correlation matrix among all pollutants would be informative. Furthermore,
13 composite correlation matrices in multi-city studies may conceal important differences among
14 the correlation matrices.

15 Multi-pollutant models may be sensitive to multi-collinearity (high correlations among
16 particle and gaseous pollutant concentrations) and to so-called “measurement errors”, possibly
17 associated with spatial variability. Combining multi-pollutant models across several cities may
18 not improve the precision of the mean combined PM effect-size estimate, if the differences
19 among the cities are as large or larger in the multi-pollutant models as in the single-pollutant PM
20 model. Second-stage regressions have been useful in identifying effect modifiers in the
21 NMMAPS and APHEA 2 studies, but may not, in general, provide a solution to the problem in
22 that confounding of effects is a within-city phenomenon.

23 Three promising alternative approaches versus simple reliance on multi-pollutant modeling
24 have begun to be used to evaluate more fully the likelihood that exposures to gaseous co-
25 pollutants can account for the ambient PM-health effects associations now having been reported
26 in numerous published epidemiology studies. The first is based on evaluation of personal
27 exposures to particles and gases, as was done for three panels of participants in Baltimore, MD
28 (Sarnat et al., 2000, 2001). This study (discussed in detail in Chapter 5) directly addressed the
29 premise that if individuals are not exposed to a potential confounder, then there is a lower
30 probability that the potential confounder contributes to the observed effect. The Sarnat results
31 support the conclusion that personal exposure to sulfates, fine particles, and PM₁₀ are well

1 correlated with their ambient concentrations measured at corresponding fixed sites, but the
2 correlations are much lower for PM_{10-2.5}, O₃, and NO₂. There is, however, a great deal of
3 variation for one of three two-week panels from one season to the next. The sample size was
4 small (N = 56), but marginally significant associations were detected between personal and
5 ambient NO₂ for the personal-ambient correlation but was much lower than for particles. There
6 were, however, some residences in which personal and ambient NO₂ were highly correlated.
7 This has been seen when residences are close to a major road, which was the case for several
8 members in each of the three studied cohorts (i.e., healthy elderly adults, adults with COPD, and
9 children 9-13 years).

10 Another promising approach is the use of principal component or factor analysis to
11 determine which combinations of gaseous criteria pollutants and PM size fractions or chemical
12 constituents together cannot be easily disentangled, and which pollutants are substantially
13 independent of the linear combinations of the others. For example, the source-oriented factor
14 analysis study of Mar et al. (2000) produced evidence suggesting independent effects of regional
15 sulfate, motor vehicle-related particles, particles from vegetative burning, and PM₁₀₋₂₅ for
16 cardiovascular mortality in Phoenix (as discussed in Section 8.2.2.4.3).

17 There are also now available some recent examples of a third promising approach, i.e., the
18 use of so-called “intervention studies.” Interesting evidence for ambient PM effects are
19 beginning to emerge from some such studies, which relate changes (decreases in health risk
20 outcomes) to decreases in airborne particles due to deliberate reductions in pollutant emissions
21 from sources that ordinarily contribute to elevated ambient PM levels in a given locale.
22 As described before (Section 8.2.3.4), some health outcome changes occurred in some studies in
23 the presence of low levels of ambient gaseous co-pollutants or little change in at least some of
24 the co-pollutants in the presence of reduced concentrations of PM mass or constituents.

25 26 **8.4.3.3 Multipollutant Modeling Outcomes**

27 As stated in the introduction to this chapter, ambient PM exists as a component of a
28 complex air pollution mixture that includes other criteria pollutants, as well as many other
29 airborne contaminants that may convey risks to health. Particulate matter is of both primary and
30 secondary origin, and two of the gaseous criteria pollutants (sulfur dioxide and nitrogen dioxide)
31 contribute to the formation of secondary particles. Because of shared sources, concentrations of

1 ambient PM, SO₂, and NO₂ may be correlated to a moderate degree in urban areas. Generally,
2 concentrations of PM and other monitored pollutants are imperfect measures of personal
3 exposures and the extent of measurement error likely varies among the pollutants and also
4 among population subgroups. In interpreting the findings of multi-pollutant models, there are
5 several alternative explanations for observed associations that need to be considered based on the
6 above points, as follows:

- 7 • An effect estimated for PM reflects a “true effect” of particulate matter (causal interpretation).
- 8 • An effect estimated for PM reflects the total effect of the overall air pollution mixture (PM is an indicator of mixture toxicity).
- 9 • An effect estimated for PM reflects confounding (at least to a degree) by another pollutant (PM effect is confounded).
- 10 • An effect estimated for PM may be modified by levels of other pollutants (there is effect modification).
- 11 • An effect estimated for PM may be an underestimate of the true effect because of the inclusion in a model of other criteria air pollutants (SO₂, NO₂, O₃) which are contributors to the PM levels observed. This latter effect can be interpreted as the estimated effect of PM on health not mediated by contributions to PM.

12
13 As also stated previously, multi-pollutant modeling has been one commonly-used method
14 employed for assessing potential confounding by co-pollutants. Figures 8-16 through 8-19
15 present results derived from multi-pollutant models in studies that either did not use GAM
16 originally or were reanalyzed using GLM.

17 As shown in Figure 8-16, the single-pollutant PM effect size estimates for total mortality
18 (with PM₁₀, PM_{2.5}, and PM_{10-2.5}) in most of the studies did not change much across the various
19 individual co-pollutants and combinations of co-pollutants as they were added into multi-
20 pollutant models, e.g., in the multi-city studies by Dominici et al. (2003) and Schwartz (2003) or
21 the single-city studies by Ito (2003), Fairley (2003), and Morgan et al. (1998). One notable
22 exception is the study by Moolgavkar (2003) in Los Angeles Co., in which the PM effect
23 estimates were substantially reduced with the inclusion of CO in the model. On the other hand,
24 in the study in Pittsburgh by Chock et al. (2000), the PM₁₀ effect estimates remained little
25 changed or were somewhat increased with the inclusion of CO and the other co-pollutants.

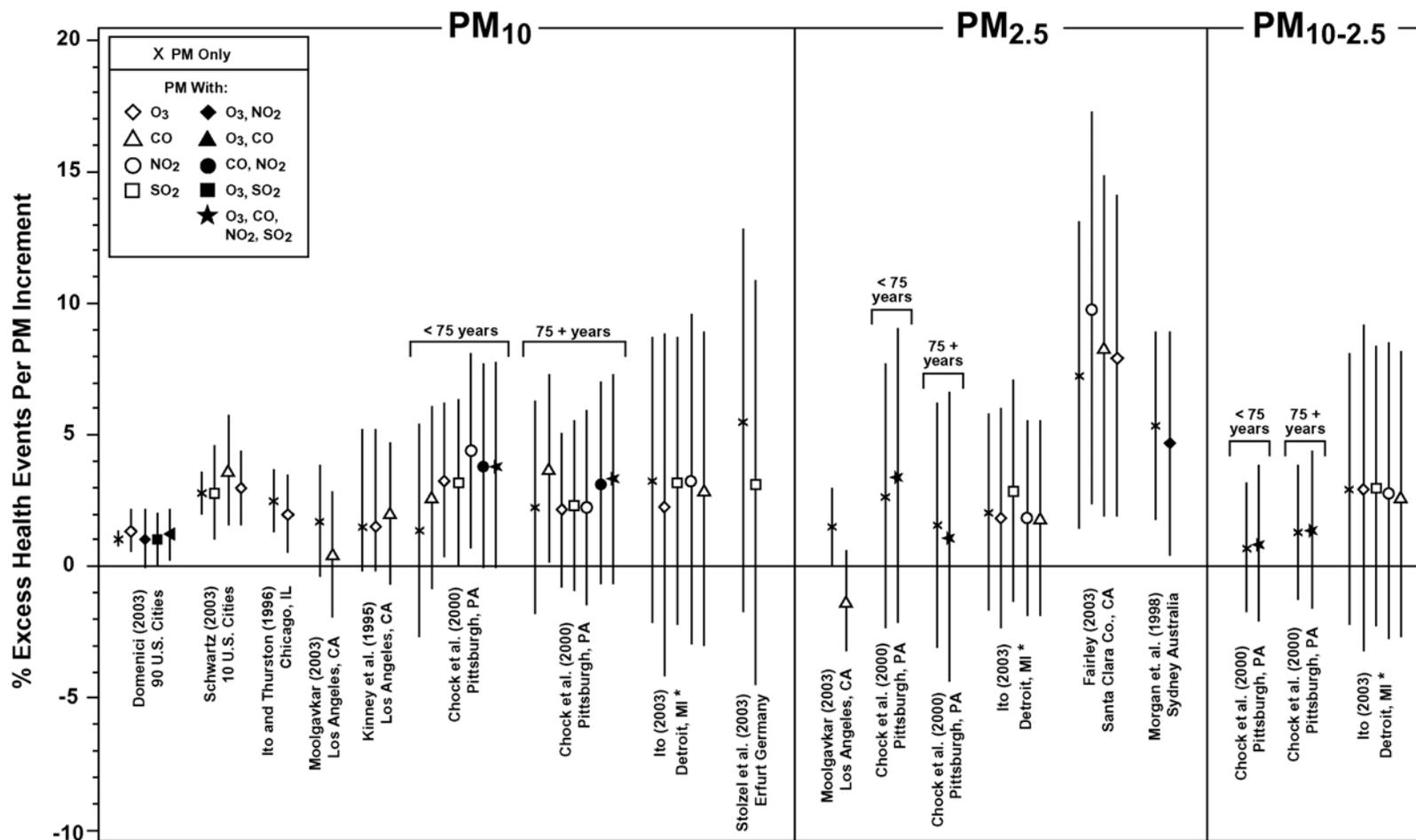


Figure 8-16. Excess risk estimates for total non-accidental mortality in single-pollutant (PM only) and multi-pollutant models. PM increments: 50 $\mu\text{g}/\text{m}^3$ for PM₁₀ and 25 $\mu\text{g}/\text{m}^3$ for PM_{2.5} and PM_{10-2.5}. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.

*Estimates for multi-pollutant models in Ito (2003) obtained from the author via personal communication (November, 2003).

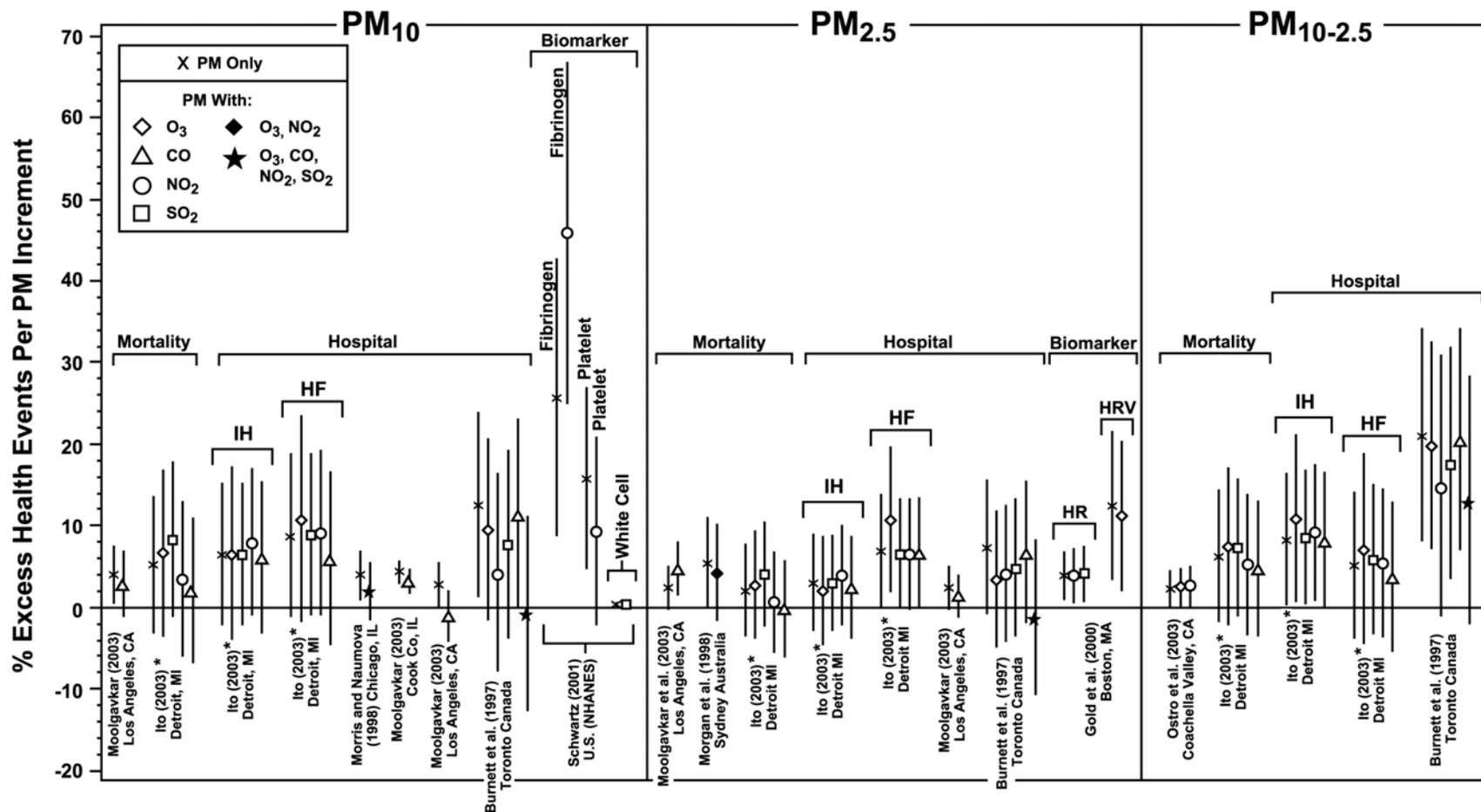


Figure 8-17. Excess risk estimates for cardiovascular-related effects, including mortality, hospital admissions, and changes in biomarkers (e.g., increases in blood parameters or decreases in heart rate variability measures) in single-pollutant (PM only) and multi-pollutant models. PM increments: 50 $\mu\text{g}/\text{m}^3$ for PM₁₀ and 25 $\mu\text{g}/\text{m}^3$ for PM_{2.5} and PM_{10-2.5}. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM. IH = ischemic heart disease; HF = heart failure; HR = heart rate; HRV = heart rate variability.

*Estimates for multi-pollutant models in Ito (2003) obtained from the author via personal communication (November, 2003).

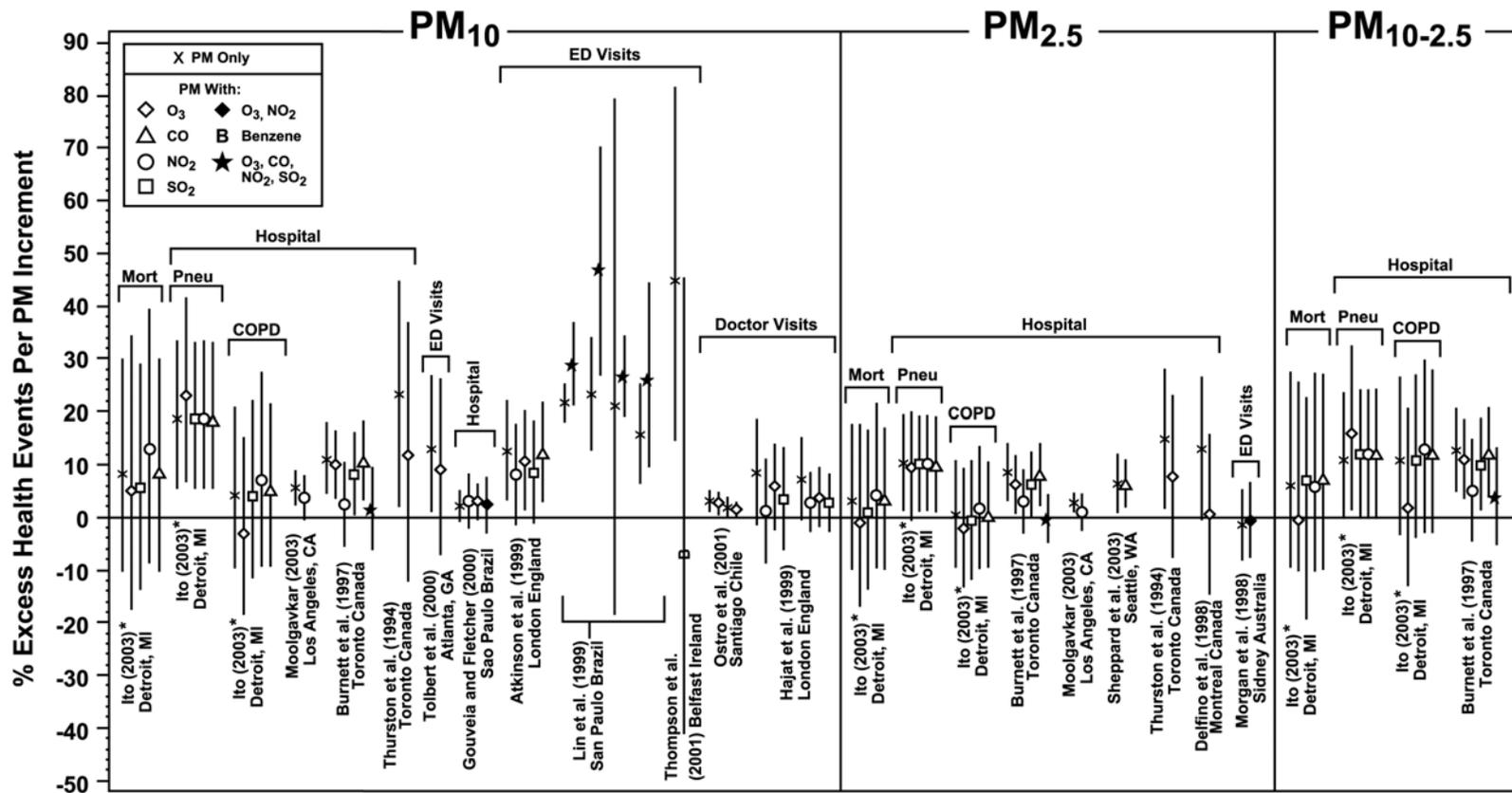


Figure 8-18. Excess risk estimates for respiratory-related effects, including mortality, hospital admissions and medical visits in single-pollutant (PM only) and multi-pollutant models. PM increments: 50 µg/m³ for PM₁₀ and 25 µg/m³ for PM_{2.5} and PM_{10-2.5}. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM. Mort = mortality; Pneu = pneumonia; COPD = chronic obstructive pulmonary disease.

*Estimates for multi-pollutant models in Ito (2003) obtained from the author via personal communication (November, 2003).

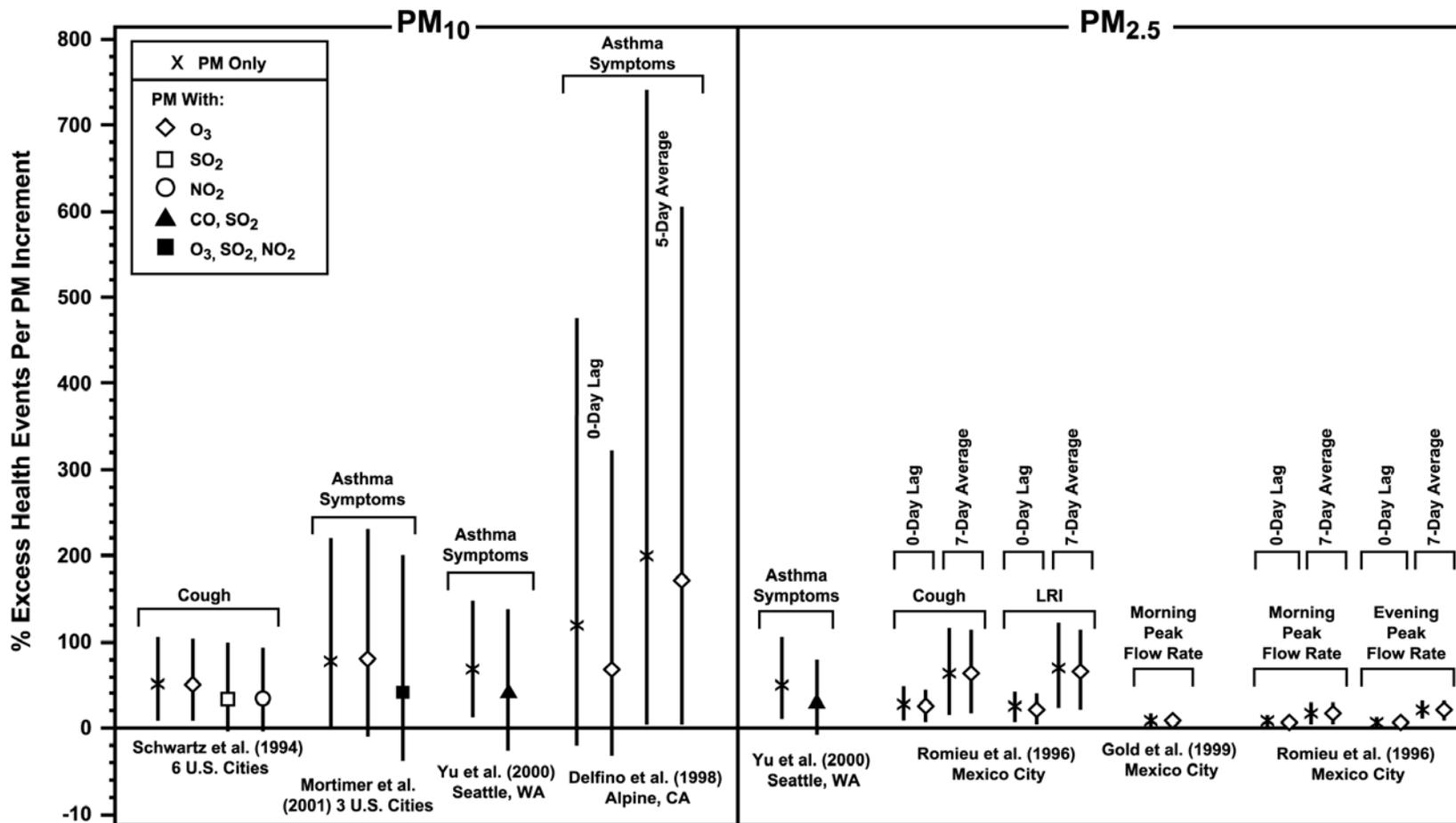


Figure 8-19. Excess risk estimates for increases in respiratory symptoms or decreases in lung function measures in single-pollutant (PM only) and multi-pollutant models. PM increments: 50 $\mu\text{g}/\text{m}^3$ for PM₁₀ and 25 $\mu\text{g}/\text{m}^3$ for PM_{2.5} and PM_{10-2.5}. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.

1 For cardiovascular mortality and morbidity (Figure 8-17), in many cases the PM effect
2 estimates were again little changed when various individual and combinations of co-pollutants
3 were added to the models, although the pattern seems to be somewhat more variable for
4 cardiovascular-related effects than for total mortality. For example, in Toronto, PM effects
5 estimates for cardiovascular hospital admissions for all three PM indicators were appreciably
6 reduced with the inclusion of NO₂, but not CO; the inclusion of all four gaseous co-pollutants
7 showed the most substantial reductions in the PM effect estimates for each indicator (Burnett
8 et al., 1997a). Ito (2003) presents results for cardiovascular mortality and hospital admissions in
9 Detroit and, in most cases, PM effect estimates are similar in models with and without
10 co-pollutants; some variability is seen across these results, however, with the cardiovascular
11 mortality effect estimates showing a decrease with the inclusion of either CO or NO₂, especially
12 for PM₁₀. In Moolgavkar (2003), the inclusion of CO resulted in variable reductions in the PM₁₀
13 effect estimates for cardiovascular mortality (L.A. Co.) and hospital admissions (Cook Co.),
14 although the PM₁₀ estimate for hospital admissions in Cook County remained significant.

15 As held for cardiovascular-related effects, the PM effect estimates for respiratory-related
16 mortality and morbidity effects also did not show much change in many cases when various
17 individual and combinations of co-pollutants were added to the models (Figure 8-18). However,
18 for some endpoints, PM effect estimates are changed substantially with the addition of specific
19 co-pollutants, most notably with O₃ or NO₂. For example, in the Toronto study by Burnett
20 et al.(1997a), PM effect estimates for respiratory hospital admissions for all three PM indicators
21 are appreciably reduced with the inclusion of NO₂, but not O₃; and an even larger reduction was
22 seen with the inclusion of all four gaseous co-pollutants, as was seen in this study for
23 cardiovascular hospital admissions. Other Canadian studies of respiratory hospital admissions or
24 medical visits show appreciable reductions in PM₁₀ and/or PM_{2.5} effects estimates with the
25 inclusion of O₃ (Thurston et al., 1994; Delfino, 1998b). In Detroit (Ito, 2003), the COPD
26 hospital admissions effect estimates for PM₁₀ and PM_{10-2.5} were reduced in models with O₃, as
27 was the respiratory mortality effect estimate for PM_{10-2.5}; whereas the PM effect estimates for
28 pneumonia hospital admissions were either unchanged or somewhat increased for all three
29 indicators. As for results of studies on respiratory symptoms and lung function changes
30 (Figure 8-19), the PM effect estimates were generally robust to adjustment for O₃, though
31 somewhat reduced in a study conducted in Alpine, CA (Delfino et al., 1998b). Effect estimates

1 for asthma symptoms were also somewhat reduced in models that included both CO and SO₂ in
2 Seattle (Yu et al., 2000) and in models that included O₃, SO₂, and NO₂ in a 3-city study by
3 Mortimer et al. (2002).

4 In addition to the above studies, a number of others only qualitatively reported results for
5 multi-pollutant models, but did not provide quantitative results and are thus not included in
6 Figures 8-16 through 8-19. From this group of studies, some reported that PM effect estimates
7 remained significant with adjustment for gaseous copollutants (e.g., Ostro et al., 2003; Cifuentes
8 et al., 2000; Sunyer and Basagaña, 2001; Lipsett et al., 1997; Desqueyroux et al., 2002), while
9 others reported more robust associations with gaseous pollutants (e.g., Lipfert et al., 2000; Stieb
10 et al., 2000; Metzger et al., 2004; Peters et al., 2000). Beyond the quantitative results presented
11 above, Moolgavkar (2003) also describes additional results of multi-pollutant models in which
12 PM effects may or may not be robust to the inclusion of gaseous co-pollutants, depending on the
13 specific lag and co-pollutants used. For example, in Cook County, for a 0-day lag, the PM₁₀
14 coefficient for total mortality remained robust and statistically significant while coefficients for
15 each of the gases were attenuated and became insignificant, whereas at a 1-day lag, the PM₁₀
16 coefficient was attenuated and became insignificant, but coefficients for each of the gases were
17 robust and remained statistically significant. In some other studies, reductions in PM effect
18 estimates were reported with adjustment for some gaseous pollutants for some, but not all,
19 endpoints studied (e.g., Kwon et al., 2001; Prescott et al., 1998). Other authors report that it is
20 difficult to distinguish among effects of closely correlated pollutants (e.g., Linn et al., 2000, for
21 CO, NO₂ and PM₁₀; Atkinson et al., 1999a, for SO₂, NO₂ and PM₁₀; Pope et al., 1999a, for CO
22 and PM₁₀).

23 For many of the studies discussed above, PM and the gaseous co-pollutants are highly
24 correlated, especially PM with CO, SO₂ and NO₂; and it is generally the case that where PM
25 effect estimates were reduced in size with the inclusion of these co-pollutants, the pollutants
26 were also highly correlated. Among the studies conducted in the U.S., O₃ was positively
27 correlated with the PM indices in Detroit (Ito 2003), Atlanta (Tolbert et al., 2000b) and Cook
28 County, IL (Moolgavkar, 2003), where in some cases PM effects were reduced with the
29 inclusion of O₃. In other locations, such as Santa Clara County, CA (Fairley, 2003) and Boston
30 (Peters et al., 2000a), O₃ was not correlated with PM and PM effect estimates were not reported
31 to change in multi-pollutant models with O₃. In contrast with many other areas of the U.S., CO

1 and NO₂ were not highly correlated with PM indices in Coachella Valley, CA (Ostro et al.,
2 2003), and the PM effects estimates for there were reported to be robust to inclusion of gaseous
3 pollutants. It should also be noted that, in a number of the studies where PM was highly
4 correlated with the gaseous pollutants, the PM effect estimates were not affected by inclusion of
5 the gaseous co-pollutants in the models.

6 Overall, then, a number of the recent studies have reported PM effect estimates that are
7 robust to adjustment for gaseous co-pollutants and, in a number of studies, independent effects
8 of the gaseous pollutants were also found. There are also a number of studies showing generally
9 independent effects of PM but, for certain health outcomes and co-pollutants, the PM effect
10 estimate is reduced. For example, in analyses of mortality and hospital admissions data in
11 Detroit, the authors concluded "...the coefficients of PM mass indices often remain significant in
12 two-pollutant models, but can be reduced, especially by O₃; and gaseous pollutants also are
13 associated with mortality and morbidity outcomes, but cause specificity of associations has not
14 been consistent."(Lippmann et al. 2000, p. 33; reanalyzed in Ito, 2003). However, some other
15 authors have concluded that PM effects were not robust to adjustment for gaseous co-pollutants.
16 One notable example is the analyses of mortality and hospital admissions data in Cook and
17 Los Angeles Counties, where the author concluded "... in Los Angeles (with the exception of
18 COPD admissions with which NO₂ appeared to show the most robust association) it is clear that
19 CO was the best single index of air pollution associations with health endpoints, far better than
20 the mass concentration of either PM₁₀ or PM_{2.5}. In Cook County the results were not so clear cut.
21 However, any one of the gases was at least as good an index of air pollution effects on human
22 health as PM₁₀" (Moolgavkar, 2003, p. 198).

23 In many of these studies, PM with and without added components of gases thusly appears
24 to be a key putative agent. However, care must be exercised in interpreting such results, taking
25 into account what is known about the toxicology and clinical studies of the gases. It is often
26 clear that these gases, at concentrations present or given the nature of the effects, do not carry
27 sufficient biologic plausibility to substantially affect the results seen. For example, SO₂ is
28 mostly absorbed in upper airways under normal breathing conditions and, although it might
29 affect airway neural reflexes to contribute to asthma exacerbation at typical U.S. ambient levels,
30 it is not likely to exert sufficient effects on COPD or CVD to contribute to excess morbidity and
31 mortality. Further, because of frequent lack of correlation, separating the effects of PM from O₃

1 seems justified on the basis of simply adjusting one for the other. The same may not be said for
2 some of the other major gaseous pollutants. It is also the case that the most consistent findings
3 from amidst the diversity of multi-pollutant evaluation results for different sites is that the PM
4 signal most often comes through most clearly.

6 **8.4.3.4 Bioaerosols as Possible Confounders or Effect Modifiers in PM** 7 **Epidemiologic Studies**

8 In addition to possible confounding or effect modification by gaseous co-pollutants,
9 possible confounding or effect modification by bioaerosols needs to be considered in evaluating
10 ambient PM epidemiologic findings. As discussed in Chapter 7, various airborne bioaerosols
11 contain allergens that can contribute to upper (oronasal) respiratory tract irritation (hay fever-
12 type allergic reactions) and/or to more serious lower respiratory tract effects (e.g., acute
13 inflammation, bronchoconstriction, exacerbation of asthma attack frequency or intensity, etc.).

14 A number of epidemiology studies have reported significant associations between ambient
15 air concentrations of fungal spores and asthma symptoms, hospital admissions, or medical visits
16 for respiratory diseases (Neas et al., 1996; Delfino et al., 1996; Delfino et al., 1998a; Delfino
17 et al., 2002; Ostro et al., 2001; Stieb et al., 2000; Lewis et al., 2000), although not all found
18 statistically significant associations (e.g., Tolbert et al., 2000b). Significant associations between
19 pollen count and respiratory health outcomes have also been reported (Moolgavkar et al., 2000;
20 Stieb et al., 2000; Lewis et al., 2000), but a number of other studies that evaluated such effects
21 did not find significant associations with pollen (Thurston et al., 1997; Delfino et al., 1998a;
22 Delfino et al., 2002; Ostro et al., 2001; Tolbert et al., 2000b; Anderson et al., 1998). Where the
23 studies have included tests for interaction or potential confounding between aeroallergens and
24 non-biological air pollutants for these health responses, all studies have indicated that the
25 aeroallergen and air pollutant effects were independent, or the authors have concluded that
26 effects were independent because the aeroallergens and pollutants were poorly correlated (Neas
27 et al., 1996; Delfino et al., 1996; Delfino et al., 1997b; Delfino et al., 1998a; Delfino et al., 2002;
28 Stieb et al., 2000; Moolgavkar et al., 2000; Anderson et al., 1998; Lewis et al., 2000).

29 It is important to emphasize, as discussed in Chapters 3 and 7, that ambient air levels of
30 bioaerosol components (e.g., fungi, fungal spores, pollen, cytoplasmic fragments of pollen,
31 endotoxin, or glucan components of bacteria cell walls, etc.) are all seasonally elevated during

1 warmer, more humid months (e.g., April / May through August / September), but are very low
2 during colder fall / winter months (October / November through March) in the U.S.

3 4 **8.4.3.5 Adjustments for Meteorological Variables**

5 As was noted earlier in this chapter, it was thought at the time of completion of the 1996
6 PM AQCD that issues related to model specifications used to control for weather effects in daily
7 time-series analyses of ambient PM relationships to mortality/morbidity had largely been
8 resolved. However, as also noted earlier, reanalyses of PM studies to address the GAM
9 convergence criteria issue led to examination of the sensitivity of PM risk estimates to different
10 model specifications and the consequent reemergence of model specification for control of
11 weather effects as an important issue in interpreting PM epidemiologic analyses. The reanalyses
12 results highlighted the sensitivity of modeling outcomes to kinds and numbers of weather-related
13 variables included in base models and also, the sensitivity of results to varying degrees of
14 freedom allotted for smoothing of weather and temporal trends.

15 Putting the issue of controlling for weather effects into a historical perspective, the 1996
16 PM AQCD noted that various approaches had previously been used to evaluate potential
17 contributions by weather to mortality or morbidity effects attributed in different studies to
18 ambient PM exposures. It noted, as one example, one approach that simply qualitatively
19 compared PM risk estimates derived from cities differing in typical climatic conditions and
20 classified as “warm” or “cold” based on long-term mean temperatures — an approach that may
21 be open to a number of questions, e.g., the fact that the “hot/cold” dichotomy does not
22 adequately consider cities with moderate climates as part of a broader continuum representative
23 of the actual range of weather conditions encountered in the U.S. (as is the case, say, for
24 San Francisco versus New Orleans or Chicago) or the fact that long-term mean temperatures
25 over several months are likely an inappropriate control for likely more acute weather changes
26 affecting mortality counts on a daily basis. Other approaches included (a) stratifying mortality
27 events in relation to one or another weather variable and discarding of the most extreme days
28 (e.g., the highest X % of mean daily temperature days) from analyses of PM effects; (b) use of
29 dummy variables that classify days as “hot” or “humid” or “hot/humid” days; or (c) use of rank-
30 ordered temperatures, or mean temperature for groupings of days, etc. — none of which, it was

1 noted in the PM AQCD, may provide adequate details to detect actual weather-mortality
2 relationships.

3 The above approaches share, to some extent, certain features that attempt, in common, to
4 adjust for the generally recognized non-linearity of weather influences in mortality/morbidity,
5 especially with regard to control for temperature effects. Results of various studies noted in the
6 PM AQCD from the late 1980's and early 1990's provide illustrative examples of outcomes
7 likely reflective of such non-linearity of temperature-mortality associations. On the one hand,
8 Ito et al. (1993) found mortality in London to be associated with BS and aerosol acidity levels
9 and to a much lesser extent to be affected by weather (perhaps not surprising given London's
10 relatively moderate marine climate with relatively infrequent temperature extremes). On the other
11 hand, several other investigators were noted in the 1996 PM AQCD as finding much more
12 marked influences of weather in locations experiencing temperature extremes; and some
13 reported findings indicative of synergistic effects of weather and ambient PM pollution and/or
14 suggestive of weather exerting notably stronger effects on mortality than pollution. Ramlow and
15 Kuller (1990), for example, found daily mortality to be more strongly related to prior day
16 average temperatures than any pollution measure in Pittsburgh (Allegheny Co.) PA, and Wyzga
17 and Lipfert (1995a) reported on apparent synergistic relationship between weather and air
18 pollution, in that days exceeding 85 °F appeared to contribute most to observed TSP-mortality
19 relationships in Philadelphia, PA. Kunst et al. (1993) and Machenback et al. (1993) found
20 temperature extremes in summer and winter to be primarily determinants of mortality in two
21 Netherlands studies, with the relationship between temperature and mortality being non-linear
22 and characterized by a U-shaped temperature curve with minimum mortality rates seen between
23 10 to 15 °C.

24 The 1996 PM AQCD went on to note further the advent of some relatively new approaches
25 to statistical evaluation of potential weather influences in time-series analyses of ambient PM
26 effects on mortality or morbidity. One approach, typified by Kalkstein et al. (1991, 1994), it was
27 noted, proposes that the meteorology of a given locale is defined by discrete, identifiable
28 situations that represent frequency modes for combinations of weather elements. Meteorological
29 delineation of synoptic weather patterns or categories that recognize the existence of such modes
30 can be used to control for weather in statistical analyses. This view basically holds that the use
31 of mean weather elements (e.g., mean daily temperature) do not permit adequate evaluation of,

1 or control for, daily weather extremes. Also, to the extent that consideration of weather in most
2 PM/mortality studies focuses almost entirely on thermal (temperature) and less frequently on
3 moisture (humidity) variables, then PM effect models may encounter potential weather control
4 problems for some cities affected by certain meteorological phenomena (e.g., stormy situations
5 associated with mid-latitude cyclones) that are not associated with thermal extremes and yet can
6 be very important contributors to acute mortality (Kalkstein et al., 1994). These are rarely
7 controlled for in PM/mortality studies, as they cannot be identified on the basis of temperature
8 and humidity.

9 Another approach is one that views adjustment for weather-related variables as being
10 needed to the extent that any empirical adjustment for such variables provides an adequate basis
11 for removing potential confounding of excess mortality with PM or other air pollutants. The
12 1996 PM AQCD noted that one of the most completely empirical methods for adjusting daily
13 time series data for covariates is by use of nonparametric functions, such as LOESS smoothers,
14 generalized splines, or generalized additive models (GAM), as demonstrated in Schwartz
15 (1994d; 1995a,b) and Schwartz and Morris (1995). These may be empirically satisfactory and
16 provide a better fit to data than synoptic categories, but at the loss of a basis for defining
17 “offensive” weather episodes. Application of synoptic climatological procedures to control for
18 weather, it was noted, has the potential to compensate for these difficulties and may add further
19 insight by defining entire sets of meteorological conditions which can lead to increases in
20 mortality.

21 Offensive air masses which lead to mortality totals significantly higher than the long-term
22 baseline have been identified for a number of U.S. cities as reported by Kalkstein (1993b).
23 In most cases “moist tropical” air masses were deemed offensive (especially in the East), but a
24 very oppressive “dry tropical” air mass category was often associated with the greatest increases
25 in mortality, especially in New York, St. Louis, Philadelphia, and in southwestern cities
26 (Kalkstein, 1993b). In some cases, daily mortality totals are over 50% above the baseline
27 (World Health Organization, 1996). Such air mass analyses support the notion that acute
28 mortality increases only after a meteorological threshold is exceeded. This threshold is not only
29 temperature dependent; it represents an overall meteorological situation which is highly
30 stressful. It is noteworthy that most cities demonstrate only one or two types of offensive air
31 masses which possess meteorological characteristics exceeding this threshold; and specific types

1 of oppressive weather patterns associated with increased mortality can vary from city to city and
2 must be defined individually for a given city for use in statistical analyses of PM effects.

3 Detailed analysis of synoptic weather pattern effects in a given city may yield additional
4 information on specific factors that may need to be accounted for in analyzing PM mortality
5 effects for that city. For example, the “moist tropical” type of air mass in Philadelphia,
6 possessing the highest daily minimum and maximum temperatures, both brought mortality
7 increases and was also associated with the greatest standard deviation in mortality of all air
8 masses evaluated. That is, although many days within the offensive air mass were associated
9 with high mortality totals, a number of days showed little mortality increase. The greatest daily
10 mortality totals during moist tropical air mass incursions occurred as part of a lengthy string of
11 consecutive days of the air mass, especially when minimum temperatures were particularly high.
12 This type of information may be important when controlling for weather in PM/mortality
13 analyses.

14 In a PM study where stressful weather days are removed from the data base, synoptic
15 categorization provides an efficient means to remove such days. In studies where weather is
16 stratified based on certain meteorological elements, synoptic categorization allows for a
17 meteorologically realistic control and may be preferable to the use of arbitrary dummy variables
18 when identifying meteorological conditions with an elevated mortality risk.

19
20 ***Evaluation of different weather and time trend model specifications for quantifying PM***
21 ***concentration-response relationships***

22 The study by Pope and Kalkstein (1996), as discussed in the 1996 PM AQCD, provided
23 detailed evaluation of the effects of several substantially different approaches to modeling PM
24 concentration-response relationships and the influence of weather variables on ambient PM
25 effects. The 1996 PM AQCD noted that the original analyses and reanalyses of the Utah Valley
26 data by Samet et al. (1995) used quintiles of PM_{10} as the indicator. The reanalyses reported by
27 Pope and Kalkstein (1996) as Models 1-8 used a linear model for 5-day moving average PM_{10}
28 and 8 different weather models: (1) no adjustment; (2) indicator variables for 20 seasons
29 (1985-1990); (3) indicators for 20 seasons and indicators for quintiles of temperature and relative
30 humidity; (4) indicators for 20 seasons and indicators for 19 synoptic weather categories;
31 (5) linear time trend and indicators for 19 synoptic categories; (6) LOESS smooth of time

1 (span = 10 percent of days); (7) LOESS smooths of time (span = 10 percent of days),
2 temperature (span = 50 percent of days), and relative humidity (span = 50 percent of days); and
3 (8) LOESS smooth of time (10 percent of days) and indicator variables for 19 synoptic
4 categories. The results (shown in Table 12-36 of the 1996 PM AQCD and reproduced here as
5 Table 8-39) were relatively insensitive to the form of time trend and adjustment for weather
6 variables, with RR for total mortality for 50 $\mu\text{g}/\text{m}^3$ increments in PM_{10} varying only from ~1.058
7 (Model 2) to 1.112 (Model 10), all of them statistically significant. The pulmonary mortality
8 models were somewhat more sensitive to the form of the covariate adjustments, with RR for
9 50 $\mu\text{g}/\text{m}^3$ ranging from 1.132 (Model 6) to 1.221 (Model 7); Model 2 showed only a marginally
10 significant PM_{10} coefficient, the others being significant with one-tailed (Models 3 and 4) or
11 two-tailed tests. The cardiovascular mortality models had RR ranging from 1.076 (Models 3 and
12 7) to 1.116 (Model 1), with Model 3 being one-tailed significant and all other models showing a
13 significant PM_{10} effect on cardiovascular mortality. While the authors commented that other
14 communities may show greater sensitivity to the statistical methods for adjusting for time trend
15 and weather, the relative lack of sensitivity of the estimated PM_{10} effect over a very wide range
16 of models is noteworthy.

17 Table 8-39 also shows subset models corresponding to Models 7 and 8. Cold season
18 models called Models 9 and 11 by Pope and Kalkstein (1996, Table 4) consist of Models 7 and 8
19 respectively, limited to the months of October to March. Intra-seasonal differences were
20 adjusted for by LOESS smoothers of time, and daily weather variation either by LOESS
21 smoothers of temperature and relative humidity (Model 9) or by indicators for synoptic
22 categories. Total mortality was highly significant in either case (1.070 for Model 9 and 1.059 for
23 Model 11). Pulmonary mortality was higher (1.145 for Model 9 and 1.120 for Model 11) and
24 marginally significant. Cardiovascular mortality had a RR = 1.062 in Model 9 (not significant)
25 but RR = 1.075 (significant) in Model 11. The corresponding Models 10 and 12 for the warm
26 season (April-September) showed higher RR effects for total and pulmonary mortality, but the
27 effects were not statistically significant. The lower statistical significance may reflect the
28 halving of the sample size in these data sets, since the effect size estimates must be similar to
29 those obtained by averaging the whole-data analyses across the corresponding seasons, with cold
30 season = fall + winter approximately, and warm season = spring + summer approximately.

31

**TABLE 8-39. EFFECTS OF DIFFERENT MODELS FOR WEATHER AND TIME TRENDS
ON MORTALITY IN UTAH VALLEY STUDY**

Model Identity*	Time Model	Weather Model	Relative Risk for PM ₁₀ 50 µg/m ³		
			Total Mortality	Pulmonary Mortality	Cardiovascular Mortality
Base I	-	-	1.076 (1.044, 1.109)	1.198 (1.035, 1.386)	1.094 (1.019, 1.174)
Base II	-	-	1.083 (1.030, 1.139)	1.215 (1.049, 1.408)	1.094 (1.020, 1.174)
1	None	None	1.074 (1.032, 1.118)	1.185 (1.056, 1.331)	1.116 (1.054, 1.181)
2	20 seasons	None	1.058 (1.002, 1.118)	1.133 (0.963, 1.333)	1.081 (1.000, 1.169)
3	20 seasons	Quintile	1.062 (1.003, 1.124)	1.150 (0.972, 1.361)	1.076 (0.992, 1.167)
4	20 seasons	Synoptic	1.068 (1.009, 1.130)	1.169 (0.988, 1.382)	1.090 (1.005, 1.183)
5	Linear	Synoptic	1.068 (1.020, 1.118)	1.183 (1.032, 1.356)	1.100 (1.030, 1.175)
6	LOESS	None	1.059 (1.017, 1.102)	1.131 (1.006, 1.273)	1.085 (1.024, 1.150)
7	LOESS	LOESS	1.077 (1.028, 1.129)	1.221 (1.063, 1.402)	1.076 (1.006, 1.152)
8	LOESS	Synoptic	1.068 (1.021, 1.117)	1.166 (1.018, 1.335)	1.099 (1.029, 1.173)
9	Cold season, LOESS	LOESS	1.070 (1.015, 1.129)	1.145 (0.981, 1.337)	1.062 (0.984, 1.146)
10	Warm season, LOESS	LOESS	1.112 (0.918, 1.346)	1.529 (0.813, 2.877)	1.053 (0.789, 1.404)
11	Cold Season, LOESS	Synoptic	1.059 (1.009, 1.111)	1.120 (0.971, 1.291)	1.075 (1.003, 1.153)
12	Warm season, LOESS	Synoptic	1.091 (0.947, 1.258)	1.394 (0.794, 2.577)	1.024 (0.780, 1.343)

*Models 1 through 5 were parametric models, and models 6 through 12 were non-parametric GAM models that have not been reanalyzed.

Source: Pope and Kalkstein (1996).

1 Pope and Kalkstein (1996) also showed four nonparametric smooth regression plots
2 corresponding to Models 1, 6, 7, and 8, respectively. All of the models using a nonparametric
3 regression for daily mortality on PM₁₀ were approximately linear, showing some suggestion of
4 nonlinear structure between roughly 60 and 100 µg/m³ PM₁₀, but in no case indicating a
5 threshold or consistent flattening of the concentration-response curve at any PM₁₀ level. The
6 authors noted that a chi-squared test comparing each non-parametric regression model for PM₁₀
7 with the corresponding linear model showed no statistically significant deviation from linearity.

8 The 1996 PM AQCD also discussed another study, by Samet et al. (1996b), that compared
9 different methods for estimating modifying effects of different weather models on the
10 relationship of TSP and SO₂ to total mortality in Philadelphia from 1973 to 1980. The models
11 included the original Schwartz and Dockery (1992a) weather specification, a nonparametric
12 regression model, LOESS smoothing of temperature and dewpoint, and Kalkstein's Temporal
13 Synoptic Index (TSI) or Spatial Synoptic Category (SSC) models. The first three methods
14 allowed the weather model to be adjusted so as to provide an optimal prediction of mortality,
15 whereas the latter two models were based completely on external criteria and the classification
16 of days by SSC or TSI categories was not adjusted to improve prediction of mortality. The
17 authors concluded that “. . . the association between air quality as measured by either TSP alone,
18 SO₂ alone, or TSP and SO₂ together, cannot be explained by replacing the original Schwartz and
19 Dockery weather model with either a nonparametric regression, LOESS, or by synoptic
20 categories using either Kalkstein's TSI or SSC systems. In addition, there is little evidence in the
21 Philadelphia total mortality data to support the hypothesis that the pollution effects are modified
22 by the type of weather conditions as measured either by TSI or by strata created from the
23 predicted weather-induced mortalities using the Dockery and Schwartz model or the LOESS
24 model. . . . We did not find variation of the effect of pollution across categories of weather.”
25 Their results are not shown here.

26 The 1996 PM AQCD noted that additional studies systematically evaluating the differential
27 effects of PM and other pollutants by weather category would be of interest. The Philadelphia
28 study by Samet et al. (1996b) used only TSP and SO₂, whereas the Utah Valley study by Pope
29 and Kalkstein (1996) did not look at the effects of weather as a modifier with other pollutants as
30 well as PM₁₀. Still, based on the above two major studies extensively evaluating a number of
31 different approaches to adjust for weather effects (including evaluations using synoptic weather

1 patterns), it was concluded in the 1996 AQCD that significant PM-mortality associations were
2 robust and verifiable via a variety of model specifications controlling for weather.

3 With the identification of GAM-related statistical issues and in view of new insights gained
4 from reanalyses addressing those issues (as discussed in Section 8.4.2), questions arise with
5 regard to the potential resiliency of the findings reported and conclusions drawn based on the
6 Pope and Kalkstein (1996) and Samet et al. (1996b) studies. Given the lack of reanalyses
7 addressing the GAM issues for these studies, it is neither clear as to the extent that use of GAM
8 strict convergence criteria or alternative models using natural or penalized splines would confirm
9 the basic results of the non-parametric GAM analyses in those studies nor as to the magnitude of
10 likely reduction in PM effect size estimates that would occur. Still, based on likely analogy to
11 reanalyses results for other GAM-related studies discussed in Section 8.4.2, it would not be
12 unreasonable to assume that similar reanalyses for the non-parametric models used in these two
13 new studies could generate PM effect estimates reduced by up to about 50% from the originally
14 published one. Thus, for example, the Pope and Kalkstein (1996) original estimates for total
15 mortality could be reduced from ~6 to 11% increase in excess deaths per 50 $\mu\text{g}/\text{m}^3$ PM_{10} to as
16 low as ~3 to 5.5%, values that comport very well with the range of results obtained for most
17 other PM_{10} total mortality studies. On the other hand, it is less possible at this time to project
18 likely outcomes of sensitivity analyses that would evaluate effects of markedly varying degrees
19 of smoothing or degrees of freedom used.

20 As noted in Section 8.4.2, based on the reanalyses results, the HEI (2003) Special Panel
21 Commentary concluded that none of the reanalyzed studies' original conclusions were changed
22 in a meaningful way by use of stricter convergence criteria. However, the sensitivity of
23 reanalyses outcomes to the choice of weather variables, to the degree of smoothing, and to the
24 numbers of degrees of freedom led the panel to note that neither the appropriate degree of
25 control for time nor appropriate specification of effects of weather in these time series has been
26 determined. And the Panel went on to recommend that the sensitivity of these studies to a wide
27 range of alternative degrees of smoothing and alternative specification of weather variables in
28 time-series models should continue to be evaluated.

29 Reanalyses conducted by Ito (2003) of PM_{10} - mortality/hospital admissions associations in
30 Detroit are illustrative of the sensitivity of PM effect size estimates to alternative model
31 specifications to control for temporal trends and potential weather effects. Sensitivity analyses

1 provided by Ito (2003) varying the extent of smoothing for temporal trends and using several
2 different specifications for weather variables (as well as varying degrees of freedom) provided
3 results as shown in Figures 8-20 and 8-21 for PM₁₀-mortality and PM₁₀-pneumonia admissions
4 during 1992-1994 in Detroit. One set of analyses in each figure shows the effect of varying the
5 extent of smoothing for temporal trends, without inclusion of any adjustments for weather
6 variables; whereas, the other sets of curves indicate the influence of several different weather
7 model specifications on the magnitude of the PM₁₀ effect estimate. In general, effect estimates
8 for models controlling only for temporal trends were notably higher (up to 2- to 3-fold) than
9 those derived from models adjusting for weather effects. However, most investigators, in fact,
10 do now make some adjustment(s) for weather. Hence, of most crucial importance are the Ito
11 (2003) results for the weather adjustment models shown in the two figures. Ignoring the
12 unadjusted-for-weather line, the coefficients for various weather adjustment models for total
13 mortality (Figure 8-20) tend to converge in a range from about a factor of ~2 to ~1.5 difference
14 as the period of temporal smoothing is shortened. Decreasing the period length for temporal
15 smoothing may, to some extent, be washing out the effects of weather (temperature and
16 dewpoint). The effect of temporal smoothing on air pollution effects can be judged by the
17 decrease in the coefficients as the temporal smoothing period decreases. Coefficients for
18 pneumonia admissions (Figure 8-21) appear to be more sensitive to adjustments for temporal
19 trends. Overall, both temporal smoothing and control for weather can decrease the size of the
20 PM₁₀ effect estimate.

21 Most investigators would use periods of length 1 to 3 months for temporal smoothing.
22 Using such periods, the agreement between the coefficients remained within about 50%, except
23 that there is more variability between the periods of the temporal smoothing for hospital
24 admissions. Ito, in a personal communication to EPA, indicated that the degree of temporal
25 smoothing should depend on the size of the population. So, for large cities or large multi-city
26 studies, more adjustment is likely warranted; but, for smaller cities, statistical power to detect the
27 PM₁₀ effect can be greatly reduced by over-adjustment for temporal effects. Considering the
28 unadjusted-for-weather results, over-adjusting for temporal effects may be allowing this curve to
29 increase as more weather effects become negatively, rather than positively, correlated with PM₁₀
30 values. This conclusion may apply only to Detroit. There, mortality/pneumonia are higher in
31 winter and PM₁₀ tends to be higher in summer due to summer sulfate in that region. So,

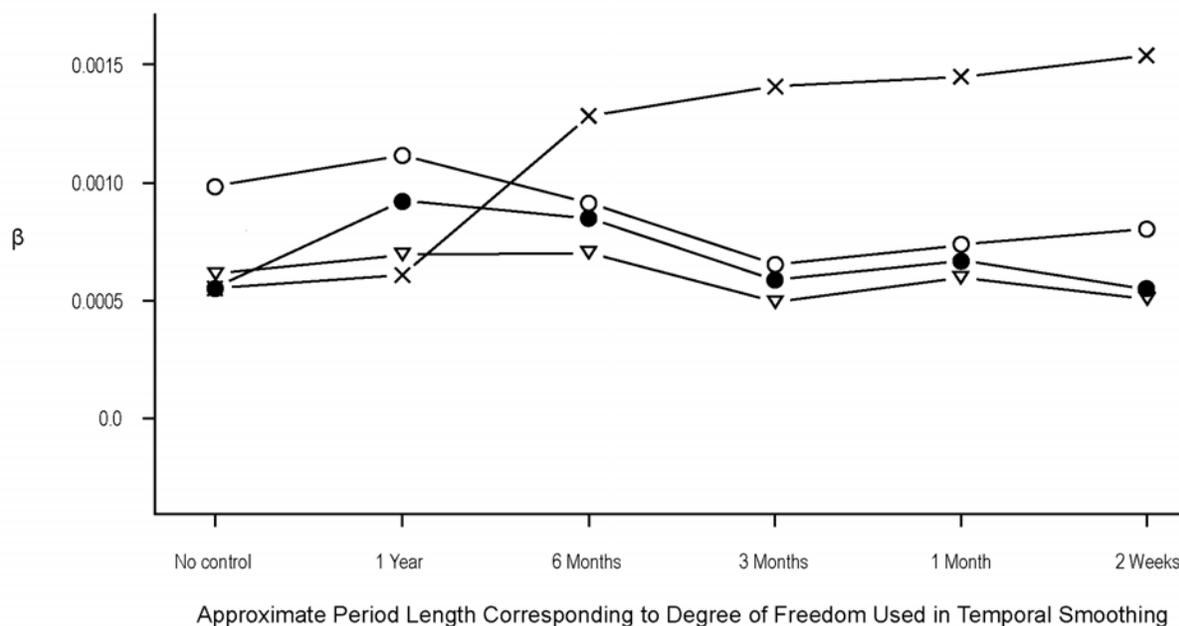


Figure 8-20. PM_{10} (lag 1 day) coefficient (β) for total mortality, for 1992-1994, as a function of alternative weather models and varying degrees of freedom for fitting temporal trends using natural splines. White circle: natural splines of same-day temperature and same-day dewpoint, both with $df = 2$; black circle: natural splines of same-day temperature ($df = 2$), the average of temperatures lagged 1 through 3 days ($df = 2$), and hot-and-humid day indicator; white triangle: natural splines of the same-day temperature ($df = 6$), the average of temperatures lagged 1 through 3 days ($df = 6$), same-day dewpoint ($df = 3$), and the average of dewpoints lagged 1 through 3 days ($df = 3$); \times : no adjustment for weather.

Source: Ito (2003).

1 adjusting for seasonal trends removes the opposing cycles and leaves the positive PM_{10} /mortality
 2 associations.

3 Some investigators (e.g., Schwartz) note that judgment on the part of the investigator is
 4 required to decide the appropriate amount of smoothing for weather and temporal effects and
 5 that case-crossover analyses can likely be applied with less judgment considerations. However,
 6 case-crossover can be very sensitive to the choice of control periods (e.g., 7 or 14 days before
 7 and after the case period). So, there are also judgment considerations in applying that

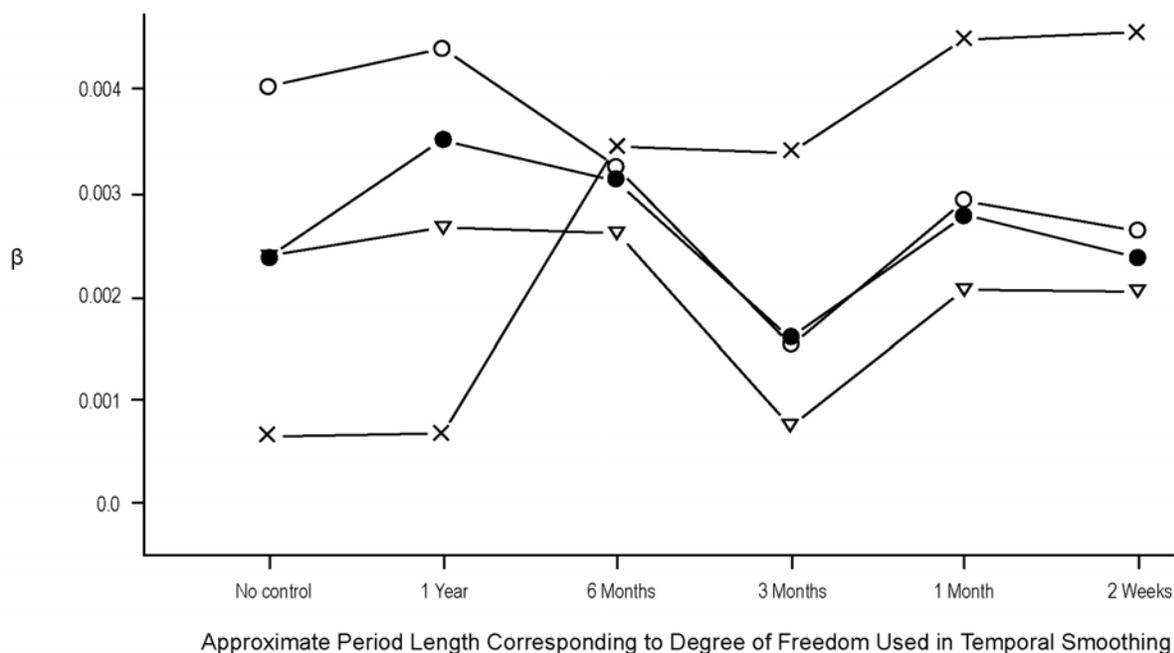


Figure 8-21. PM_{10} (lag 1 day) coefficient (β) for hospital admissions for pneumonia among the elderly, for 1992-1994, as a function of alternative weather models and varying degrees of freedom for fitting temporal trends using natural splines. White circle: natural splines of same-day temperature and same-day dewpoint, both with $df = 2$; black circle: natural splines of same-day temperature ($df = 2$), the average of temperatures lagged 1 through 3 days ($df = 2$); white triangle: natural splines of the same-day temperature ($df = 6$), the average of temperatures lagged 1 through 3 days ($df = 6$), same-day dewpoint ($df = 3$), and the average of dewpoints lagged 1 through 3 days ($df = 3$); x: no adjustment for weather.

1 method as well. Still, future use of the case-crossover approach may add information to
 2 supplement outcomes from PM time series analyses.

3 Several studies published in recent years since the 1996 PM AQCD and not discussed
 4 elsewhere in this chapter provide interesting new information bearing on weather-related effects
 5 that should likely be of value in controlling for weather effects in future PM epidemiologic
 6 analyses. First, the study by Smoyer et al (2000a) of summer weather effects on mortality
 7 among the elderly (≥ 64 yrs old) showed marked increases in mortality among the elderly over a
 8 17-yr. period in five Southern Ontario metropolitan areas (Toronto, London, Windsor, Hamilton,

1 Kitchner-Waterloo-Cambridge) on heat-stress days defined as those with an “apparent
2 temperature” (heat index) above 32 °C. The study illustrates the likely need to consider
3 combined effects of temperature and humidity/dewpoint rather than evaluating independent
4 effects of such variables in controlling for weather effects. Also, relative vulnerability to heat-
5 related weather effects may be increasing for U.S. populations with the aging of disproportionate
6 numbers of individuals (“baby boomers”) into older middle age groups. This may complicate
7 future epidemiologic/statistical attempts at disentangling potential PM effects from those of
8 weather.

9 Another paper by Smoyer et al. (2000b) evaluated the effects of “offensive weather events”
10 and air pollution (TSP, O₃) in Birmingham, AL and Philadelphia, PA and found that in both
11 cities offensive weather events had a higher impact on mortality than did high concentrations of
12 TSP or O₃. The authors reported that the highest mortality levels occur when the hottest, but not
13 necessarily the most polluted, air mass occurs over each of the two cities. Still, lesser increases
14 in mortality were observed to be associated with TSP in Philadelphia during non-offensive
15 weather situations, and neither TSP nor O₃ seemed to have any add-on effect to weather-related
16 mortality. In contrast, potential interactive effects seem to be implied by the Birmingham
17 results. That is, the authors noted that although Birmingham’s high-mortality (offensive) air
18 mass is not the most polluted, offensive air mass days with high pollutant concentrations still
19 exhibit higher mean mortality than offensive air mass days with low pollution concentrations.
20 Also different from the Philadelphia results was the lack of associations in Birmingham between
21 air pollution levels and mortality on non-offensive air mass days. These results appear to
22 reinforce the need for city-specific evaluation of weather-related effects; and, they also hint at
23 potential additive or synergistic effects of weather and air pollution, i.e., the joint occurrence of
24 elevations of TSP and/or O₃ together with high heat-index conditions may increase mortality
25 over levels than would have been associated with each factor alone.

26 Two other studies by Braga et al. (2001b, 2002) provide additional interesting results
27 concerning the time course of weather-related deaths of possible importance for development of
28 model specifications for control of weather effects in PM epidemiology studies. Braga et al.
29 (2001b) modeled daily death counts in a Poisson regression, examining effects of temperature
30 and humidity out to lags of 3 weeks and controlling for other covariables (i.e., season, day of
31 week, barometric pressure) using nonparametric smoothing in GLM analyses for 12 U.S. cities

1 that represented a wide range of typical climatic conditions and geographic regions (e.g.,
2 Northeast, Midwest, Northwest, South, etc.). Based on distributed lag modeling, the authors
3 noted that both high and low temperatures were associated with increased total deaths in “cold”
4 cities; and that the effects of cold temperatures persisted for days, whereas high-temperature
5 effects were restricted to the day of death or to the immediately preceding day (likely reflecting
6 harvesting by high temperatures, as also suggested by other patterns of results). In hot cities,
7 neither hot nor cold temperatures per se had much effect on mortality; however, the effect of hot
8 temperature varied with the range of summer temperature variations and the use of air
9 conditioning. The authors noted that such dissimilarities between cities indicate that analyses of
10 climate change (and presumably, other weather-related effects) should be taken into account
11 when evaluating regional differences and temperature-associated harvesting.

12 The Braga et al. (2002) study used similar methods to evaluate weather-related effects on
13 cause-specific (i.e., respiratory and cardiovascular) deaths in the same 12 U.S. cities. The effects
14 and associated lag structures for both temperature and humidity were evaluated based on a
15 distributed lag model. In cold cities, the authors noted that both low and high temperatures were
16 associated with CVD deaths, with low-temperature effects persisting for days while high-
17 temperature effects were restricted to extreme temperatures on the day of death or the day
18 before. For myocardial infarction (MI) deaths, hot-day effects were twice those of cold-day
19 effects; but hot day effects were five times lower than cold days for all CVD causes. Harvesting
20 effects on hot days were suggested by temporary deficits in numbers of deaths a few days later
21 (not seen after days with cold temperature deaths). In hot cities, neither hot nor cold temperature
22 days appeared to affect mortality counts for CVD or pneumonia deaths, but lagged effects were
23 seen for MI or COPD deaths associated with high temperatures (lagged 4-6 and 3-4 days,
24 respectively). For respiratory deaths, it was noted that wider variations in summer and winter
25 temperatures were related to larger effects for hot and cold days, respectively. However, no
26 clear patterns of results were discerned for humidity effects. Overall, these results suggest that
27 individuals in cities (e.g., Houston, Atlanta, etc.) with generally warmer weather become adapted
28 to such and cope better with high-temperature extremes. They also suggest potentially varying
29 lags for different types of weather-related effects (hot versus cold) and for different cause-
30 specific endpoints – which may be important to consider in model specifications for control of
31 weather-related effects in future epidemiologic studies of ambient PM effects.

1 **8.4.4 The Question of Lags**

2 The effect of lag selection on resulting models for PM health effects is an important issue
3 affecting overall interpretation of epidemiologic analyses. Some interesting and highly
4 informative points related to lag selection can be discerned based on certain newly available
5 individual study results and on several illustrative examples comparing lag-related results
6 obtained by different investigators for analyses of PM effects in the same U.S. city.

7 Using simulated data with parameters similar to a Seattle PM_{2.5} data series, Lumley and
8 Sheppard (2000) showed that potential bias resulting from lag selection can be of similar size to
9 the relative risk estimates from the measured data. The simulations included a data set where
10 PM_{2.5} was significantly associated with hospital admissions for asthma and another data set
11 where there was no such association. The selection rule used was to choose the single-day lag
12 (between 0 and 6 days) with the largest estimated relative risk. In the “positive control” model,
13 where there was a known positive association, the bias associated with selecting the lag with the
14 largest effect size from a series of lags was negligible. However, in the analyses using simulated
15 data where no association was present, selecting the lag with the largest effect size resulted in a
16 positive bias. The mean bias found in this analysis of simulated data was about half the size of
17 the effect estimate from a previous publication on associations between PM_{2.5} and asthma
18 hospital admissions (from Sheppard et al., 1999), and the authors reported that the relative risk
19 from the previous study was at the 90th percentile of the bias distribution in this analysis. In
20 comparisons to real data from Seattle for other years and from Portland, OR (with similar
21 weather patterns to Seattle), similar bias issues became evident. Thus, if no association actually
22 exists in the data, this analysis suggests that selecting the largest risk estimate from a series of
23 lag periods can lead to potential positive bias toward finding an association.

24 In considering the results of models for a series of lag days, it is important to consider the
25 pattern of results that is seen across the series of lag periods. If there is an apparent pattern of
26 results across the different lags, (such as that seen in Figure 8-22 for results obtained by Peters
27 et al., 2001), then selecting the single-day lag with the largest effect from a series of positive
28 associations is reasonable, although it is, in fact, likely to underestimate the overall effect size
29 (since the largest single-lag day results do not fully capture the risk also distributed over adjacent
30 or other days). The importance of considering the pattern of results is further illustrated by the
31 study of Sheppard et al. (1999), in which the pollutant effects reported for asthma hospitalization

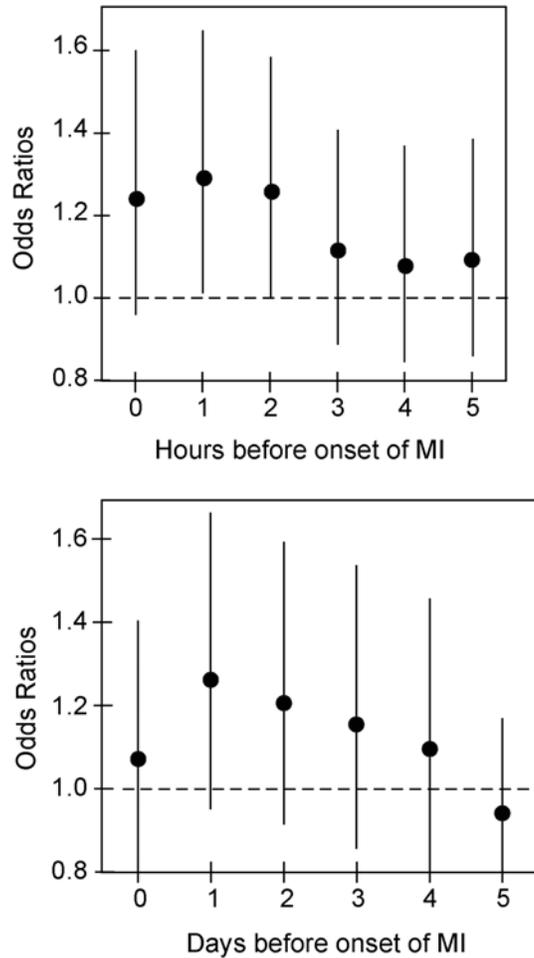


Figure 8-22. Odds ratios (and 95% confidence intervals) for associations between onset of myocardial infarction (MI) and $25 \mu\text{g}/\text{m}^3$ increase in hourly (upper panel) or daily 24-h average (bottom panel) $\text{PM}_{2.5}$ concentrations. Based on univariate analyses of ambient $\text{PM}_{2.5}$ data measured in South Boston and interviews of patients with MI in greater Boston area during Jan. 1995-May 1996.

Source: Peters et. al. (2001).

1 at specific lag periods were larger than and consistent with estimates obtained for adjacent lags,
 2 thus lending support for selection of particular lag periods for reporting results. In contrast,
 3 analyses reported by Sheppard et. al. (1999) for admissions for appendicitis yielded estimates
 4 from adjacent lags that changed abruptly and an overall unstable pattern was consistent with the
 5 pattern expected for a health endpoint not plausibly associated with air pollution.

1 In the NMMAPS analysis for mortality, a systematic approach across different data sets
 2 was used to investigate the question of lag selection. The Samet et al. (2000b) analysis, and the
 3 reanalysis by Dominici et al. (2002), for the 90 largest U.S. cities provide particularly useful
 4 information on this matter. Figure 8-23 depicts the Dominici et al. (2002) overall pooled results,
 5 showing the posterior distribution of PM₁₀ effects on total mortality for the 90 cities for lag 0, 1,
 6 and 2 days. It can be seen that the effect size estimate for lag 1 day is about twice that for lag 0
 7 or lag 2 days, although their distributions overlap. The pattern of lagged effects pooled for each
 8 of the seven regions (see Figure 8-5) in the 90 cities study also shows that the lag with the largest
 9 effect was at 1 day, except for Upper Midwest results where the estimated PM₁₀ effect was about
 10 the same for lag 0 and 1 days.

11
 12

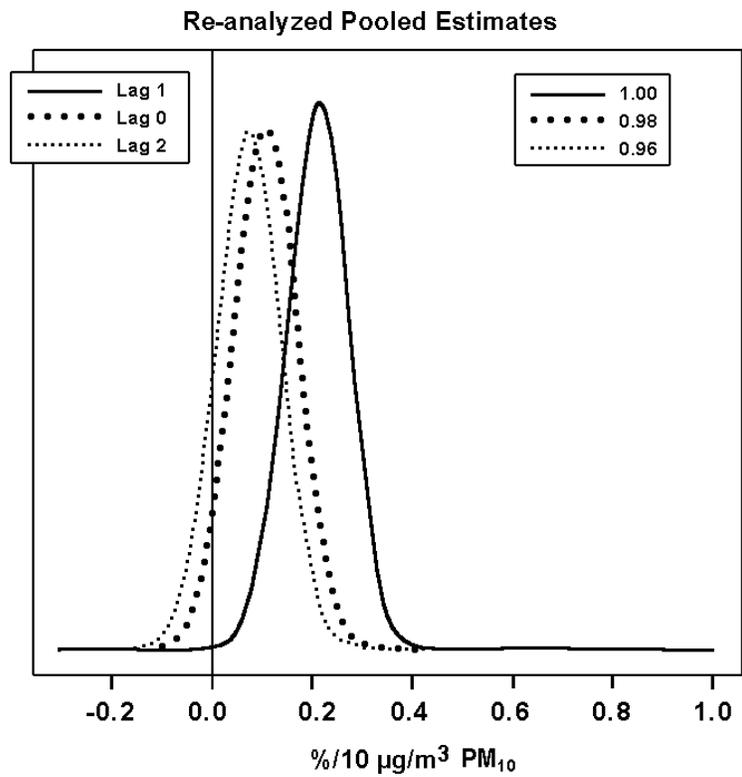


Figure 8-23. Marginal posterior distribution for effects of PM₁₀ on all-cause mortality at lag 0, 1, and 2 for the 90 cities. From Dominici et al. (2002a). The numbers in the upper right legend are posterior probabilities that overall effects are greater than 0.

Source: Dominici et al. (2002).

1 A review of current studies on short-term health effects of air pollution indicates that there
2 are essentially three different approaches to deal with temporal structure: (1) assume all sites
3 have the same lag (e.g., 1 day, for a given effect); (2) use the lag or moving average giving the
4 largest or most significant effect and for each pollutant and endpoint; and (3) use a flexible
5 distributed lag model, with parameters adjusted to each site. All three approaches apply to
6 multi-city studies, while the last two also apply to single-city studies. The NMMAPS mortality
7 analyses used the first approach. This approach introduces a consistent response model across
8 all locations. However, since the cardiovascular, respiratory, or other causes of acute mortality
9 usually associated with PM are not at all specific, there is little *a priori* reason to believe that
10 they must have the same relation to current or previous PM exposures at different sites. The
11 obvious advantage of the first approach in dealing with multi-city data is its consistency in
12 summarizing the point estimate. Conversely, a disadvantage to this approach is that effects may
13 be underestimated in models using a single lag day. A major factor that makes it difficult to
14 conduct a meta-analysis of existing PM health effects studies is the lack of consistency in how
15 lag structures were modeled across the studies.

16 Figures 8-24 through 8-28 depict results obtained for PM-mortality and/or PM-morbidity
17 associations as found and reported by different investigators for five U.S. cities. In most single-
18 city air pollution health effects time-series studies, after the basic model (the best model with
19 weather and seasonal cycles as covariates) was developed, several pollution lags (usually 0 to
20 3 or 4 days) were individually introduced and the most significant lag(s) were typically chosen
21 for presentation of modeling results. Among the U.S. and Canadian mortality studies discussed
22 in Section 8.2, a number of authors tested associations across a series of lag periods, as was
23 reported in the NMMAPS multi-city analysis. These studies reported stronger associations with
24 shorter lags, with a pattern of results showing larger associations at the 0- and 1-day lag period
25 that taper off with successive lag days for varying PM indicators (Moolgavkar, 2003; Ostro
26 et al., 2000, reanalyzed Ostro et al., 2003; Tsai et al., 2000; Burnett et al., 2000, reanalyzed in
27 Burnett and Goldberg, 2003; Mar et al., 2000, reanalyzed in Mar et al., 2003; Ito and Thurston,
28 1996). Several studies used only 0- and 1-day lags in the analyses for PM_{10} , $PM_{2.5}$ and $PM_{10-2.5}$
29 (for example, Schwartz et al., 1996; Lipfert et al., 2000; Klemm and Mason, 2000) and Chock
30 et al. (2000) presented results for models in which 0- to 3- day lags for PM_{10} were included
31 simultaneously, with stronger effects generally being seen with the 0-day lag period. However,

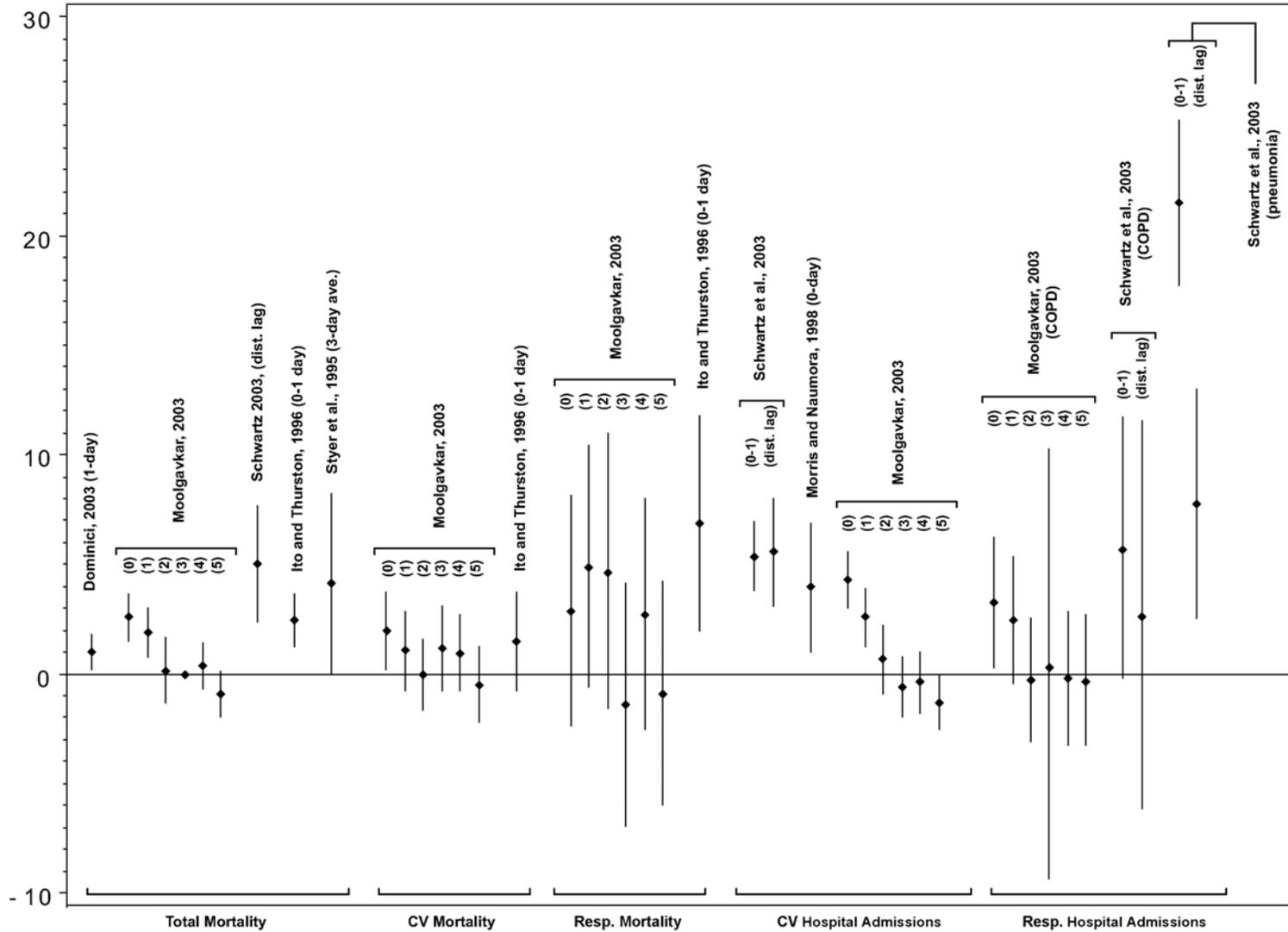


Figure 8-24. Excess risk estimates for associations between various health outcomes and PM₁₀ (50 µg/m³ increment) from different studies conducted in Cook County, IL. Results presented are for different PM₁₀ lag periods from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

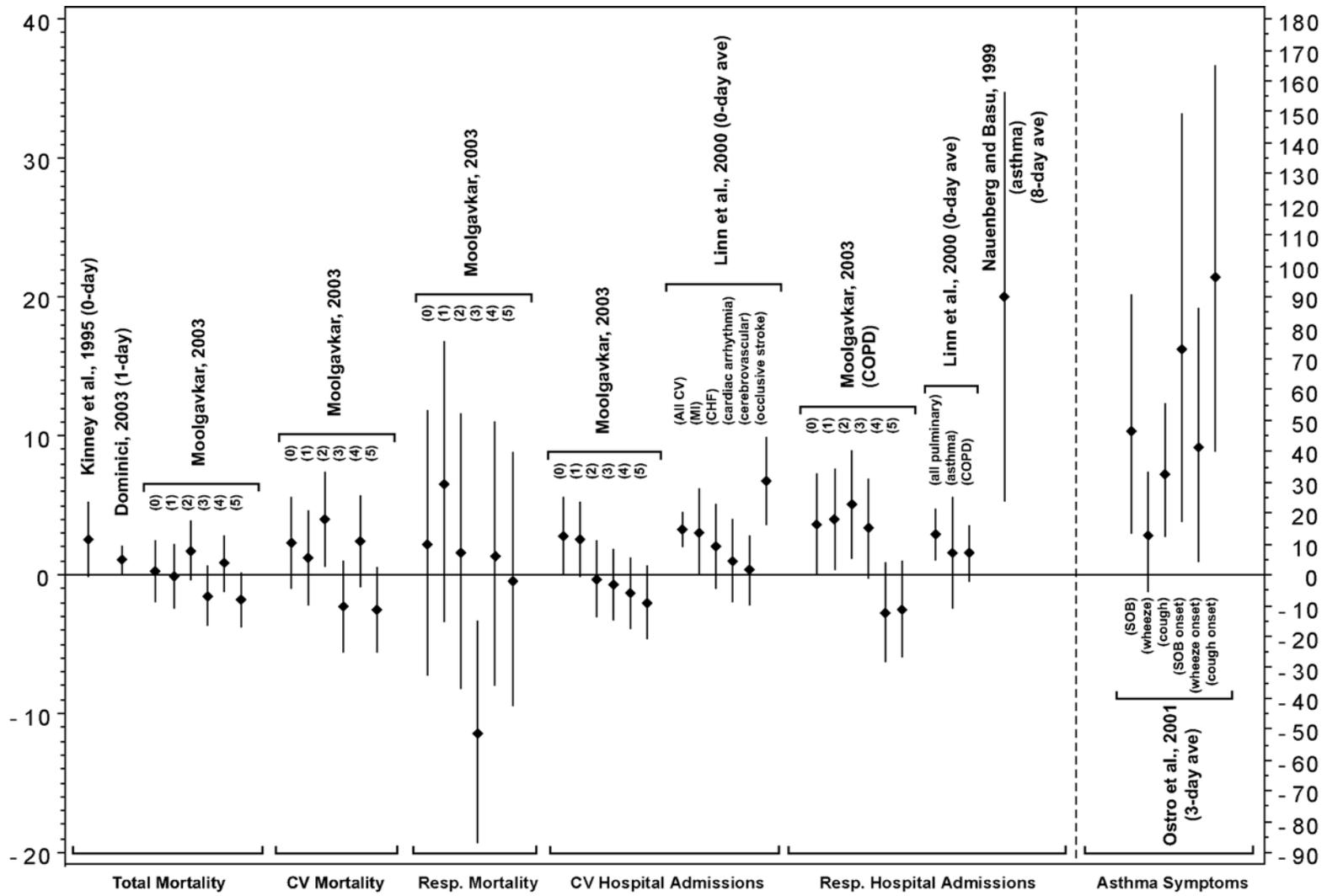


Figure 8-25. Excess risk estimates for associations between various health outcomes and PM_{10} ($50 \mu g/m^3$ increment) from studies conducted in Los Angeles County, CA. Results presented are for different PM_{10} lag periods from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

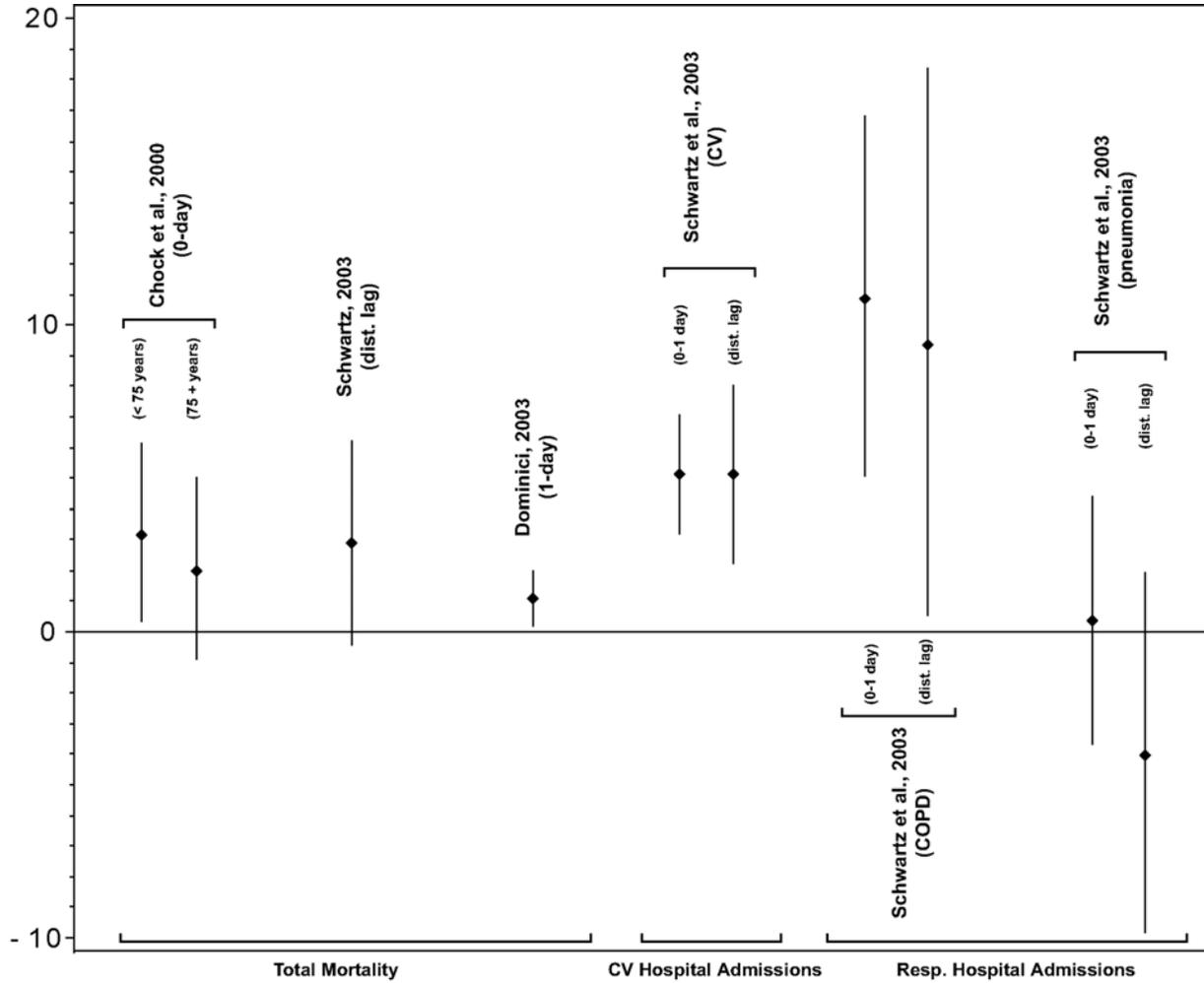


Figure 8-26. Excess risk estimates for associations between various health outcomes and PM₁₀ (50 µg/m³ increment) from studies conducted in Pittsburgh, PA. Results presented for different PM₁₀ lag periods are from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

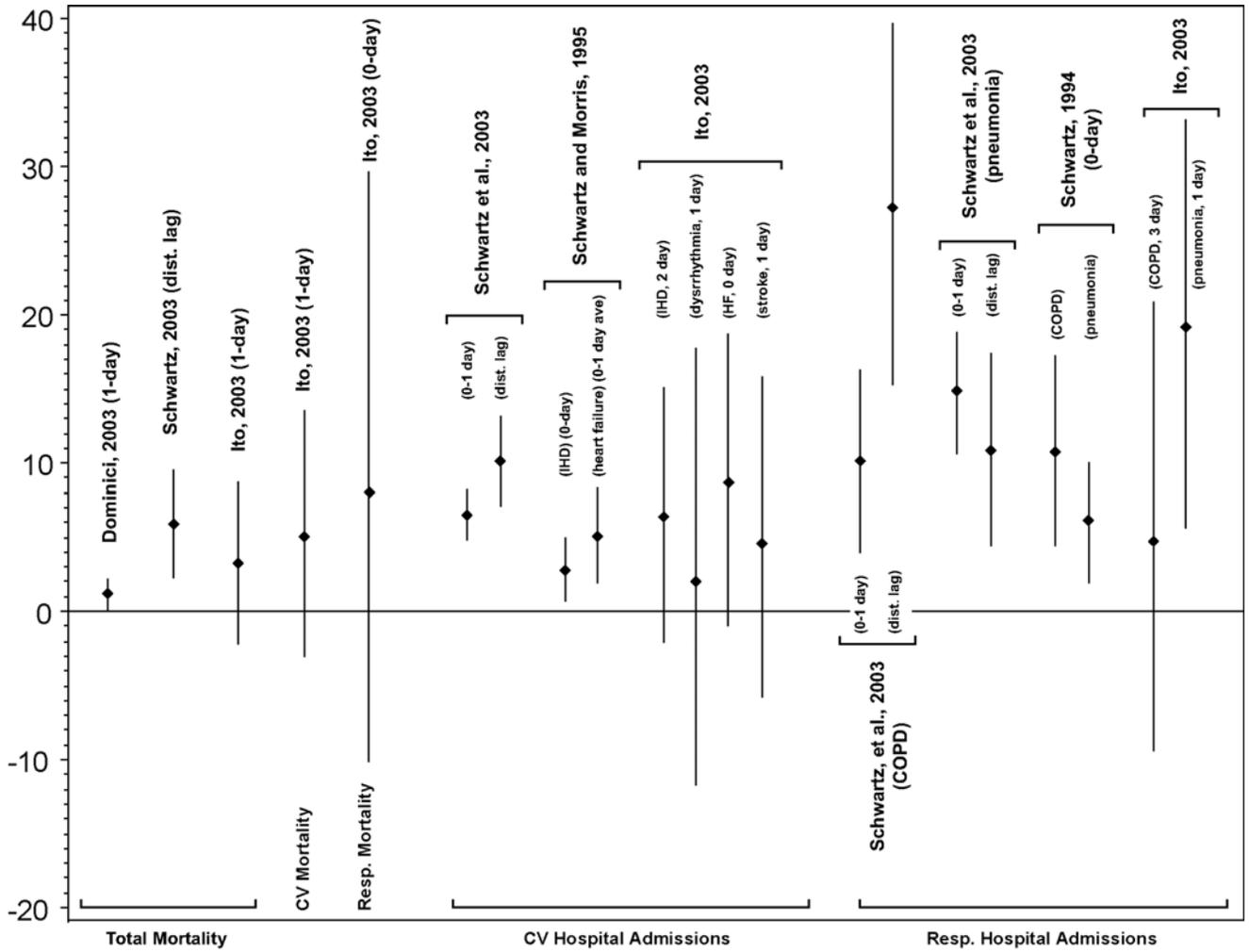


Figure 8-27. Excess risk estimates for associations between various health outcomes and PM₁₀ (50 µg/m³ increment) from studies conducted in Detroit, MI. Results presented are for different PM₁₀ lag periods from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

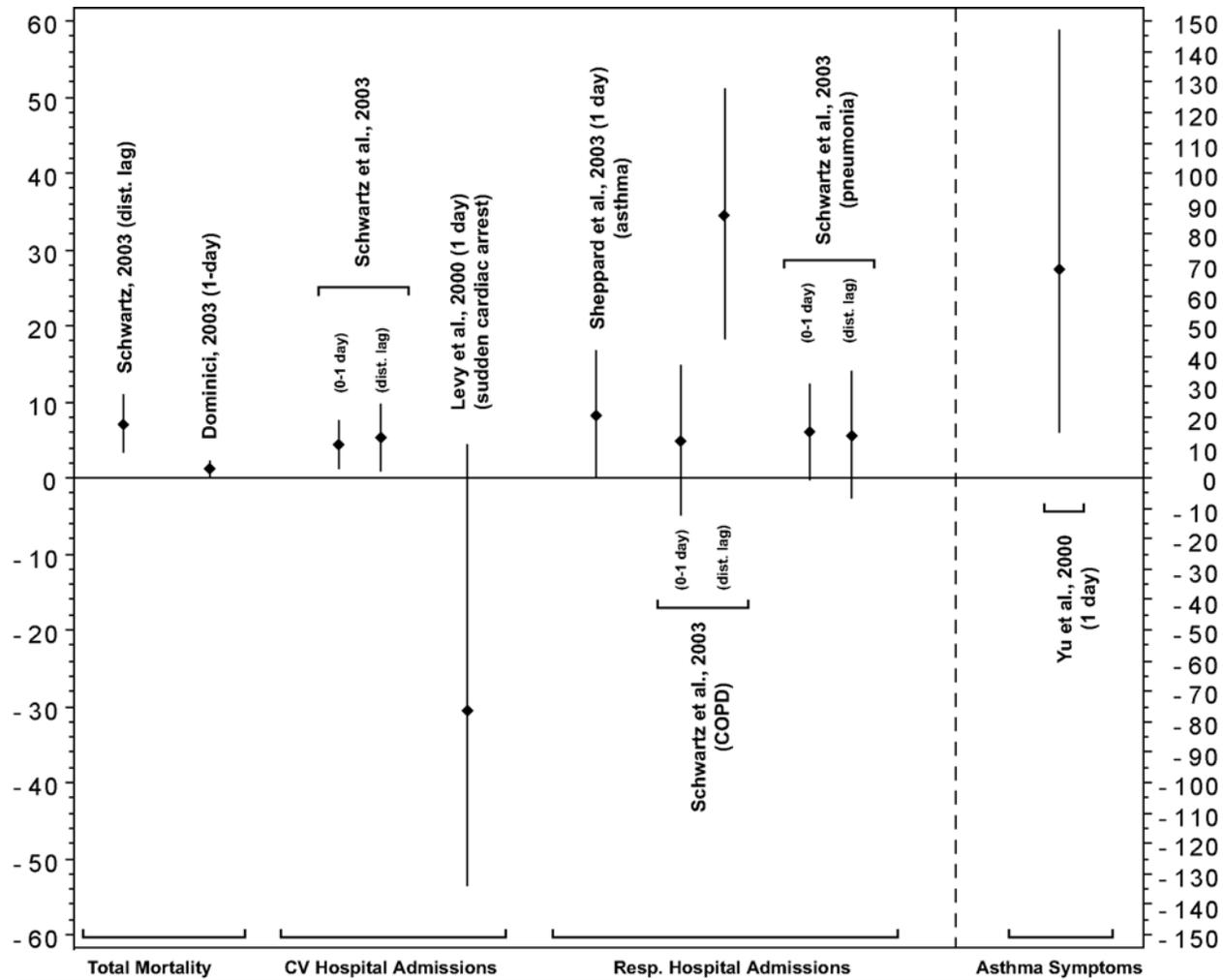


Figure 8-28. Excess risk estimates for associations between various health outcomes and PM₁₀ (50 µg/m³ increment) from studies conducted in Seattle or King County, WA. Results presented for different PM₁₀ lag periods are from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

1 some research groups selected longer moving average lag periods for PM_{10} as providing the best
2 model fit (Pope et al., 1992, 5-day moving average; Styer et al., 1995, 3-day moving average).
3 In selecting the lag periods to publish, these authors also discussed the pattern of effect size
4 estimates across the different lag periods, analogous to what was described previously for
5 Sheppard et al. (1999, reanalyzed in Sheppard et al., 2003).

6 Among the U.S. and Canadian studies on cardiovascular and respiratory morbidity, there is
7 somewhat more variability in which lag periods have been selected for the best-fitting models
8 than shown for the mortality studies. In Section 8.3.2, it was found that the time-series studies of
9 cardiovascular hospital admissions or emergency department visits suggest that PM effects are
10 stronger at lag 0 with some carryover to lag 1; for cardiac physiology studies the results vary,
11 with strongest associations for some effects seen with 1- to 2-hour lag periods (e.g., Peters et al.,
12 2001a). Sheppard et al. (1999, reanalyzed Sheppard et al., 2003), reported stronger associations
13 with asthma hospitalization for 1-day lag periods for PM_{10} , $PM_{10-2.5}$ and $PM_{2.5}$; and Tolbert et al.
14 (2000a) reported significant associations for asthma hospitalization in children with 1-day lagged
15 PM_{10} . Lipsett et al. (1997) and Lin et al. (2001) presented results for asthma hospitalization or
16 emergency department visits which indicate that longer moving average lag periods (out to 5- to
17 7-day moving averages) yield larger PM_{10} or $PM_{10-2.5}$ effect estimates and that the estimates are
18 also fairly consistent across the different lag periods. In panel studies for respiratory symptoms,
19 several research groups also reported larger effect sizes for longer moving average lag periods,
20 including 2-, 3- and 4-day lags (e.g., Mortimer et al., 2002; Vedal et al., 1998; Ostro et al., 2001).
21 Again, however, it is noted that authors generally report finding a pattern of PM-related effects;
22 for example, Yu et al. (2000) reported a consistent pattern of PM results for asthma symptoms
23 across 0-, 1- and 2-day lags and selected the 1-day lag for further investigation in multi-pollutant
24 models.

25 It should also be noted that if one chooses the most significant single-lag day only, and if
26 more than one lag day shows positive (significant or otherwise) associations with mortality, then
27 reporting a RR for only one lag would also underestimate the pollution effects. Schwartz
28 (2000b; reanalysis 2003b) investigated this issue, using the 10 U.S. cities data where daily PM_{10}
29 values were available for 1986-1993. Daily total (non-accidental) deaths of persons 65 years of
30 age and older were analyzed. For each city, a GAM Poisson model (with stringent convergence
31 criteria) and penalized splines adjusting for temperature, dewpoint, barometric pressure, day-of-

1 week, season, and time were fitted. Effects of distributed lag were examined using two models:
2 second-degree distributed lag model using lags 0 through 5 days; and unconstrained distributed
3 lag model using lags 0 through 5 days. The inverse variance weighted averages of the ten cities'
4 estimates were used to combine results. The results indicated that the effect size estimates for
5 the quadratic distributed model and unconstrained distributed lag model using GAM were
6 similar: 6.3% (95% CI: 4.9-7.8) per 50 $\mu\text{g}/\text{m}^3$ increase for the quadratic distributed lag model,
7 and 5.8% (95% CI: 4.4-7.3) for the other model. These risk estimates are about twice as large as
8 the two-day average (lag 0 and 1 day) estimate (3.4%; 95% CI: 2.6-4.1) obtained in the
9 reanalysis of the original 10 cities study (Schwartz, 2003b). There are indications that such
10 distributed lag estimates are even larger when cause-specific of deaths are examined (see 10 U.S.
11 cities study description in section 8.2.2.3).

12 The Mar et al. (2000, 2003) study of pollutant-mortality associations in Phoenix offers an
13 interesting insight into lag structure. It is the only study to have everyday data (except for a few
14 missing days) for PM_{10} , $\text{PM}_{2.5}$, $\text{PM}_{10-2.5}$, NO_2 , CO , SO_2 , and PM source category factors. Phoenix
15 is also different from most cities studied in two important ways. As a high-temperature city,
16 associations of mortality with high or low temperatures are minimal and hence more easily
17 controlled for in data analysis. Correlations of $\text{PM}_{2.5}$ and $\text{PM}_{10-2.5}$ between four sites in Phoenix
18 indicate high correlations for both $\text{PM}_{2.5}$ and $\text{PM}_{10-2.5}$ (Smith et al., 2000). In addition, the
19 mortality data were limited in the Mar et al. (2000, 2003) analyses to ZIP code areas around the
20 sampling site, further reducing the exposure error.

21 The pollution variables and the lag days for which the associations with cardiovascular
22 mortality were statistically significant ($p < 0.05$, GLM with natural splines) are: PM_{10} , 0 and 1;
23 $\text{PM}_{10-2.5}$, 0; $\text{PM}_{2.5}$, 1; CO , 1 and 4; NO_2 , 1 and 4; SO_2 , 4; regional sulfate, 0; motor vehicle and
24 resuspended dust (MVRD), 1; vegetative burning, 3. It is reasonable that the $\text{PM}_{10-2.5}$ (lag 0) and
25 the $\text{PM}_{2.5}$ (lag 1) would both contribute to a PM_{10} effect on lag days 0 and 1. Thus, to choose
26 either a lag 0 or lag 1 for PM_{10} in Phoenix would underestimate the effects of PM_{10} , given that
27 lag 0 would only capture the $\text{PM}_{10-2.5}$ effects and lag 1 would only capture the $\text{PM}_{2.5}$ effects. The
28 Mar et al. source category analysis shows an association on lag day 1 for the MVRD factor.
29 High loadings of CO and NO_2 on this source factor suggest that the lag 1 associations with CO
30 and NO_2 are due to their high correlation with the MVRD factor. Because the correlation of
31 sulfate with $\text{PM}_{10-2.5}$ was only 0.13, the association of the regional sulfate source factor on lag 0

1 may be considered to be independent of $PM_{10-2.5}$. There is also an association of the vegetative
2 burning factor on lag 3. The effects of these two sources are not strong enough to show up as
3 statistically significant as part of the $PM_{2.5}$ effects, although they may contribute to the positive
4 risks on lag 0 and 3 and might well contribute to the risk determined in a distributed lag analysis.
5 The associations on lag 4 are interesting, but as yet unexplained. The Mar et al. (2000, 2003)
6 Phoenix results suggest that different pollutants are associated with cardiovascular mortality at
7 different lags. It is also possible that different types of mortality may have different lags for
8 different pollutants. Hence, the use of PM_{10} and total mortality would integrate across a variety
9 of pollutant-type of mortality effects. Selection of any one lag day would neglect associations
10 on other lag days. Thus, a distributed lag model should more correctly capture all associations.
11 Few data sets exist with the everyday data required for a distributed lag analysis. However,
12 those that do and that have been analyzed for distributed lag (Schwartz, 2003b), show more
13 excess risk associated with a distributed lag analysis than from any single day analyses.

14 An additional complication in assessing the shape of a distributed lag is that the apparent
15 spread of the distributed lag may depend on the pattern of persistence of air pollution (i.e.,
16 episodes may persist for a few days), which may vary from city to city and from pollutant to
17 pollutant. If this is the case, fixing the lag across cities or across pollutants may not be ideal, and
18 may tend to obscure important nuances of lag structures that might provide important clues to
19 possible different lags between PM exposures and different cause-specific effects.

20 One consideration for the evaluation of different lag periods is the availability of data.
21 Where studies have used PM_{10} measured on an every-sixth-day sampling schedule, as is common
22 in many U.S. cities, it is not possible to evaluate multi-day lag models, such as moving average
23 models and distributed lag models, that may be likely to have greater biological plausibility.
24 It should also be noted that, with the every-sixth-day PM data, a different set of days of mortality
25 series were evaluated at each lag. For example, an every-other-day sampling schedule was used
26 in the Harvard Six City Study, for which the PM data on a given day has been used as though it
27 were a two-day moving average, alternately concurrent with mortality on half the days and
28 lagging mortality by one day on the other days.

29 In summary, the NMMAPS 90 cities study indicated that, of the 0, 1, and 2 day PM_{10} lags
30 examined, lag 1 day showed the strongest mortality associations. However, other lags are

1 reported for various mortality and morbidity outcomes from other studies of one or another
2 individual city.

3 4 **8.4.5 Measurement Error: Concepts and Consequences**

5 **8.4.5.1 Theoretical Framework for Assessment of Measurement Error**

6 Since the 1996 PM AQCD, much progress has been made in developing conceptual
7 frameworks to evaluate potential measurement error effects on the estimation of PM health
8 effects in time-series studies. Several new studies evaluate the extent of bias caused by
9 measurement errors under scenarios that differ in extent of error variance and in covariance
10 structure between co-pollutants.

11 Zidek et al. (1996) investigated, through simulation, the joint effects of multi-collinearity
12 and measurement error in Poisson regression model, with two covariates with varying extent of
13 relative errors and correlation. Their error model was of classical error form ($W = X + U$, where
14 W and X are surrogate and true measurements, respectively, and the error U is normally
15 distributed). The results illustrated the transfer of effects from the “causal” variable to the
16 confounder. However, in order for the confounder to have larger effect size than the true
17 predictor, the correlation between the two covariates had to be very high ($r \geq 0.9$), with moderate
18 error ($\sigma > 0.5$) for the true predictor and no error for the confounder in their scenarios. The
19 transfer-of-causality effect was lessened when the confounder also became subject to error.
20 Another interesting finding was the behavior of the standard errors of the coefficients: when the
21 correlation between the covariates was high ($r = 0.9$) and both covariates had no error, the
22 standard errors for both coefficients were inflated by a factor of 2; but this phenomenon
23 disappeared when the confounder had error. Thus, multi-collinearity influences the significance
24 of the coefficient of the causal variable only when the confounder is accurately measured.

25 Marcus and Chapman (1998) also did a mathematical analysis of PM mortality effects in
26 ordinary least square model (OLS) with the classical error model, under varying extent of error
27 variance and correlation between two predictor variables. The error was analytical error (e.g.,
28 discrepancy between co-located monitors). Only positive regression coefficients were found to
29 be attenuated; and null predictors (zero coefficient) or weak predictors only appeared stronger
30 than true positive predictors under unusual conditions, i.e.: (1) true predictors must have very
31 large positive or negative correlation (i.e., $r \geq 0.9$); (2) measurement error must be substantial

1 (i.e., error variance \approx signal variance); and (3) measurement errors must have high negative
2 correlation. They concluded that fine particle health effects are likely underestimated, but the
3 bias due to analytical measurement error is not large.

4 Zeger et al. (2000) illustrated implications of the classical error model and the Berkson
5 error model (i.e., $X = W + U$) in the context of time-series study design. Their simulation of the
6 classical error model with two predictors, with various combinations of error variance and
7 correlation between the predictors/error terms, showed results similar to those reported by Zidek
8 et al. (1996). Most notably, for the transfer of the effects of one variable to another (i.e., error-
9 induced confounding) to be large, the two predictors or their errors must to be highly correlated.
10 Also, for the spurious association of a null predictor to be more significant than the true
11 predictor, their measurement errors have to be extremely negatively correlated—a condition not
12 yet seen in actual air pollution data sets.

13 Zeger et al. (2000) also laid out a comprehensive framework for evaluating effects of
14 exposure measurement error on estimates of air pollution mortality relative risks in time-series
15 studies. The error, i.e., the difference between personal exposure and an ambient pollutant
16 concentration measured at a community monitoring site, was decomposed into three parts:
17 (1) the error due to having aggregate rather than individual exposure; (2) the difference between
18 the average personal exposure and the true ambient concentration level; and, (3) the difference
19 between the true and measured ambient concentration level. By aggregating individual risks to
20 obtain expected number of deaths, they found the first component of error (the aggregate rather
21 than individual) to be a Berkson error and, therefore, not a significant contributor to bias in the
22 estimated risk. The second error component is a classical error and can introduce bias if short-
23 term associations exist between indoor source contributions and ambient concentration levels.
24 Some analyses, however, both using experimental data (Mage et al., 1999; Wilson et al., 2000)
25 and theoretical interpretations and models (Ott et al., 2000) indicate that there is no relationship
26 between ambient concentrations and nonambient components of personal exposure to PM. Still,
27 a bias could arise due to differences between personal exposures to ambient PM (indoors plus
28 outdoors) and ambient concentrations. The third error component is the difference between the
29 true and the measured ambient concentration. According to Zeger et al., the final term is largely
30 of the Berkson type if the average of the available monitors is an unbiased estimate of the true
31 spatially averaged ambient level.

1 Using this framework, Zeger et al. (2000) then used PTEAM Riverside, CA data to
 2 estimate the second error component and its influence on estimated risks. The correlation
 3 coefficient between the error (the average population PM₁₀ total exposure minus the ambient
 4 PM₁₀ concentration) and the ambient PM₁₀ concentration was estimated to be -0.63. Since this
 5 correlation is negative, the $\hat{\beta}_z$ (the estimated value of the pollution-mortality relative risk in the
 6 regression of mortality on z_t , the daily ambient concentration) will tend to underestimate the
 7 coefficient $\hat{\beta}_x$ that would be obtained in the regression of mortality on \bar{x}_t , the daily average total
 8 personal exposure, in a single-pollutant analysis. Zeger et al. (2000) then assessed the size of the
 9 bias that will result from this exposure misclassification, using daily ambient concentration, z_t .
 10 As shown in Equation 9, the daily average total personal exposure, \bar{x}_t , can be separated into a
 11 variable component, $\theta_1 z_t$, dependent on the daily ambient concentration, z_t , and a constant
 12 component, θ_0 , independent of the ambient concentration:
 13

$$\bar{x}_t = \theta_0 + \theta_1 z_t + \epsilon_t \quad (8-5)$$

14 where ϵ_t is an error term.

15 If the nonambient component of the total personal exposure is independent of the ambient
 16 concentration, as appears to be the case, Equation 9 from Zeger et al. (2000) becomes the
 17 regression analysis equation familiar to exposure analysts (Dockery and Spengler, 1981; Ott
 18 et al., 2000; Wilson et al., 2000). In this case, θ_0 gives the average nonambient component of the
 19 total personal exposure and θ_1 gives the ratio of the ambient component of personal exposure to
 20 the ambient concentration. (The ambient component of personal exposure includes exposure to
 21 ambient PM while outdoors and, while indoors, exposure to ambient PM that has infiltrated
 22 indoors.) In this well-known approach to adjust for exposure measurement error, called
 23 regression calibration (Carroll et al., 1995), the estimate of β_x has the simple form $\hat{\beta}_x = \hat{\beta}_z / \hat{\theta}_1$.
 24 Thus, for the regression calibration, the value of β_x (based on the total personal exposure) does
 25 not depend on the total personal exposure but is given by β_z , based on the ambient concentration,
 26 times θ_1 , the ratio of the ambient component of personal exposure to the ambient concentration.
 27 A regression analysis of the PTEAM data gave an estimate $\theta_1 = 0.60$.

1 Zeger et al. (2000) used Equation 9, with $\hat{\theta}_0 = 59.95$ and $\theta_1 = 0.60$, estimated from the
2 PTEAM data, to simulate values of daily average personal exposure, x_t^* , from the ambient
3 concentrations, z_t , for PM_{10} in Riverside, CA, 1987-1994. They then compared the mean of the
4 simulated $\hat{\beta}_x$ s, obtained by the series of log-linear regressions of mortality on the simulated x_t^* ,
5 with the normal approximation of the likelihood function for the coefficient $\hat{\beta}_z$ from the
6 log-linear regression of mortality directly on z_t . The resulting $\hat{\beta}_z / \hat{\beta}_x = 0.59$ is very close to
7 $\theta_1 = 0.60$. Dominici et al. (2000b) provide a more complete analysis of the bias in $\hat{\beta}_z$ as an
8 estimate of β_x using the PTEAM Study and four other data sets and a more complete statistical
9 model. Their findings were qualitatively similar in that $\hat{\beta}_x$ was close to $\hat{\beta}_z / \theta_1$. Thus, it appears
10 that the bias is very close to θ_1 , which depends not on the total personal exposure but only on the
11 ratio of the ambient component of personal exposure to the ambient concentration.

12 Zeger et al. (2000), in the analyses described above, also suggested that the error due to the
13 difference between the average personal exposure and the ambient level (the second error type
14 described above) is likely the largest source of bias in estimated relative risk. This suggestion at
15 least partly comes from the comparison of PTEAM data and site-to-site correlation (the third
16 type of error described above) for PM_{10} and O_3 in 8 US cities. While PM_{10} and O_3 both showed
17 relatively high site-to-site correlation ($\approx 0.6-0.9$), a similar extent of site-to-site correlation for
18 other pollutants is not necessarily expected. Ito et al. (2001) estimated site-to-site correlations
19 (after adjusting for seasonal cycles) for PM_{10} , O_3 , SO_2 , NO_2 , CO , temperature, dewpoint
20 temperature, and relative humidity, using multiple stations' data from seven central and eastern
21 states (IL, IN, MI, OH, PA, WV, WI), and found that, in a geographic scale of less 100 miles,
22 these variables could be categorized into three groups in terms of the extent of correlation:
23 weather variables ($r > 0.9$); O_3 , PM_{10} , NO_2 ($r: 0.6-0.8$); CO and SO_2 ($r < 0.5$). These results
24 suggest that the contribution from the third component of error, as described in Zeger et al.
25 (2000), would vary among pollution and weather variables. Furthermore, the contribution from
26 the second component of error would also vary among pollutants; i.e., the ratio of ambient
27 exposure to ambient concentration, called the attenuation coefficient, is expected to be different
28 for each pollutant. Some ongoing studies are expected to shed light on this issue, but more
29 information is needed on attenuation coefficients for a variety of pollutants.

1 With regard to the PM exposure, longitudinal studies (Wallace, 2000; Mage et al., 1999),
2 show reasonably good correlation ($r = 0.6$ to 0.9) between ambient PM concentrations and
3 average population PM exposure, lending support for the use of ambient data as a surrogate for
4 personal exposure to ambient PM in time-series mortality or morbidity studies. Furthermore,
5 fine particles are expected to show even better site-to-site correlation than PM_{10} . Wilson and
6 Suh (1997) examined site-to-site correlation of PM_{10} , $PM_{2.5}$, and $PM_{10-2.5}$ in Philadelphia and
7 St. Louis, and found that site-to-site correlations were high ($r \approx 0.9$) for $PM_{2.5}$ but low for
8 $PM_{10-2.5}$ ($r \approx 0.4$), indicating that fine particles have smaller errors in representing community-
9 wide exposures. This finding supports Lipfert and Wyzga's (1997) speculation that the stronger
10 mortality associations for fine than coarse particles found in the Schwartz et al. (1996a) study
11 may be in part due to larger measurement error for coarse particles.

12 However, as Lipfert and Wyzga (1997) suggested, the issue is not whether the fine particle
13 association with mortality is a "false positive", but rather, whether the weaker mortality
14 association with coarse particles is a "false negative." Carrothers and Evans (2000) also
15 investigated the joint effects of correlation and relative error, but they specifically addressed the
16 issue of fine (FP) versus coarse particle (CP) effect, by assuming three levels of relative toxicity
17 of fine versus coarse particles ($\beta_{FP} / \beta_{CP} = 1, 3, \text{ and } 10$) and, then, evaluating the bias,
18 ($B = \{E[\beta_F] / E[\beta_C]\} / \{\beta_F / \beta_C\}$), as a function of FP-CP correlation and relative error associated
19 with FP and CP. Their results indicate: (1) if the FP and CP have the same toxicity, there is no
20 bias (i.e., $B=1$) as long as FP and CP are measured with equal precision; but, if, for example,
21 FP is measured more precisely than CP, then FP will appear to be more toxic than CP (i.e.,
22 $B > 1$); but (2) when FP is more toxic than CP (i.e., $\beta_{FP}/\beta_{CP} = 3$ and 10), the equal precision of FP
23 and CP results in downward bias of FP ($B < 1$), implying a relative overestimation of the less
24 toxic CP. That is, to achieve non-bias, FP must be measured more precisely than CP, even more
25 so as the correlation between FP and CP increases. In applying this model to real data from the
26 Harvard Six Cities Study, estimation of spatial variability for Boston was based on external data
27 and a range of spatial variability for Knoxville (since no spatial data were available for this city).
28 For Boston, where the estimated FP-CP correlation was low ($r = 0.28$), the estimated error was
29 smaller for FP than for CP (0.85 versus 0.65, as correlation between true versus error-added
30 series), and the observed FP to CP coefficient ratio was high (11), the calculated FP to CP
31 coefficient ratio was even larger (26) - thus providing evidence against the hypothesis that FP is

1 absorbing some of the CP coefficient. For Knoxville, where FP-CP correlation was moderate
2 (0.54), the error for FP was smaller than for CP (0.9 versus 0.75), and the observed FP to CP
3 coefficient ratio was 1.4, the calculated true FP to CP coefficient ratio was smaller (0.9) than the
4 observed value. This indicates that the coefficient was overestimated for the better-measured
5 FP, while the coefficient was underestimated for the poorer-measured CP. Since the amount
6 (and the direction) of bias depended on several variables (i.e., correlation between FP and CP;
7 the relative error for FP and CP; and, the underlying true ratio of the FP toxicity to CP toxicity),
8 the authors concluded "...it is inadequate to state that differences in measurement error among
9 fine and coarse particles will lead to false negative findings for coarse particles."

10 Fung and Krewski (1999) conducted a simulation study of measurement error adjustment
11 methods for Poisson models, using scenarios like those used in the simulation studies that
12 evaluated implications of joint effects of correlated covariates with measurement error. The
13 measurement error adjustment methods used were the Regression Calibration (RCAL) method
14 (Carroll et al., 1995) and the Simulation Extrapolation (SIMEX) method (Cook and Stefanski,
15 1994). Briefly, the RCAL algorithm consists of: (1) estimation of the regression of X on W
16 (observed version of X, with error) and Z (covariate without error); (2) replacement of X by its
17 estimate from (1) and conducting the standard analysis (i.e., regression); and (3) adjustment of
18 the resulting standard error of coefficient to account for the calibration modeling. The SIMEX
19 algorithm consists of: (1) addition of successively larger amount of error to the original data;
20 (2) obtaining naive regression coefficients for each of the error added data sets; and (3) back
21 extrapolation of the obtained coefficients to the error-free case using a quadratic or other
22 function. Fung and Krewski examined the cases for: (1) $\beta_x = 0.25$; $\beta_z = 0.25$; (2) $\beta_x = 0.0$;
23 $\beta_z = 0.25$; (3) $\beta_x = 0.25$; $\beta_z = 0.0$., all with varying level of correlation (-0.8 to 0.8) with and
24 without classical additive error, and also considering Berkson type error. The behaviors of naive
25 estimates were essentially similar to other simulation studies. In most cases with the classical
26 error, RCAL performed better than SIMEX (which performed comparably when X-Z correlation
27 was small), recovering underlying coefficients. In the presence of Berkson type error, however,
28 even RCAL did not recover the underlying coefficients when X-Z correlation was large (> 0.5).
29 This is the first study to examine the performance of available error adjustment methods that can
30 be applied to time-series Poisson regression. The authors recommend RCAL over SIMEX, but
31 did not discuss possible reasons why RCAL performed better than SIMEX in these scenarios;

1 nor are the reasons clear from information given in the publication. Also, these error adjustment
2 methods have not been used in real time-series health effects studies and require either replicate
3 measurements or some knowledge on the nature of the error (i.e., distributional properties,
4 correlation, etc.).

5 Another issue that measurement error may affect is the detection of threshold in time-series
6 studies. Lipfert and Wyzga (1996) suggested that measurement error may obscure the true shape
7 of the exposure-response curve, and that such error could have flattened the exposure-response
8 curve to appear linear even when a threshold may exist. However, based on a simulation with
9 realistic range of exposure error (due to site-to-site correlation), Cakmak et al. (1999) illustrated
10 that the modern smoothing approach, LOESS, could adequately detect threshold levels
11 ($12.8 \mu\text{g}/\text{m}^3$, $24.6 \mu\text{g}/\text{m}^3$, and $34.4 \mu\text{g}/\text{m}^3$) even with the presence of exposure error.

12 Other issues related to exposure error that have not been investigated include potential
13 differential error among subpopulations. If the exposure errors are different between susceptible
14 population groups (e.g., people with COPD) and the rest of the population, the estimation of bias
15 may need to take such differences into account. Also, exposure errors may vary from season to
16 season, due to seasonal differences in the use of indoor emission sources and air exchange rates
17 due to air conditioning and heating. This may possibly explain reported season-specific effects
18 of PM and other pollutants. Such season-specific contributions of errors from indoor and
19 outdoor sources are also expected to be different from pollutant to pollutant.

20 In summary, studies that examined joint effects of correlation and error suggest that (a) PM
21 effects are likely underestimated and (b) spurious PM effects (i.e., qualitative bias such as
22 change in the sign of coefficient) due to transferring of effects from other covariates require
23 extreme conditions and are, therefore, unlikely. Also, one simulation study suggests that, under
24 the likely range of error for PM, it is unlikely that a threshold is ignored by common smoothing
25 methods. More data are needed to examine exposure errors for other co-pollutants, since their
26 relative error contributions will influence their relative significance in relative risk estimates.

8.4.5.2 Measurement Error Issues Related to Divergence Between Monitors and to Monitoring Frequency

The measurement error framework posed in Dominici et al. (2000b) and Zeger et al. (2000) explicitly assumes that one of the error components has a Berkson error structure. As noted in (Zeger et al., 2000, p. 421): “This Berkson model is appropriate when z represents a measurable factor [e.g., measured PM or another pollutant] that is shared by a group of participants whose individual [true] exposures x might vary because of time-activity patterns. For example, z might be the spatially averaged ambient level of a pollutant without major indoor sources and x might be the personal exposures that, when averaged across people, match the ambient level.” This assumption is likely accurate for sulfates, less so for fine particles and for PM_{10} , and almost certainly incorrect for gases such as CO and NO_2 that may vary substantially on an intra-urban spatial scale with widely distributed local sources.

The usual characterization of longitudinal or temporal pollutant correlation may not adequately reflect the spatial variation that is the more crucial aspect of association in evaluating possible Berkson errors. Temporal correlation coefficients, even across large distances (e.g., Ito et al., 2001) may be due to large-scale weather patterns affecting concentrations of many pollutants. Local concentrations for some pollutants with strong local sources and low regional dispersion (especially for CO and NO_2 , and $PM_{10-2.5}$ to a lesser extent) may have somewhat smaller temporal correlations and much greater relative spatial variations than PM. Thus, persons in a large metropolitan area may have roughly similar levels of PM exposure x on any given day for which the ambient average PM concentration z is an adequate surrogate, whatever their space-time activity patterns, residence, or non-residential micro-environments, whereas the same individuals may be exposed to systematically higher or lower concentrations of a co-pollutant than the spatial average of the co-pollutant. This violates the basic assumption of the Berkson error model that within each stratum of the measured (spatially averaged) level z , the average value of the true concentration x is equal to z , i.e.,

$$E \{ x \mid z \} = z, \quad (8-6)$$

where $E\{.\}$ is the average or expected value over the population.

1 There are empirical reasons to believe that if the strata are chosen to be locations within a
2 metropolitan area, some individuals far from local sources have consistently less exposure than
3 the average ambient concentration (denoted p) for co-pollutants from local sources such as CO
4 and NO₂, and PM_{2.5}, whose true exposure (denoted q) depends on the location of the person's
5 residence or other micro-environment where most exposure occurs. For this group,

$$6 \qquad E \{ q \mid p \} < p, \qquad (8-7)$$

7
8
9
10 while others in locations near the local source (such as a busy highway) have systematically
11 higher exposure, so that

$$12 \qquad E \{ q \mid p \} > p. \qquad (8-8)$$

13
14
15 There is a growing body of evidence that adverse health effects are associated with
16 proximity to a major road or highway (Wjst et al., 1993; Monn, 2001; Roemer and Van Wijnen,
17 2001). As shown below, there is good reason to believe that intra-city variation (even in PM_{2.5})
18 is substantial within some U.S. cities. If we assume for the sake of argument that concentrations
19 of PM₁₀ or PM_{2.5} are relatively uniformly distributed, then associations of adverse health effects
20 with proximity to a source cannot be readily attributed to a pollutant such as PM with a uniform
21 spatial distribution. NO₂ is a pollutant often used to illustrate the spatial non-uniformity of the
22 gaseous co-pollutants. Monn et al. (1997) compared the concentrations of NO₂ and PM₁₀ as a
23 function of curbside distance in a moderately busy urban street in Zurich and found that PM₁₀
24 levels decrease only slightly with increasing distance from the roadway, the decrease more likely
25 being due to decreasing coarse than decreasing fine particle concentrations. The NO₂ levels
26 showed a much stronger seasonal dependence, decreasing rapidly with increasing distance in the
27 summer and showing little decrease with distance in the winter. However, the belief that PM_{2.5}
28 is spatially uniform should also not be accepted uncritically, as recent analyses for 27 U.S. cities
29 shown in Chapter 3 and Appendix 3A of this document demonstrate.

30 The 90th percentile difference (P_{90}) between a pair of sites may provide a useful guide to
31 the differences between monitor pairs (and by implication, personal exposure to fine particles)

1 that might be reasonably expected within a metropolitan area. Table 8-40 shows statistics
2 summarizing the spatial behavior of $PM_{2.5}$ concentrations, based on detailed analyses presented
3 in Appendix 3A. The mean Pearson correlation coefficient for all site pairs considered in a
4 given MSA, the average of the annual mean concentrations and the range of annual means at the
5 sites considered, the average 90th percentile value (P90) of the absolute concentration difference
6 and the average coefficient of determination (COD) are shown in Table 8-40 for MSAs
7 satisfying data completeness criteria used for inclusion in Appendix 3A. Data in Table 8-40
8 show the ranges in the metrics (annual means) considered for all the MSAs included in the
9 analyses. Typically, the range (i.e., the difference between the lowest and highest means for
10 sites in an MSA) for annual mean concentrations is about one-quarter of the mean values.
11 However, for about 10% of the time the average intersite difference in concentrations is greater
12 than roughly one-half of the annual mean concentration, based on the P90 values. This result
13 suggests that substantial concentration gradients exist on many days across some MSAs. The
14 effects of outlying sites on the summary statistics were examined for the Atlanta, GA,
15 Washington, DC, Seattle, WA and Los Angeles MSAs by removing them from the analyses.
16 Their deletion either had no effect (as in Washington, DC) or a very large effect (as in Seattle,
17 WA). In addition to outlying monitoring sites, located outside of the main urban air shed,
18 monitoring sites within the urban core can also enhance the spatial variability in MSAs, as
19 shown for Detroit, MI. As discussed in Chapter 3, there are a number of factors that contribute
20 to spatial variability in ambient $PM_{2.5}$ concentrations in urban areas.

21 The data shown in Table 8-40 can be used to rank different MSAs according to the relative
22 degree of spatial homogeneity that concentrations exhibit in them. In Table 8-41, MSAs are first
23 ranked according to the mean Pearson correlation coefficient (r) for site pairs considered in the
24 MSA, and then they are ranked according to the average P90 for concentration differences.
25 It appears that, in general, the western MSAs are not as homogeneous as many in the East, but
26 there are a number of MSAs in the East where $PM_{2.5}$ levels are as heterogeneous as in the West.
27 It can be seen that there are often substantial differences in rankings according to which of the
28 two parameters, r or P90, is used. This result suggests that concentration gradients can exist in
29 MSAs whose monitoring sites are highly correlated and that use of correlation coefficients alone
30 is not enough to characterize spatial variability. Because of incomplete data capture for some

TABLE 8-40. SUMMARY STATISTICS SHOWING MEAN SITE-PAIR PEARSON CORRELATION COEFFICIENTS, ANNUAL MEAN PM_{2.5} CONCENTRATIONS (µg/m³), THE RANGE IN ANNUAL MEAN CONCENTRATIONS (µg/m³), MEAN OF 90th PERCENTILE DIFFERENCES IN CONCENTRATIONS BETWEEN ALL SITE PAIRS (µg/m³), AND COEFFICIENTS OF DIVERGENCE (COD) FOR MSAs MEETING SELECTION CRITERIA GIVEN IN APPENDIX 3A. VALUE IN () REFERS TO NUMBER OF SITES.

	Mean Correlation	Annual Mean Concentration (µg/m ³)	Range in Annual Means (µg/m ³)	Mean P ₉₀ (µg/m ³)	Mean COD
<i>Eastern U.S.</i>					
Philadelphia, PA-NJ (5)	0.89	15.3	2.3	5.1	0.12
Washington, DC (6)	0.84	14.6	3.4	7.1	0.17
Washington, DC* (5)	0.85	14.6	3.4	6.1	0.17
Norfolk, VA (5)	0.96	13.5	0.7	3.6	0.08
Columbia, SC (4)	0.92	15.6	1.8	4.3	0.09
Atlanta, GA (7)	0.71	20.2	4.5	10.3	0.18
Atlanta, GA* (6)	0.78	20.6	3.5	8.5	0.15
Birmingham, AL (5)	0.83	20.3	5.3	11.5	0.18
Tampa, FL (4)	0.74	12.4	1.6	4.3	0.12
<i>Central U.S.</i>					
Cleveland, OH (8)	0.9	17.1	6.2	8.8	0.17
Pittsburgh, PA (11)	0.81	17.9	8.2	11.8	0.16
Steubenville, OH-WV (5)	0.86	17.7	2.4	8.1	0.18
Detroit, MI (10)	0.89	16.7	6.4	9	0.17
Detroit, MI ** (9)	0.92	15.9	4.7	8.2	0.16
Grand Rapids, MI (4)	0.96	12.7	1.2	4.6	0.13
Milwaukee, WI (8)	0.9	13.7	1.3	4	0.12
Chicago, IL (11)	0.89	17.6	6.1	7.4	0.14
Gary, IN (4)	0.75	15.8	3.6	7.7	0.18
Louisville, KY (5)	0.9	17.1	2.7	5.1	0.12
St. Louis, MO-IL (11)	0.83	17.4	5.6	8.8	0.15
Baton Rouge, LA (3)	0.95	14.3	0.4	2.7	0.08
Kansas City, KS-MO (6)	0.91	12.6	2.4	4.2	0.13
Dallas, TX (7)	0.94	12.6	2.2	4.1	0.11
<i>Western U.S.</i>					
Boise, ID (4)	0.88	9.5	1.6	6.4	0.17
Salt Lake City, UT (6)	0.91	11.3	5.0	7.9	0.21
Seattle, WA (5)	0.62	8.9	6.1	10.8	0.3
Seattle, WA* (4)	0.85	10.4	3.0	6.1	0.17
Portland, OR (4)	0.83	7.7	2.8	5.3	0.19
Los Angeles, CA*** (5)	0.61	17.9	13.9	21.4	0.28
Los Angeles, CA (6)	0.77	21	5.4	12.2	0.18
Riverside, CA (5)	0.89	27.5	5.0	12.3	0.17
San Diego, CA (4)	0.79	15.8	2.4	8.7	0.17

* outlying site removed.

** interior site removed.

*** Results from analysis including site in Lancaster, CA (included in L.A. MSA, but located across mountains to east of downtown LA)..

TABLE 8-41. SUMMARY OF RELATIVE HOMOGENEITY / HETEROGENEITY CHARACTERISTICS FOR MSAs GIVEN IN TABLE 8-40. RANKINGS ARE MADE ACCORDING TO THE MEAN PEARSON CORRELATION COEFFICIENT (left side) AND 90th PERCENTILE DIFFERENCE IN PM_{2.5} CONCENTRATIONS (right side).

Spatial Variability ¹	r		P ₉₀	
	East	West	East	West
<i>Relatively Homogenous</i>	Norfolk, VA		Baton Rouge, LA	
	Grand Rapids, MI		Norfolk, VA	
	Baton Rouge, LA		Milwaukee, WI	
	Dallas, TX		Dallas, TX	
	Detroit, MI**		Kansas City, KS-MO	
	Columbia, SC		Columbia, SC	
	Kansas City, KS-MO	Salt Lake City, UT	Tampa, FL	
	Cleveland, OH		Grand Rapids, MI	
	Milwaukee, WI		Louisville, KY	
	Louisville, KY		Philadelphia, PA	Portland, OR
<i>Intermediate</i>	Chicago, IL	Riverside, CA	Washington, DC*	Seattle, WA*
	Detroit, MI	Boise, ID	Washington, DC	Boise, ID
	Philadelphia, PA		Chicago, IL	
	Steubenville, OH		Gary, IN	Salt Lake City, UT
	Washington, DC*	Seattle, WA*	Steubenville, OH	
	Washington, DC		Detroit, MI**	
	St. Louis, MO	Portland, OR	Atlanta, GA*	
	Birmingham, AL		St. Louis, MO	San Diego, CA
	Pittsburgh, PA	San Diego, CA	Cleveland, OH	
	Atlanta, GA*		Detroit, MI	
<i>Heterogeneous</i>	Gary, IN	Los Angeles, CA*	Atlanta, GA	Seattle, WA
	Tampa, FL		Birmingham, AL	Los Angeles, CA*
	Atlanta, GA		Pittsburgh, PA	Riverside, CA
		Seattle, WA		Los Angeles, CA***
<i>Very Heterogeneous</i>		Los Angeles, CA***		

* outlying site removed. ** interior site removed. *** Results from analysis including site in Lancaster, CA.

Homogeneous: $r \geq .90$; $P90 \leq 5.0$. Intermediate: $r = .80 - .89$; $P90 = 5.1 - 10.0$
Heterogeneous: $r = .90 - .79$; $P90 = 10.1 - 20.0$; Very Heterogeneous: $r \leq .69$; $P90 \geq 20.0$

1 individual monitors on a given day in a particular MSA, when large concentration gradients exist
2 across that MSA, day-to-day differences in calculated area-wide 24-h average PM levels may
3 not accurately reflect the day-to-day changes that would be obtained by the full set of monitors.

4 The above results provide clear evidence that fine particle concentrations may be less
5 homogenous in at least some MSAs than has been previously assumed. As noted in Chapter 3,
6 these differences may not be strictly related to the distance between monitors, especially where
7 topography and sources of primary PM play a role. In many eastern sites, however, particle
8 distribution may be more substantially governed by regional rather than by local sources.
9 Considerable heterogeneity much more often exists across monitoring sites in a given MSA or
10 county for PM_{10} values and/or for coarse fraction ($PM_{10-2.5}$) concentrations typically estimated by
11 differencing between PM_{10} and $PM_{2.5}$ readings on a given day in a given MSA. When the
12 differencing is done between daily averages for PM_{10} and $PM_{2.5}$ values derived from sets of non-
13 collocated operative monitors in an MSA that may vary from day to day, the resulting estimates
14 of $PM_{10-2.5}$ can be subject to considerable error, even leading to such anomalies as negative
15 values for MSA-wide 24-h average coarse-fraction ($PM_{10-2.5}$) levels on some days. Estimates of
16 MSA- or county-wide averages for coarse-fraction thoracic particles derived by first subtracting
17 $PM_{2.5}$ from PM_{10} readings from collocated samplers (or the same dichotomous sampler with
18 PM_{10} and $PM_{2.5}$ cutpoints) and then averaging of those values across the MSA or county should
19 yield more credible estimates of MSA-or county-wide $PM_{10-2.5}$ concentrations.

20 Some studies have examined potential implications of variations in addressing the role of
21 spatial siting of monitors and/or the influence of frequency of data collection on the estimating
22 of PM effects. Ito et al. (1995) evaluated the influence of the use of different monitors with
23 varying monitoring schedules on associations between total mortality with PM_{10} in Cook Co., IL
24 and Los Angeles Co., CA. The authors used data from six PM_{10} monitors in Cook Co., with one
25 monitor operating on a daily basis and the remaining monitors operating on a 1-in-6 day
26 schedule, and four sites in Los Angeles Co., all of which operated on a 1-in-6 day schedule. The
27 monitoring sites were located in urban and suburban settings, according to the State's objectives.
28 Three of the LA sites were located in residential areas and one was located in an area zoned for
29 commercial use. One of the Cook Co. sites was classified as residential, two as commercial, and
30 three as industrial. One of the Cook Co. sites was intended to monitor population exposure,
31 three to monitor maximum concentrations, and two to monitor both maximum concentrations

1 and population exposure. There was considerable variation among the distribution of PM_{10}
2 concentrations in both cities, especially at the upper ends of the distributions. The authors tested
3 for correlation between individual site pairs, located from 4 to 26 miles apart. The sites were all
4 temporally well correlated in Cook Co., with correlation coefficients of 0.63 to 0.83 for the site
5 pairs. Site pairs using three of the Los Angeles Co. sites also had high correlation coefficients
6 ranging from 0.7 to 0.9, but site pairs that included the fourth monitor had correlation
7 coefficients ranging from 0.36 to 0.47.

8 For illustrative epidemiological analyses, Ito et al (1995) then used a sinusoidal model to
9 account for temporal components. Two methods were used for averaging PM_{10} data across
10 monitors: (1) averaging data from all sites, as available; and (2) averaging data from all sites
11 after first filling in missing data with regression analyses using data from other available
12 monitors. The authors tested associations between mortality and PM_{10} measurements averaged
13 across all sites by each of these methods and at each individual monitor for LA Co. and Cook
14 Co. Similar results were obtained for both counties, in that (after detrending) the strongest
15 correlations between PM_{10} and mortality were found for same-day (lag 0) data in each county
16 and O_3 also showed positive associations for up to 2 days lagged with mortality in each county.

17 Because more sites were available in Cook Co., additional regression analyses were run to
18 examine the sensitivity of using data from alternative PM_{10} sites and/or alternate every 6-day
19 samples from one PM_{10} site. In those analyses, the data from the monitor running every day in
20 Cook Co. were divided into six data sets to study the influence of the 1-in-6 day monitoring
21 schedule on the PM_{10} -mortality associations observed, and such associations were also evaluated
22 with a 1-in-6 day subset from the two average data sets. The results of these analyses are
23 summarized in Figure 8-29. Similar associations can be seen using the two methods of
24 averaging PM_{10} data. Site 2 is the monitor that operated on a daily basis. The PM_{10} -mortality
25 association using data from this site is very similar in magnitude to that for the average across all
26 sites ("avg A"), showing the influence of this site's data on the daily average. Using the PM_{10}
27 average with data filled in for the remaining sites ("avg B"), the PM_{10} -mortality association is
28 slightly larger but is not significantly different from the association using the first averaging
29 method. For analyses using 1-in-6 day subsets of the averaged PM_{10} data ("avg A_6" and
30 "avg B_6"), the associations are slightly larger (but confidence intervals much wider) than
31 associations using average data for all study days.

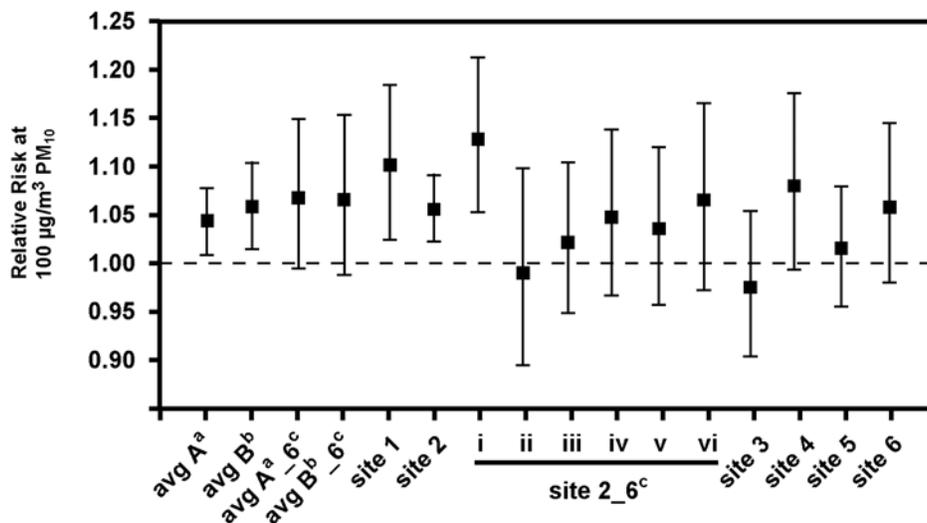


Figure 8-29. Relative risk estimates and 95% confidence intervals for total mortality per 100 µg/m³ increase in PM₁₀, adjusting for ozone, temperature, seasonal cycles, day of week, and linear trend for 1985-1990 in Cook County, IL. Key: a = average of data from any available sites; b = average of data from all sites after filling missing data for each site; c = subsample for 1-in-6 day monitor frequency, with i through vi representing each 6th day subsample from site 2.

Source: Ito et al. (1995).

1 In contrast, there is considerable variation in the associations reported for modeling based
 2 on data from one or another individual monitor, i.e., for sites 1 through 6. In addition, the PM₁₀-
 3 mortality associations shown for the six 1-in-6 day subsets of data from site 2 vary widely as
 4 well. The risk estimate sizes derived from the different 1-in-6 day data from site 2 vary in a
 5 range similar to that shown for the individual PM₁₀ monitoring sites. The authors observed that
 6 it is not clear whether this sensitivity is due to exposure errors in assigning the PM₁₀ values at
 7 individual sites to the area population, or to exposure errors related to an individual monitor
 8 (possibly from local sources), or to both.

9 To the extent that the use of less-than-every-day monitoring data is a source of uncertainty
 10 for time-series analyses, it is important to note that many (but not all) U.S. and Canadian time-
 11 series epidemiological studies have used every-day monitoring for PM, with the availability of
 12 daily monitoring data often being described as an important study site selection criterion.

1 However, a few studies have used data from monitors operating less frequently. One of the more
2 notable examples is the NMMAPS 90 U.S. cities mortality analyses (Samet et al., 2000;
3 Dominici, 2003), where every-day PM₁₀ monitoring data were available for just a few of the
4 cities (e.g., Pittsburgh, Chicago, St. Paul, Seattle), but PM₁₀ data were collected on varying
5 schedules (mainly 1-in-6 days) for most of the cities. However, the 14 U.S. cities selected for
6 use in the NMMAPS morbidity analyses all had every-day monitoring for PM₁₀. Some other
7 studies used data from monitors that operated on varying schedules, including the Harvard Six
8 Cities Study (Schwartz et al., 1996; reanalyzed Schwartz, 2003), which used dichot impactor
9 data collected daily during some periods or at least 1-in-2 days for the full monitoring period.
10 As for another multi-city study, PM data collected on a 1-in-6 day monitoring schedule were
11 used in the Canadian eight cities study (Burnett et al., 2000; Burnett and Goldberg, 2003). The
12 single-city analyses for San Jose (Fairley 1999; reanalyzed Fairley, 2003), Los Angeles
13 (Moolgavkar, 2000; reanalyzed Moolgavkar, 2003; Kinney et al., 1995) and Toronto (Lin et al.,
14 2002) also used 1-in-6 day PM monitoring data; whereas the single-city city studies in Detroit
15 (Lippmann 2000, reanalyzed Ito 2003) and Santa Clara County, LA (Lipsett et al., 1997) used
16 PM data derived from varying sampling schedules.

17 Lipfert et al. (2000a) examined relationships between the areas in which mortality occurred
18 among residents and the locations of monitoring sites or averages over monitoring sites for
19 several particle size components and particle metrics. The mortality data were located for
20 Philadelphia, PA, for three additional suburban Philadelphia counties, and for Camden, NJ and
21 other New Jersey counties in the Philadelphia – Camden MSA. A single site was used to obtain
22 data for fine and coarse particles from Harvard School of Public Health monitors. Additional
23 PA and NJ thoracic particle data were available for 2 to 4 stations and results were averaged for
24 at least two stations reporting data. The authors concluded that mortality in any part of the
25 region may be associated with air pollution concentrations or average concentrations in any other
26 part of the region, whether particles or gases. The authors suggest two interpretations: (a) the
27 associations of mortality with pollution were random (from carrying out multiple significance
28 tests) and not causal, or (b) both particles and gaseous pollutants have a broad regional
29 distribution. They also noted that interpretation (b) may lead to large uncertainties in identifying
30 which pollutant exposures for the population are primarily responsible for the observed effects.

1 These data could be studied further to evaluate smaller-scale spatial relationships among health
2 effects and gases.

3 Lippmann et al. (2000) evaluated the effects of monitor siting choice using 14 TSP
4 monitoring stations in Detroit, MI, and nearby Windsor, ON, Canada. The stations operated
5 from 1981-1987 with almost complete data. When a standard log-linear link Poisson regression
6 model for mortality was fitted to TSP data for each of the 14 sites, the relative risk estimates
7 were similar for within-site increments of 5th to 95th percentiles, generally highest and positive at
8 lag day 1 but not statistically significant at $p < 0.05$, except for site “w” (site 12, south of the
9 urban center of Wayne County) and nearly significant at sites “f” (west of the city of Detroit),
10 “g” (south of the city) and “v” (suburban site in northwestern Wayne County, MI, generally
11 “upwind” of the urban center). However, as the authors noted, all of the reported relative risks
12 were for site-specific increments, which varied by a factor of about 2.5 across the Wayne
13 County-Windsor area. When converted to a common increment of $100 \mu\text{g}/\text{m}^3$ TSP, the largest
14 excess risks were found when data used in the model were from site “f” (4.5%), “v” (4.2%), or
15 “w” (3.8%), which also showed the most significant effects among the 14 monitors. As the
16 authors noted, “. . . the distributional increments [used] to calculate relative risk tend to
17 standardize the scale of relative risks. This actually makes sense in that if there is a
18 concentration gradient of TSP within a city, and if the various TSP concentrations fluctuate
19 together, then using a site with a low mean TSP for time-series analysis would result in a larger
20 coefficient. This result does warn against extrapolating the effects from one city to another
21 using a raw regression coefficient [excess relative risk].”

22 Other recent studies also point out other aspects of intra-urban spatial variation in PM
23 concentrations. Kinney et al. (2000) noted that, in a study of personal and ambient $\text{PM}_{2.5}$ and
24 diesel exhaust particle (DEP) exposure in a dense urban area of New York City, $\text{PM}_{2.5}$ levels
25 showed only a moderate site-to-site variation (37 to $47 \mu\text{g}/\text{m}^3$) due, probably, to broader regional
26 sources of $\text{PM}_{2.5}$, but elemental carbon (EC) concentrations showed a four-fold range of site-to-
27 site variations, reflecting greater local variation in EC as a marker for DEP than for $\text{PM}_{2.5}$ in
28 general.

29 Several PM health studies for Seattle (King County), WA (e.g., Levy et al., 2001, for
30 out-of-hospital primary cardiac arrests) found few statistically significant relationships, partly
31 attributed by the authors to Seattle having a topographically diverse terrain with local “hot spots”

1 of residential wood burning, especially in winter. Sheppard et al. (2001) explored reasons for
2 these findings, focusing on adjustments for location by use of a “topographic index” that
3 included “downstream” normal flow of wood smoke from higher elevations and trapping of
4 wood smoke in topographic bowls or basins even at higher elevations. They also adjusted for
5 weather using a “stagnation index” (average number of hours per day with wind speed $\leq 25^{\text{th}}$
6 percentile of wind speeds) and temperature, as well as interaction terms for stagnation on hilltop
7 sites and temperature at suburban wood smoke-exposed valley sites. Adjustments for exposure
8 measurement error based on methods developed in Sheppard and Damian (2000) and Sheppard
9 et al. (2001) had little effect on effect size estimates for the case-crossover study (Levy et al.,
10 2001), but may be useful in other studies where localized pollutant exposures are believed to be
11 important.

12 Daniels et al. (2001) evaluated relative sources of variability or heterogeneity in 1996 PM₁₀
13 monitoring in the Pittsburgh, PA area, a data-rich area having 25 monitors in a ~40 by 80 km
14 rectangle. The authors found no isotropic spatial dependence after accounting for other sources
15 of variability, but indications of (a) heterogeneity in variability of small-scale processes over
16 time and space and (b) heterogeneity in the mean values and covariate effects across sites.
17 Important covariates included temperature, precipitation, wind speed and direction. The authors
18 concluded that significant unmeasured processes might be in operation.

19 20 **8.4.5.3 Measurement Error and the Assessment of Confounding by Co-Pollutants in** 21 **Multi-Pollutant Models**

22 The Zeger et al. (2000) discussion may be interpreted as addressing the extent to which the
23 apparent lack of a PM_{10-2.5} effect in models with both fine and coarse particles demonstrates a
24 “false negative” due to larger measurement error of coarse particle concentrations. However, a
25 more important question may involve the relative attenuation of estimated effects of PM_{2.5} and
26 gaseous co-pollutants, especially those such as CO that are known to be highly correlated with
27 PM_{2.5}. Tables 1 and 2 in Zeger et al. (2000) may be particularly relevant here. The evidence
28 discussed in this chapter supports the hypothesis that PM has adverse health effects, but leaves
29 open the question as to the extent the gaseous co-pollutants may contribute to the observed
30 effects as well when their exposure is measured much less accurately than that of the PM metric.
31 If both the PM metric and the co-pollutant have effects, Table 1 of Zeger et al. (2000) shows that

1 the co-pollutant effect size estimate may be greatly attenuated and the PM effect size estimate
2 much less so, depending on the magnitude of correlation between the true PM and gaseous
3 pollutant exposures and the correlation between their measurement errors. One would expect
4 that PM_{2.5}, CO, and NO₂ would often have a high positive correlation and their “exposure
5 measurement errors” would also be positively correlated if PM and the gaseous pollutants were
6 positively correlated due to common activity patterns, weather, and source emissions. In view of
7 the substantially greater spatial heterogeneity of traffic-generated ambient pollutants such as CO
8 and NO₂ and the relative (though not absolute) regional spatial uniformity of ambient PM_{2.5} in
9 some cities (but not others), it then seems reasonably likely that effect size estimates in multi-
10 pollutant models are attenuated downward to a greater extent for gaseous co-pollutants than for
11 PM metrics in some cities. This may explain part of the heterogeneity of findings for multi-
12 pollutant models in different cities. Low effect size estimates for the gaseous co-pollutants in a
13 multi-pollutant model should be interpreted cautiously. The representativeness of the
14 monitoring sites for population exposure of both the particle metrics and gaseous pollutants
15 should be evaluated as part of the interpretation of the analysis. Indices such as the maximum
16 90th percentile of the absolute difference in concentrations between pairs of sites and the median
17 cross-correlation across sites may be useful for characterizing spatial heterogeneity of gaseous
18 co-pollutants as well as for particles.

19 20 **8.4.6 Role of Particulate Matter Components**

21 In the 1996 PM AQCD, extensive epidemiologic evidence substantiated very well positive
22 associations between ambient PM₁₀ concentrations and various health indicators, e.g., mortality,
23 hospital admissions, respiratory symptoms, pulmonary function decrements, etc. Some studies
24 were also then available which mortality and morbidity associations with various fine particle
25 indicators (e.g., PM_{2.5}, sulfate, H⁺, etc.). One mortality study, the Harvard Six Cities analysis by
26 Schwartz et al. (1996a), evaluated relative contributions of the fine (PM_{2.5}) versus the coarse
27 (PM_{10-2.5}) fraction of PM₁₀, and found, overall, that PM_{2.5} appeared to be associated more strongly
28 with mortality effects than PM_{10-2.5}. A few studies seemed to be indicative of possible coarse
29 particle effects, e.g., increased asthma risks associated with quite high PM₁₀ concentrations in a
30 few locations where coarse particles strongly dominated the ambient PM₁₀ mix.

1 **8.4.6.1 Thoracic Particle (PM₁₀) Mortality/Morbidity Effects**

2 Many new studies have reported associations between mortality and PM₁₀, as discussed in
3 Section 8.2.2.2. Several new PM epidemiology studies which conducted time-series analyses in
4 multiple cities were noted to be of particular interest, in that they provide evidence of effects
5 across various geographic locations (using standardized methodologies) and more precise pooled
6 effect size estimates with narrow confidence bounds, reflecting the typically much stronger
7 power of such multi-city studies over individual-city analyses to estimate a mean effect. Based
8 on pooled analyses across multiple cities, using GAM stringent convergence criteria, the percent
9 total (non-accidental) excess deaths per 50 µg/m³ PM₁₀ (24-h) increment were estimated in
10 different multi-city analyses to be: (a) 1.4% in the 90 largest U.S. cities; (b) 3.4% in 10 large
11 U.S. cities; (c) 3.6% in the 8 largest Canadian cities; and (d) 3.0% in European cities.

12 As discussed in Section 8.3.1, a substantial body of new results has emerged since the 1996
13 PM AQCD that evaluates PM₁₀ effects on cardiovascular-related hospital admissions and visits.
14 Especially notable new evidence has been provided by multi-city studies (Samet et al., 2000a,b;
15 Zanobetti and Schwartz, 2003b) that yield pooled estimates of PM-CVD effects across numerous
16 U.S. cities and regions. This study found not only significant PM associations, but also
17 associations with other gaseous pollutants as well, thus hinting at likely independent effects of
18 certain gases (O₃, CO, NO₂, SO₂) and/or interactive effects with PM. These and other
19 individual-city studies generally appear to confirm likely excess risk of CVD-related hospital
20 admission for U.S. cities in the range of 2 to 9% per 50 µg/m³ PM₁₀, especially among the
21 elderly (≥ 65 yr).

22 In addition, a number of new studies for respiratory-related hospital admissions and
23 medical visits have reported results that are generally consistent with and supportive of the
24 findings presented in the 1996 PM AQCD. As summarized in Section 8.3.3, the excess risk
25 estimates fall most consistently in the range of 5 to 20% per 50 µg/m³ PM₁₀, with those for
26 asthma visits and hospital admissions generally somewhat higher than for COPD and pneumonia
27 hospital admissions.

8.4.6.2 Fine and Coarse Fraction Particle Effects on Mortality

The 1996 PM AQCD included results from a small number of studies in which air quality measurements of fine and coarse fraction thoracic particles were used. Some more recent additional studies are now available that have evaluated associations between various health outcomes and fine and coarse-fraction particles, the key findings of which are discussed below.

Short-term exposure studies

PM-mortality effect estimates from studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ were measured are shown in Figure 8.5 (Section 8.2.2.5; Pg. 8-58). Among the more important newly available results are those derived from reanalyses of two major U.S. and Canadian multi-city studies that investigated associations between $PM_{2.5}$ and $PM_{10-2.5}$ and total nonaccidental mortality. These include (1) the Schwartz (2003a), the Klemm and Mason (2000) and Klemm and Mason (2003) reanalyses of the Harvard Six Cities data, all confirming the basic original findings by Schwartz et al. (1996a); and (2) the Burnett et al. (2000) study of the 8 largest Canadian cities and Burnett and Goldberg (2003) reanalysis of that study. These studies found roughly comparable, statistically significant excess risk estimates of ~ 2% increased total mortality risk per $25 \mu\text{g}/\text{m}^3$ $PM_{2.5}$. In the Harvard Six cities reanalyses, as reported for the original study, $PM_{10-2.5}$ was not significantly associated with total mortality across the six cities, though a significant association was reported for one of the cities (Steubenville, OH). Burnett and colleagues reported an association of ~ 2% increased total mortality risk per $25 \mu\text{g}/\text{m}^3$ $PM_{10-2.5}$, though it was noted that this association was more sensitive than that with $PM_{2.5}$ in the reanalyses.

Effect estimates of about the same size for $PM_{2.5}$ and $PM_{10-2.5}$ were reported for single-city analyses conducted in Philadelphia (Lipfert et al., 2000a), Pittsburgh (Chock et al., 2000), and Detroit (Ito, 2003), as well as in some areas outside the U.S. such as Santiago, Chile (Cifuentes et al., 2000). Several U.S. and Canadian studies reported larger effect estimates for $PM_{2.5}$ than for $PM_{10-2.5}$. Of these, Fairley (2003) reported significant associations for $PM_{2.5}$ only for Santa Clara Co., CA; and in the preliminary analyses by Klemm and Mason (2000), associations with both $PM_{2.5}$ and $PM_{10-2.5}$ in Atlanta, GA did not achieve statistical significance. In two western areas – Coachella Valley, CA (Ostro et al., 2003) and Phoenix, AZ (Clyde et al., 2000) – associations between mortality and $PM_{10-2.5}$ were reported to be greater than those for $PM_{2.5}$. In all studies, positive associations were reported; however, most associations with $PM_{2.5}$ were

1 statistically significant while statistically significant associations with $PM_{10-2.5}$ were reported for
2 just a few locations.

3 In addition, a number of new studies reported associations between both $PM_{2.5}$ and $PM_{10-2.5}$
4 with mortality from cardiovascular or respiratory causes. For cardiovascular mortality, Mar
5 et al. (2003) reported significant associations with both $PM_{2.5}$ and $PM_{10-2.5}$ though the confidence
6 intervals for associations with $PM_{2.5}$ were very broad. Also, for both cardiovascular and
7 respiratory mortality, effect estimates of about the same size for $PM_{2.5}$ and $PM_{10-2.5}$ were reported
8 in single-city analyses conducted for Philadelphia (Lipfert et al., 2000a), Santa Clara Co.
9 (Fairley, 2003) and Detroit (Ito, 2003). For both $PM_{2.5}$ and $PM_{10-2.5}$, the associations were all
10 positive and many were statistically significant for cardiovascular mortality, but for respiratory
11 mortality the confidence intervals were broader and the associations generally did not reach
12 statistical significance.

13 While the associations reported for coarse fraction particles are often not statistically
14 significant, the findings may well reflect actual associations between mortality and $PM_{10-2.5}$, at
15 least in some locations. This may most consistently be the case in arid areas, e.g., in the Phoenix
16 area (e.g., Mar et al., 2000, 2003) and in Santiago, Chile (Cifuentes et al., 2000). Elevations in
17 coarse fraction particle mortality risks have also been reported for Steubenville, OH, an eastern
18 U.S. urban area in the Harvard Six City study (Schwartz et al., 1996a, Schwartz 2003; Klemm et
19 al., 2000; Klemm and Mason, 2003). These results may reflect contamination of later-
20 resuspended coarse particles by metals in fine particles emitted from smelters (Phoenix) or steel
21 mills (Steubenville) that was earlier deposited on nearby soils.

22 Three new papers discussed below provide particularly interesting new information on
23 relationships between short-term fine and coarse particle exposures and total elderly mortality
24 (age 65 and older), using TEOM data from the same EPA ORD/NERL monitoring site in
25 Phoenix, AZ to index PM exposures. Each study, most notably, used quite different models but
26 each found statistically significant relationships between total mortality and coarse PM
27 (specifically $PM_{10-2.5}$) and some associations with $PM_{2.5}$.

28 Smith et al. (2000), using a three-day running average as the exposure metric, performed
29 linear regression of the square root of daily mortality on the long-term trend, meteorological and
30 air pollution variables. Analyses were done with mortality data obtained for the city of Phoenix,
31 and for a larger regional area. Two mortality variables were used: (a) total (non-accidental)

1 deaths for the city of Phoenix regressed against central EPA site $PM_{2.5}$ data (assuming $PM_{2.5}$
2 levels to be homogeneous in that area) and (b) total mortality for a larger, regional area within
3 50 miles around Phoenix regressed against central EPA site $PM_{10-2.5}$ concentrations (assuming
4 such levels to be homogeneous in areas around Phoenix). Using linear analysis, associations
5 between mortality and $PM_{10-2.5}$ were statistically significant for both regions, whereas
6 associations with $PM_{2.5}$ were not. When the possibility of a nonlinear response was taken into
7 account, no evidence was found for a nonlinear concentration-response relationship for $PM_{10-2.5}$,
8 but for $PM_{2.5}$ there was evidence suggesting a threshold for effects at 20 to 25 $\mu\text{g}/\text{m}^3$. There was
9 no evidence of confounding between fine and coarse fraction PM, suggesting that the two are
10 “essentially separate pollutants having distinct effects”. Smith et al. (2000) also observed a
11 seasonal effect for $PM_{10-2.5}$, the effect being statistically significant only during spring and
12 summer. Based on a principal component analysis of elemental concentrations, crustal elements
13 are highest in spring and summer and anthropogenic elements lowest, but Smith et al. (2000)
14 observed that the implication that crustal, rather than anthropogenic elements, were responsible
15 for the observed relationship with mortality was counterintuitive.

16 Clyde et al. (2000) used a more conventional model, a Poisson regression of log-
17 transformed mortality data with linear pollution variables; and also employed Bayesian model
18 averaging to consider a wide variety of variations in the basic model. They conducted analyses
19 that related mortality for three regions (the Phoenix metropolitan area; a small subset of zip
20 codes to give a region with presumably uniform $PM_{2.5}$ concentrations; and a still smaller zip
21 code-based region surrounding the monitoring site that was considered to have uniform PM_{10}
22 concentrations) to the air pollution data from the central EPA site. Lag periods of 0, 1, 2, or
23 3 days were considered. Stronger associations were reported with $PM_{10-2.5}$ than $PM_{2.5}$; the
24 association between total mortality and $PM_{2.5}$ was found only in the uniform $PM_{2.5}$ concentration
25 region.

26 Mar et al. (2000, 2003) used conventional Poisson regression methods, but limited their
27 mortality analyses to residents living in zip code locations near the EPA monitoring site (an area
28 in Phoenix termed “uniform PM_{10} in Clyde et al., 2000). Mar et al. reported modeling data for
29 lag days 0 to 4. Positive associations with cardiovascular mortality were reported for both $PM_{2.5}$
30 and $PM_{10-2.5}$; associations were significant at a 0-day lag for $PM_{10-2.5}$ and at a 1-day lag for $PM_{2.5}$.
31 A significant association was also reported with a regional sulfate factor derived from source

1 apportionment. The low correlation coefficient between sulfur in $PM_{2.5}$ (measured by XRF) with
2 $PM_{10-2.5}$ (0.13) suggested separate and distinct effects for regional fine particle sulfate and
3 $PM_{10-2.5}$.

4 In summary, the effects estimates from the newly reported studies are generally consistent
5 with those derived from the earlier 1996 PM AQCD assessment, which reported risk estimates
6 for excess total (nonaccidental) deaths associated with short-term (e.g., 24-hour) PM exposures
7 as generally falling within the range of 1 to 8% increased per $50 \mu\text{g}/\text{m}^3$ PM_{10} and 2 to 6% per
8 $25 \mu\text{g}/\text{m}^3$ $PM_{2.5}$; the few earlier studies with $PM_{10-2.5}$ data provided little evidence for associations
9 with mortality. Many new single-city studies have reported positive associations (many
10 statistically significant at $p < 0.05$) between $PM_{2.5}$ and mortality, with effect estimates from U.S.
11 and Canadian studies typically ranging from 1.5 to 6.5% increase per $25 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ for total
12 mortality. Excess total mortality risks reported to be associated with short-term exposure to
13 $PM_{10-2.5}$ generally fall in the range of 0.2 to 6.0% increase per $25 \mu\text{g}/\text{m}^3$ $PM_{10-2.5}$, though many of
14 the results are not statistically significant. Cause-specific estimates appear to mainly fall in the
15 range of 3.0 to 7.0% increase per $25 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ for cardiovascular or combined
16 cardiorespiratory mortality and 2.0 to 7.0% increase per $25 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ for respiratory mortality
17 in U.S. cities. Effect size estimates for $PM_{10-2.5}$ generally fall in the range of 3.0 to 8.0% for
18 cardiovascular mortality and 3.0 to 16.0% for respiratory mortality per $25 \mu\text{g}/\text{m}^3$ $PM_{10-2.5}$.

19 20 *Long-term exposure / mortality risk studies*

21 Evidence for relationships between long-term exposures to fine and coarse fraction
22 particles and mortality risk is available from extensive analyses using the Six Cities and ACS
23 cohorts (original analyses, reanalyses and “extended” analyses with additional cohort follow-up)
24 and from analyses using the AHSMOG and VA study cohorts. As discussed in Section 8.2.3,
25 emphasis is placed on the results of the Six Cities and ACS prospective cohort studies, based on
26 several factors – the larger study population in the ACS study, the larger air quality data set in
27 the Six Cities study, the more generally representative study populations used in the Six Cities
28 and ACS studies, and the fact that these studies have undergone extensive reanalyses. These
29 prospective cohort studies have reported statistically significant risk estimates for total mortality
30 in the range of 14 to 28% per $10 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ (annual average) but no significant associations
31 with $PM_{10-2.5}$. While placing emphasis on the results of the Six Cities and ACS studies, it is

1 noted that larger associations with $PM_{2.5}$ than with $PM_{10-2.5}$ were reported for males in the
2 AHSMOG cohort, though none of the associations reached statistical significance and the effect
3 estimates for $PM_{2.5}$ were in the same range as reported for the ACS and Six Cities cohorts. In the
4 VA study, the results were more inconsistent from the analyses of differing subsets of data.

5 Significant associations have also been reported between $PM_{2.5}$ and cardiorespiratory and
6 lung cancer mortality in the Six Cities and ACS cohort studies, with effect estimate sizes ranging
7 from about 6 to 23% per $10 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ for cardiorespiratory mortality and from 8 to 21% per
8 $10 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ for lung cancer mortality. Again, no statistically significant associations have
9 been reported between long-term exposure to coarse fraction particles and cause-specific
10 mortality.

11 Significant associations for total and cardiopulmonary mortality were also reported with
12 sulfates, an indicator of fine particles. In the reanalyses of the ACS study, Krewski and
13 colleagues (2000) reported that the associations between total mortality and $PM_{2.5}$ or sulfates
14 were unchanged in models including variables on other risk factors such as personal health or
15 demographic factors. These associations were also robust to the inclusion of gaseous co-
16 pollutants in the models, with the exception of SO_2 . However, SO_2 emissions are linked with the
17 formation of sulfates and secondarily-formed fine particles, so it can be difficult to disentangle
18 their effects.

19 Past cross-sectional studies have generally found the fine particle component, as indicated
20 either by $PM_{2.5}$ or sulfates, to be the PM constituent most consistently associated with mortality.
21 While relative measurement errors of various PM indicators must be further evaluated as a
22 possible source of bias in these estimate comparisons, the new evidence from prospective cohort
23 studies indicates that the fine mass components of PM are more strongly associated with
24 mortality effects of chronic PM exposure than are coarse fraction indicators.

25 26 **8.4.6.3 Source-Oriented Analyses of PM and Mortality**

27 Other recent studies on the relation of mortality to particle composition and source (Laden
28 et al., 2000; Mar et al., 2000; Tsai et al., 2000) suggest that particles from certain sources may
29 have much higher potential for adverse health effects than others, as shown by source-oriented
30 evaluations involving factor analyses. For example, Laden et al. (2000) conducted factor
31 analyses of the elemental composition of $PM_{2.5}$ for Harvard Six Cities study data for 1979-1988.

1 For all six cities combined, the excess risk for daily mortality was estimated to be 9.3% (95% CI;
2 4.0, 14.9) per 25 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ (average of 0 and 1 day lags) increment in a mobile source factor;
3 2.0% (95% CI; -0.3, 4.4) for a coal source factor, and -5.1% (95% CI; -13.9, 4.6) for a crustal
4 factor. There was large variation among the cities and suggestion of an association (not
5 statistically significant) with a fuel oil factor identified by V or Mn.

6 Mar et al. (2000) applied factor analysis to evaluate mortality in relation to 1995-1997 fine
7 particle elemental components and gaseous pollutants (CO , NO_2 , SO_2) in an area of Phoenix,
8 AZ, close to the air pollution monitors. The $\text{PM}_{2.5}$ constituents included sulfur, Zn, Pb, soil-
9 corrected potassium, organic and elemental carbon, and a soil component estimated from oxides
10 of Al, Si, and Fe. Based on models fitted using one pollutant at a time, statistically significant
11 associations were found between total mortality and PM_{10} , CO (lags 0 and 1), NO_2 (lags 0, 1, 3,
12 4), S (negative), and soil (negative). Statistically significant associations were also found
13 between cardiovascular mortality and CO (lags 0 to 4), NO_2 (lags 1 and 4), SO_2 (lags 3 and 4),
14 $\text{PM}_{2.5}$ (lags 1, 3, 4), PM_{10} (lag 0), $\text{PM}_{10-2.5}$ (lag 0), and elemental, organic, or total carbon.
15 Cardiovascular mortality was significantly related to a vegetative burning factor (high loadings
16 on organic carbon and soil-corrected potassium), motor vehicle exhaust/resuspended road dust
17 factor (with high loadings on Mn, Fe, Zn, Pb, OC, EC, CO , and NO_2), and a regional sulfate
18 factor (with a high loading on S). However, total mortality was negatively associated with a soil
19 factor (high loadings on Al, Fe, Si) and a local SO_2 source factor, but was positively associated
20 with the regional sulfate factor.

21 Tsai et al. (2000) analyzed daily time-series of total and cardiorespiratory deaths, using
22 short periods of 1981-1983 data for Newark, Elizabeth, and Camden, NJ. In addition to
23 inhalable particle mass (PM_{15}) and fine particle mass ($\text{PM}_{2.5}$), the study evaluated data for metals
24 (Pb, Mn, Fe, Cd, V, Ni, Zn, Cu) and for three fractions of extractable organic matter. Factor
25 analyses were carried out using the metals, CO , and sulfates. The most significant sources or
26 factors identified as predictors of daily mortality were oil burning (targets V, Ni), Zn and Cd
27 processing, and sulfates. Other factors (dust, motor vehicles targeted by Pb and CO , industrial
28 Cu or Fe processing) were not significant predictors. In Newark, oil burning sources and
29 sulfates were positive predictors, and Zn/Cd a negative predictor for total mortality. In Camden
30 oil burning and motor vehicle emissions predicted total mortality, but copper showed a marginal
31 negative association. Oil burning, motor vehicle emissions, and sulfates were predictors of

1 cardiorespiratory mortality in Camden. In Elizabeth, resuspended dust indexed by Fe and Mn
2 showed marginal negative associations with mortality, as did industrial sources traced by Cu.

3 The set of results from the above factor analyses studies do not yet allow one to identify
4 with great certainty a clear set of specific high-risk chemical components of PM. Nevertheless,
5 some commonalities across the studies seem to highlight the likely importance of mobile source
6 and other fuel combustion emissions (and apparent lesser importance of crustal particles) as
7 contributing to increased total or cardiorespiratory mortality.

8 9 **8.4.6.4 Fine and Coarse Fraction Particle Effects on Morbidity**

10 *Short-term exposure / morbidity studies*

11 A body of new studies published since the 1996 PM AQCD provides further evidence
12 examining ambient PM association with increased human morbidity. At the time of the 1996
13 PM AQCD, fine particle morbidity studies were mostly limited to Schwartz et al. (1994) , Neas
14 et al. (1994, 1995); Koenig et al. (1993); Dockery et al. (1996); and Raizenne et al. (1996); and
15 discussion of coarse particles morbidity effects was also limited to only a few studies (Gordian
16 et al., 1996; Hefflin et al., 1994). Since the 1996 PM AQCD, several new studies have been
17 published in which newly available size-fractionated PM data allowed investigation of the
18 effects of both fine ($PM_{2.5}$) and coarse fraction ($PM_{10-2.5}$) particles. PM_{10} , fine (FP) and coarse
19 fraction (CP) particle results are noted below for studies by morbidity outcome areas, as follows:
20 cardiovascular disease (CVD) hospital admissions (HA's); respiratory medical visits and
21 hospital admissions; and respiratory symptoms and pulmonary function changes.

22 Several new U.S. and Canadian studies evaluated fine-mode PM effects on cardiovascular
23 outcomes. Lippmann et al. (2000) and Ito (2003) report a positive but not a significant
24 association with $PM_{2.5}$; and Moolgavkar (2003) reported $PM_{2.5}$ to be significantly associated with
25 CVD HA for lag 0 and 1 in Los Angeles. Burnett et al. (1997a) reported that fine particles were
26 significantly associated with CVD HA in a single pollutant model, but not when gases were
27 included in multipollutant models for the 8 largest Canadian city data. Stieb et al. (2000)
28 reported both PM_{10} and $PM_{2.5}$ to be associated with CVD emergency department (ED) visits in
29 single pollutant, but not multipollutant models. Similarly, Morgan et al. (1998) reported that
30 $PM_{2.5}$ measured by nephelometry was associated with CVD HA for all ages and 65+ yr, but not
31 in the multipollutant model. Tolbert et al. (2000a) reported that coarse particles were

1 significantly associated with dysrhythmias, whereas $PM_{2.5}$ was not. Other studies (e.g., Liao
2 et al., 1999; Creason et al., 2001; Pope et al., 1999b,c) reported associations between increases in
3 $PM_{2.5}$ and several measures of decreased heart rate variability, but Gold et al. (2000) reported a
4 negative association of $PM_{2.5}$ with heart rate and decreased variability in r-MSSD (one heart rate
5 variability measure). A study by Peters and colleagues (2001a) reported significant temporal
6 associations between acute (2-h or 24-h) measures of $PM_{2.5}$ and myocardial infarction. Overall,
7 these new studies collectively appear to implicate fine particles, as well as possibly some
8 gaseous co-pollutants, in cardiovascular morbidity, but the relative contributions of fine particles
9 acting alone or in combination with gases such as O_3 , CO, NO_2 or SO_2 remain to be more clearly
10 delineated and quantified. The most difficult issue relates to interpretation of reduced PM effect
11 size and /or statistical significance when co-pollutants derived from the same source(s) as PM
12 are included in multipollutant models.

13 Section 8.3.1 also discussed U.S. and Canadian studies that present analyses of coarse
14 fraction particles (CP) relationships to CVD outcomes. Lippmann et al. (2000) and Ito (2003)
15 found significant positive associations of $PM_{10-2.5}$ with ischemic heart disease hospital
16 admissions in Detroit (RR = 1.08, CI 1.04, 1.16). Tolbert et al. (2000a) reported significant
17 positive associations of heart dysrhythmias with CP ($p = 0.04$) as well as for elemental carbon
18 ($p = 0.004$), but these preliminary results must be interpreted with caution until more complete
19 analyses are carried out and reported. Burnett et al. (1997b) noted that CP was the most robust
20 of the particle metrics examined to inclusion of gaseous covariates for cardiovascular
21 hospitalization, but concluded that particle mass and chemistry could not be identified as an
22 independent risk factor for exacerbation of cardiorespiratory disease in this study. Based on
23 another Canadian study, Burnett et al. (1999), reported statistically significant associations for
24 CP in univariate models but not in multipollutant models; but the use of estimated rather than
25 measured PM exposures indices limits the interpretation of the PM results reported.

26 The collective evidence reviewed above, in general, appears to suggest excess risks for
27 CVD-related hospital admissions of ~ 1 to 10% per $25 \mu\text{g}/\text{m}^3$ per $PM_{2.5}$ or $PM_{10-2.5}$ 24-h
28 increment.

29 Section 8.3.2 also discussed new studies of effects of short-term PM_{10} , $PM_{2.5}$, and $PM_{10-2.5}$
30 exposure on the incidence of respiratory hospital admissions and medical visits. Several new
31 U.S. and Canadian studies have yielded particularly interesting results that are also suggestive of

1 roles of both fine and coarse particles in respiratory-related hospital admissions. In an analysis
2 of Detroit data, Lippmann et al. (2000) and Ito (2003) found comparable effect size estimates for
3 $PM_{2.5}$ and $PM_{10-2.5}$. That is, the excess risk for pneumonia hospital admissions (in no co-pollutant
4 model) was 18.6% (CI 5.6, 33.1) per $50 \mu\text{g}/\text{m}^3$ PM_{10} , 10% (CI 1.5, 19.5) per $25 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ and
5 11.2% (CI -0.02, 23.6) per $25 \mu\text{g}/\text{m}^3$ $PM_{10-2.5}$. Because $PM_{2.5}$ and $PM_{10-2.5}$ were not highly
6 correlated, the observed association between coarse particles and health outcomes were possibly
7 not confounded by smaller particles. Despite the greater measurement error associated with
8 $PM_{10-2.5}$ than with either $PM_{2.5}$ and PM_{10} , this indicator of the coarse particles within the thoracic
9 fraction was associated with some of the outcome measures. The interesting result is that
10 $PM_{10-2.5}$ appeared to be a separate factor from other PM metrics. Burnett et al. (1997b) also
11 reported PM (PM_{10} , $PM_{2.5}$, and $PM_{10-2.5}$) associations with respiratory hospital admissions in
12 10 Canadian cities, even with O_3 in the model. Notably, the $PM_{10-2.5}$ association was significant
13 (RR = 1.13 for $25 \mu\text{g}/\text{m}^3$; CI = 1.05 - 1.20); and inclusion of ozone still yielded a significant
14 coarse mass RR = 1.11 (CI = 1.04 - 1.19). Moolgavkar (2000a, 2003) reported that, in
15 Los Angeles, both PM_{10} and $PM_{2.5}$ yielded both positive and negative associations at different
16 lags for single pollutant models but not in two pollutant models. Delfino et al. (1997) reported
17 that both $PM_{2.5}$ and PM_{10} are positively associated with ED visits for respiratory disease.
18 Morgan et al. (1998) reported that $PM_{2.5}$ estimated from nephelometry yielded a $PM_{2.5}$
19 association with COPD hospital admissions for 1-hr max PM that was more positive than 24-h
20 average $PM_{2.5}$.

21 A new study examines PM associations with asthma-related hospital admissions.
22 Sheppard et al. (1999) and Sheppard (2003) studied relationships between PM metrics that
23 included $PM_{10-2.5}$ and non-elderly adult hospital admissions for asthma in the greater Seattle area
24 and reported significant relative risks for PM_{10} , $PM_{2.5}$ and $PM_{10-2.5}$ (lagged 1 day). For $PM_{10-2.5}$,
25 the relative risk was 1.05 (95% CI 1.0, 1.14) and for $PM_{2.5}$, the relative risk 1.07 (1.02, 1.11).

26 Thus, although PM_{10} mass has most often been implicated as the PM pollution index
27 affecting respiratory hospital admissions, the overall collection of new studies reviewed in
28 Section 8.3.2 appears to suggest relative roles for PM_{10} and for both fine and coarse thoracic PM
29 mass fractions, such as $PM_{2.5}$ and $PM_{10-2.5}$.

1 Section 8.3.3 assessed relationships between PM exposure on lung function and respiratory
2 symptoms. While most data examined PM₁₀ effects, several studies also examined fine and
3 coarse fraction particle effects.

4 Several new asthma studies report associations with ambient PM measures. The peak flow
5 analyses results for asthmatics tend to show small decrements for both PM₁₀ and PM_{2.5}. Several
6 studies included PM_{2.5} and PM₁₀ independently in their analyses of peak flow. Of these,
7 Pekkanen et al. (1997) and Romieu et al. (1996) found comparable results for PM_{2.5} and PM₁₀
8 and the study of Peters et al. (1997c) found slightly larger effects for PM_{2.5}. Of studies that
9 included both PM₁₀ and PM_{2.5} in their analyses of respiratory symptoms, the studies of Peters
10 et al. (1997c) and found similar effects for the two PM measures. Only the Romieu et al. (1996)
11 study found slightly larger effects for PM_{2.5}. While the PM associations with adverse health
12 effects among asthmatics and others are well documented, the type/source(s) of those particles
13 most associated with adverse health effects among asthmatics are not known at this time.
14 Indeed, the makeup of PM varies greatly from place to place and over time, depending upon
15 factors such as the sources that contribute to the pollution and the prevailing atmospheric
16 conditions, affecting particle formation, coagulation, transformation, and transport.

17 For non-asthmatics, several studies evaluated PM_{2.5} effects. Naeher et al. (1999) reported
18 similar AM PEF decrements for both PM_{2.5} and PM₁₀. Neas et al. (1996) reported a
19 nonsignificant negative association for PEF and PM_{2.1}, and Neas et al. (1999) also reported
20 negative but nonsignificant PEF results. Schwartz and Neas (2000) reported a significant PEF
21 association with PM_{2.5}, and Tiittanen et al. (1999) also reported negative but nonsignificant
22 association between PEF and PM_{2.5}. Gold et al. (1999) reported significant PEF associations
23 with PM_{2.5}. Schwartz and Neas (2000) reported significant PM_{2.5} effects relative to lower
24 respiratory symptoms. Tiittanen et al. (1999) showed significant effects for cough and PM_{2.5} for
25 a 4-day average.

26 Non-asthmatics were evaluated in fewer studies for coarse fraction particle effects.
27 Schwartz and Neas (2000) report that cough was the only response in which coarse fraction
28 particles appeared to provide an independent contribution to explaining the increased incidence.
29 The correlation between CP and PM_{2.5} was moderate (0.41). Coarse fraction particles had little
30 association with evening peak flow. Tiittanen et al. (1999) also reported a significant effect of
31 PM_{10-2.5} for cough. Thus, cough may be an appropriate outcome related to coarse fraction

1 particle effects. However, the limited data base suggests that further study is appropriate. The
2 report by Zhang, et al. (2000) of an association between coarse fraction particles and the
3 indicator “runny nose” is noted also.

4 The above new studies offer much more information than was available in 1996. Effects
5 were noted for several morbidity endpoints: cardiovascular hospital admissions, respiratory
6 hospital admissions and cough. The data from these relatively limited studies are still
7 insufficient to allow strong conclusions at this time as to which size-related ambient PM
8 components may be most strongly related to one or another morbidity endpoints. Very
9 preliminarily, however, fine particles appear to be more strongly implicated in cardiovascular
10 outcomes than are coarse fraction particles, whereas both seem to impact respiratory endpoints.
11

12 *Long-term exposure / morbidity studies*

13 Evidence available in the 1996 PM AQCD included cross-sectional studies using data from
14 a cohort of children in 24 U.S. and Canadian cities (Dockery et al., 1996; Raizenne et al., 1996).
15 Positive associations were reported with incidence of respiratory illness or symptoms (Dockery
16 et al., 1996), and negative associations with lung function measurements (Raizenne et al., 1996)
17 for changes in $PM_{2.1}$, though the associations were stronger and more likely to reach statistical
18 significance with measurements of aerosol acidity. Results were not presented for coarse
19 fraction particles.

20 The best evidence for effects associated with chronic exposure to fine or coarse-fraction
21 particles are found in the newer studies that combine the features of cross-sectional and cohort
22 studies. These include several reports from the Southern California children’s cohort study
23 (McConnell et al., 1999; Gauderman et al., 2000, 2002). McConnell et al. (1999) present results
24 of cross-sectional analyses using pulmonary function measured upon initiation of the children’s
25 cohort, where positive but not statistically significant associations were reported with some
26 measures of increased respiratory illness in children with asthma; no associations were reported
27 for children without asthma. Gauderman et al. (2000, 2002) analyzed lung function growth
28 using spirometry measurements made in 4th and 7th grades for two separate cohorts, each having
29 been recruited as 4th grade children. Gauderman et al. (2000) reported results for both $PM_{2.5}$ and
30 $PM_{10-2.5}$, noting that decreased lung function growth was associated with $10 \mu\text{g}/\text{m}^3$ changes for
31 both indices (some but not all associations reached statistical significance). Gauderman et al.

1 (2002) also later reported decreased lung function growth with $PM_{2.5}$ (though the associations
2 were not statistically significant) but did not report results using $PM_{10-2.5}$ data.

3 The recent studies suggest that long-term exposure to fine particles is associated with
4 development of chronic respiratory disease and reduced lung function growth; little evidence is
5 available on potential effects of exposure to coarse fraction particles. These findings build upon
6 the information available in the 1996 PM AQCD. As was true then, there are fewer studies of
7 long-term exposure effects than short-term exposures, but the evidence indicates fine particle
8 exposures may result in chronic respiratory effects.

9 10 *Long-term PM exposure and lung cancer*

11 Of particular interest with regard to PM-related cause-specific mortality is growing
12 evidence linking long-term PM exposure with increased risk of lung cancer mortality. Historical
13 evidence includes studies of lung cancer trends, studies of occupational groups, comparisons of
14 urban and rural populations, and case-control and cohort studies using diverse exposure metrics
15 (Cohen and Pope, 1995). Numerous past ecological and case-control studies of PM and lung
16 cancer incidence and mortality have generally indicated positive associations with living in areas
17 having higher PM exposures despite possible problems with respect to potential exposure and
18 other risk factor measurement errors. Table 8-42 provides a partial listing of such studies
19 beyond those discussed below.

20 Prospective cohort studies offer a potentially more powerful approach to evaluation of
21 apparent associations between PM exposures and development of lung cancer. The 1996 PM
22 AQCD (U.S. Environmental Protection Agency, 1996a) summarized three of these more
23 elaborate studies that carefully evaluated PM air pollution exposure effects on lung cancer using
24 the prospective cohort design. In the AHSMOG Study, Abbey et al. (1991) followed a cohort of
25 Seventh Day Adventists, whose extremely low prevalence of smoking and uniform, relatively
26 healthy dietary patterns reduce the potential for confounding by these factors. Excess lung
27 cancer incidence was observed in females in relation to both particle (TSP) and O_3 exposure after
28 6 years follow-up time. Dockery et al. (1993) reported the results of a 14- to 16-year prospective
29 follow-up of 8,111 adults living in six U.S. cities that evaluated associations between air
30 pollution and mortality. After controlling for individual differences in age, sex, cigarette
31 smoking, BMI, education, and occupational exposure, Dockery et al. (1993) found an elevated

TABLE 8-42. SUMMARY OF PAST ECOLOGIC AND CASE-CONTROL EPIDEMIOLOGIC STUDIES OF OUTDOOR AIR AND LUNG CANCER

Study Type	Authors	Locale	Exposure Classification	Rate Ratio (95% CI)
Ecologic	Henderson et al., 1975	Los Angeles, CA	High PAH Areas	1.3 @ 96-116 ug/m ³ TSP (CI: N/A)
	Buffler et al., 1988	Houston, TX	TSP by Census Tract	1.9 @ 16 ug/m ³ TSP (CI: N/A)
	Archer, 1990	Utah	TSP by county	1.6 @ 85 ug/m ³ TSP (CI: N/A)
Case-Control	Pike et al., 1979	Los Angeles	BAP Geo. Areas	1.3 @ 96-116 ug/m ³ TSP
	Vena, 1982	Buffalo, NY	TSP Geo. Areas	1.7 @ 80-200 ug/m ³ TSP (CI: 1.0-2.9)
	Jedrychowski, et al., 1990	Cracow, Poland	TSP and SO ₂ Geo. Areas	1.1 @ TSP > 150 ug/m ³ (CI: N/A)
	Katsouyanni, et al., 1990	Athens, Greece	Soot Concentration Geo. Areas	1.1 @ soot up to 400 ug/m ³ (CI: N/A)
	Barbone et al., 1995	Trieste, Italy	High Particle Deposition Areas	1.4 @ > 0.3 g/m ² /day (CI: 1.1-1.8)
	Nyberg et al., 2000	Stockholm, Sweden	High NO ₂ Areas	1.3 (CI: 0.9-1.9)

Source: Derived from Cohen (2000).

1 but non-significant risk for lung cancer mortality (RR = 1.37; 95% CI = 0.81 to 2.31) for a
2 difference in PM_{2.5} pollution equal to that of the most polluted versus the least polluted city.
3 Pope et al. (1995) similarly analyzed PM_{2.5} and sulfate (SO₄⁻) air pollution as predictors of
4 mortality in a prospective study of 7-year survival data (1982 to 1989) for about 550,000 adult
5 volunteers obtained by the American Cancer Society (ACS).

6 Both the ACS and Harvard studies have been subjected to much scrutiny, including an
7 extensive independent audit and reanalysis of the original data (Krewski et al., 2000) that
8 confirmed the originally published results. The ACS study controlled for individual differences
9 in age, sex, race, cigarette smoking, pipe and cigar smoking, exposure to passive cigarette
10 smoke, occupational exposure, education, BMI, and alcohol use. In the original ACS study, lung
11 cancer mortality was significantly associated with particulate air pollution when SO₄⁻ was used

1 as the index,, but not when PM_{2.5} mass was used as the index for a smaller subset of the study
2 population that resided in metropolitan areas where PM_{2.5} data were available from the Inhalable
3 Particle (IP) Network. Thus, while these prospective cohort studies have also indicated that
4 long-term PM exposure is associated with an increased cancer risk, the effect estimates were
5 generally not statistically significant, quite possibly due to inadequate statistical power by these
6 studies at that time (e.g., due to inadequate population size and/or follow-up time for long-
7 latency cancers).

8 A recent follow-up analysis of the major ACS study by Pope et al. (2002) responds to a
9 number of criticisms previously noted for the earlier ACS analysis (Pope et al., 1995) in the
10 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). Most notably, the new study
11 examined other pollutants, had better occupational indices and diet information, and also
12 addressed possible spatial auto-correlations due to regional location. The recent extension of the
13 ACS study included ~500,000 adult men and women drawn from ACS-CPS-II enrollment and
14 follow-up during 1982-1998. This new analysis of the ACS cohort substantially expands the
15 prior analysis, including: (1) more than doubling of the follow-up time to 16 years (and more
16 than tripling of the number of deaths in the analysis); (2) substantially expanded exposure data,
17 including gaseous co-pollutant data and new PM_{2.5} data collected in 1999-2001; (3) improved
18 control of occupational exposures; (4) incorporation of dietary variables that account for total fat
19 consumption, as well as that of vegetables, citrus and high-fiber grains; and (5) utilization of
20 recent advances in statistical modeling, including incorporation of random effects and non-
21 parametric spatial smoothing components in the Cox proportional hazards model.

22 In the extended ACS analysis, long-term exposure to air pollution, and especially to PM_{2.5},
23 was found to be associated with increased annual risk of mortality. With the longer 16-year
24 follow-up period and improved PM_{2.5} exposure metrics, this study detected for the first time, a
25 statistically significant association between living in a city with higher PM_{2.5} and increased risk
26 of dying of lung cancer. Each 10 ug/m³ increment in annual average fine PM was associated
27 with a 13 percent (95% CI=4%-23%) increase in lung cancer mortality. Coarse particles and
28 gaseous pollutants were generally not significantly associated with excess lung cancer mortality.
29 SO₄⁻² was significantly associated with mortality and lung cancer deaths in this extended data
30 set, yielding RR's consistent with (i.e., not significantly different from) the SO₄⁻² RR's reported
31 in the previously published 7-year follow-up (Pope et al, 1995). However, while PM_{2.5} was

1 specific to the causes most biologically plausible to be influenced by air pollution in this analysis
2 (i.e., cardiopulmonary and cancer), SO_4^{-2} was significantly associated with every mortality
3 category in this new analysis, including that for “all-other causes”. This suggests that the $\text{PM}_{2.5}$
4 associations found are more biologically plausible than the less specific SO_4^{-2} associations found.
5 The $\text{PM}_{2.5}$ cancer mortality risk appears greatest for non-smokers and among those with lower
6 socioeconomic status (as indicated by lower educational attainment).

7 The AHSMOG investigators have re-examined the association between long-term PM
8 exposure and increased risk of both lung cancer incidence and lung cancer mortality in
9 nonsmokers using longer-term follow-up of this cohort and improved analytical approaches.
10 Beeson et al. (1998) considered this cohort of some 6,338 nonsmoking, non-Hispanic, white
11 Californian adults, ages 27-95, that was followed from 1977 to 1992 for newly diagnosed
12 cancers. Among the AHSMOG cohort, incident lung cancer in males was positively and
13 significantly associated with interquartile range (IQR) increases for mean concentrations of PM_{10}
14 (RR = 5.21; 95% CI = 1.94-13.99). For females in the cohort, incident lung cancer was
15 positively and significantly associated with increases in SO_2 (RR = 2.14; CI, 1.36-3.37) and
16 frequency of PM_{10} levels above $50 \mu\text{g}/\text{m}^3$ (RR = 1.21; 95% CI = 0.55-2.66) and $60 \mu\text{g}/\text{m}^3$
17 (RR = 1.25; 95% CI = 0.57-2.71). Thus, increased risks of incident lung cancer were deemed by
18 the authors to be associated with elevated long-term ambient concentrations of PM_{10} and SO_2 in
19 both genders. The higher PM_{10} effect estimate for cancer in males appeared to be partially due to
20 gender differences in long-term air pollution exposures. Abbey et al. (1999) also related long-
21 term ambient concentrations of PM_{10} , SO_4^{-2} , SO_2 , O_3 , and NO_2 to 1977-1992 mortality in the
22 AHSMOG cohort. After adjusting for a wide array of potentially confounding factors, including
23 occupational and indoor sources of air pollutants, PM_{10} showed a strong association with lung
24 cancer deaths in males (PM_{10} IQR RR=2.38; 95% CI: 1.42 - 3.97). In this cohort, males spent
25 more time outdoors than females, thus having higher estimated air pollution exposures than the
26 cohort females. Ozone showed an even stronger association with lung cancer mortality for
27 males, and SO_2 showed strong associations with lung cancer mortality for both sexes. The
28 authors reported that other pollutants showed weak or no association with mortality. Therefore,
29 increases in both lung cancer incidence and lung cancer mortality in the extended follow-up
30 analysis of the AHSMOG study were found to be most consistently associated with elevated
31 long-term ambient concentrations of PM_{10} , O_3 , and SO_2 , especially among males.

1 Overall, these new cohort studies confirm and strengthen the published older ecological
2 and case-control evidence indicating that living in an area that has experienced higher PM
3 exposures can cause a significant increase in the RR of lung cancer incidence and associated
4 mortality. In particular, the new ACS cohort analysis more clearly indicates that living in a city
5 with higher PM_{2.5} levels is associated with an elevated risk of lung cancer amounting to an
6 increase of some 10 to 15% above the lung cancer mortality risk in a cleaner city.

7 With regard to specific ambient fine particle constituents that may significantly contribute
8 to the observed ambient PM-related increases in lung cancer incidence and mortality, PM
9 components of gasoline and diesel engine exhaust represent one class of hypothesized likely
10 important contributors. Such mobile source PM typically comprises a noticeable fraction of
11 ambient fine particles in many urban areas, having been estimated to comprise from ~5 to 30%
12 of ambient PM_{2.5} in some U.S. urban areas (see Chapter 3). These mobile sources are reasonable
13 candidates as contributors to ambient PM-lung cancer risks, given their being sources of known
14 cancer-causing agents (e.g., PAHs), as are other coal-combustion and/or woodburning emission
15 sources (at least during some seasons).

17 **8.4.7 Concentration-Response Relationships for Ambient PM**

18 In the 1996 PM AQCD, the limitations of identifying possible “thresholds” in the
19 concentration-response relationships in observational studies were discussed, including
20 difficulties related to the low data density in the lower PM concentration range, the small
21 number of quantile indicators often used, and the possible influence of measurement error. Also,
22 a threshold for a population, as opposed to a threshold for an individual, has some conceptual
23 issues that should be noted. For example, since individual thresholds vary from person to person
24 due to individual differences in genetic level susceptibility and pre-existing disease conditions
25 (and even can vary from one time to another for a given person), it is extremely difficult
26 mathematically to demonstrate convincingly that a clear threshold exists in the population
27 studies. This is especially true if the most sensitive members of a population are unusually
28 sensitive even down to very low concentrations. The person-to-person difference in the
29 relationship between personal exposure and the concentration observed at a monitor may also
30 add to the variability in observed exposure-response relationships, possibly obscuring otherwise
31 more evident thresholds. Since one cannot directly measure but can only compute or estimate a

1 population threshold, it would be difficult to interpret an observed population threshold
2 biologically, without pertinent collateral dosimetric/toxicologic information. Despite these
3 issues, several PM-related epidemiologic studies have attempted to address the question of
4 threshold.

5 Cakmak et al. (1999) investigated methods to detect and estimate threshold levels in time-
6 series studies. Based on the realistic range of error observed from actual Toronto pollution data
7 (average site-to-site correlation: 0.90 for O₃; 0.76 for CoH; 0.69 for TSP; 0.59 for SO₂; 0.58 for
8 NO₂; and 0.44 for CO), pollution levels were generated with multiplicative error for six levels of
9 exposure error (1.0, 0.9, 0.8, 0.72, 0.6, 0.4, site-to-site correlation). Mortality series were
10 generated with three PM₁₀ threshold levels (12.8 µg/m³, 24.6 µg/m³, and 34.4 µg/m³). LOESS
11 with a 60% span was used to observe the exposure-response curves for these 18 combinations of
12 exposure-response relationships with error. A parameter threshold model was also fit using non-
13 linear least squares. Both mortality and PM₁₀ data were pre-filtered for the influence of seasonal
14 cycles using LOESS smooth function. The threshold regression models were then fit to the
15 pre-filtered data. Graphical presentations indicate that LOESS adequately detects threshold
16 under no error, but the thresholds were “smoothed out” under the extreme error scenario. Use of
17 a parametric threshold model was adequate to give “nearly unbiased” estimates of threshold
18 concentrations even under the conditions of extreme measurement error, but the uncertainty in
19 the threshold estimates increased with the degree of error. They concluded, “if threshold exists,
20 it is highly likely that standard statistical analysis can detect it.”

21 Daniels et al. (2000; reanalysis by Dominici et al., 2003) tested for presence of a threshold
22 using data for the largest 20 U.S. cities during 1987-1994. In their original analyses, the authors
23 compared three log-linear GAM regression models: (1) using a linear PM₁₀ term; (2) using a
24 natural cubic spline of PM₁₀ with knots at 30 and 60 µg/m³ (corresponding approximately to
25 25 and 75 percentile of the distribution); and, (3) using a threshold model with a grid search in
26 the range between 5 and 200 µg/m³ with 5 µg/m³ increment. The covariates included in these
27 models are similar to those previously used by the same research group (Kelsall et al., 1997;
28 Samet et al., 2000a,b), including the smoothing function of time, temperature and dewpoint, and
29 day-of-week indicators. The 2003 reanalysis evaluated total, cardiorespiratory, and “other”
30 mortality series by means of covariate adjustments made using natural splines in GLM models.
31 These models were fit for each city separately and, for model (1) and (2), the combined

1 estimates across cities were then obtained by using inverse variance weighting if there was no
2 heterogeneity across cities or by using a two-level hierarchical model if there was heterogeneity.
3 The best fits among the models, within each city and over all cities, were also determined using
4 Akaike's Information Criterion (AIC).

5 As seen in Figure 8-30, the results using the natural spline model showed that, for total and
6 cardiorespiratory mortality, the exposure-response spline curves for mean lag were roughly
7 linear, but less so for current and previous day PM₁₀, making it difficult to discern any evident
8 threshold. However, the curves for mortality from other causes, most clearly increased once
9 PM₁₀ concentrations exceeded 50 µg/m³. The posterior probabilities for a threshold for PM₁₀
10 effects on total and cause-specific mortality groupings are shown in Figure 8-31 (CVDRESP =
11 cardiorespiratory causes). There appears to be a reasonably likely possibility of a threshold
12 existing for daily total or CVDRESP mortality at PM₁₀ levels of ~15-20 µg/m³ or below; but the
13 likelihood of a threshold occurring above ~25 µg/m³ seems to be essentially zero, based on the
14 latter analyses. The hypothesis of linearity was examined more formally by comparing AIC
15 values across models, with the results indicating that the linear model was preferred over the
16 spline and the threshold models. Thus, these findings do not rule out the possibility that linear
17 models without a threshold may be appropriate for estimating the effects of PM₁₀ on the types of
18 mortality of main interest. The available information simply does not allow for a clear choice of
19 "threshold" or "no threshold" over the other.

20 Smith et al. (1999) analyzed the slope of the PM₁₀-mortality relationship in Birmingham,
21 AL and in Cook County, IL. Temperature was modeled using piece-wise linear term with a
22 change point. PM₁₀ data were modeled at lag 0 through 3 and 3-day averages at these lags.
23 In addition to the linear model, the existence of a threshold was also investigated by using
24 B-splines and a parametric threshold model with the profile log likelihood evaluated at changing
25 threshold points. B-splines results suggest that an increasing effect above 80 µg/m³ for
26 Birmingham, and above 100 µg/m³ for Chicago. The threshold model through examination of
27 log likelihood across the range of threshold levels also suggested similar change points, but not
28 to an extent that statistically significant distinctions were demonstrated.

29 The Smith et al. (2000) study of associations between daily total mortality and PM_{2.5} and
30 PM_{10-2.5} in Phoenix, AZ (during 1995-1997) also investigated the possibility of a threshold.
31 In the linear model, the authors found that mortality was significantly associated with PM_{10-2.5},

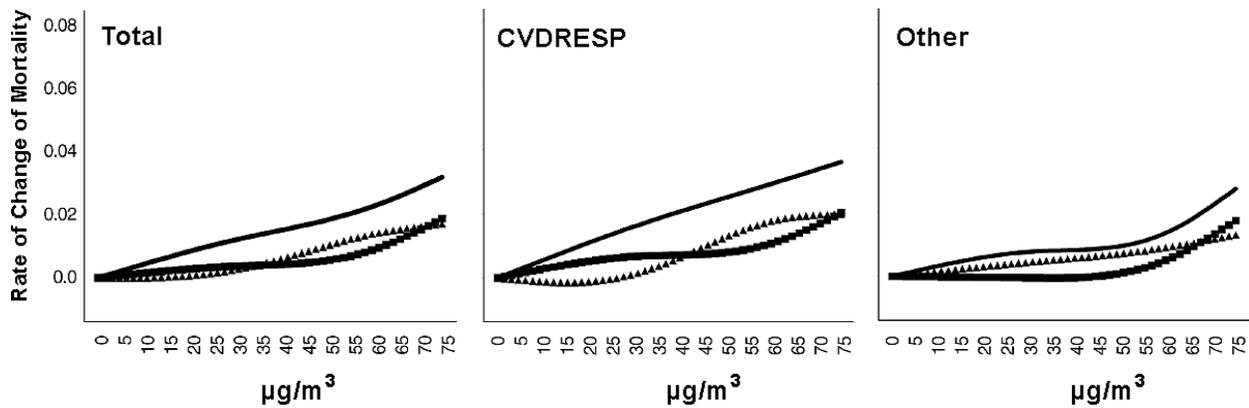


Figure 8-30. Concentration-response curves for PM₁₀ mortality relationships in 20 largest U.S. cities (1987-1994), for total (TOTAL) mortality, cardiovascular and respiratory (CVDRESP) mortality, and other causes (Other) mortality. The concentration-response curves for the mean lag, current day, and previous day PM₁₀ are denoted by solid lines, squared points, and triangle points, respectively.

Source: Dominici et al. (2003).

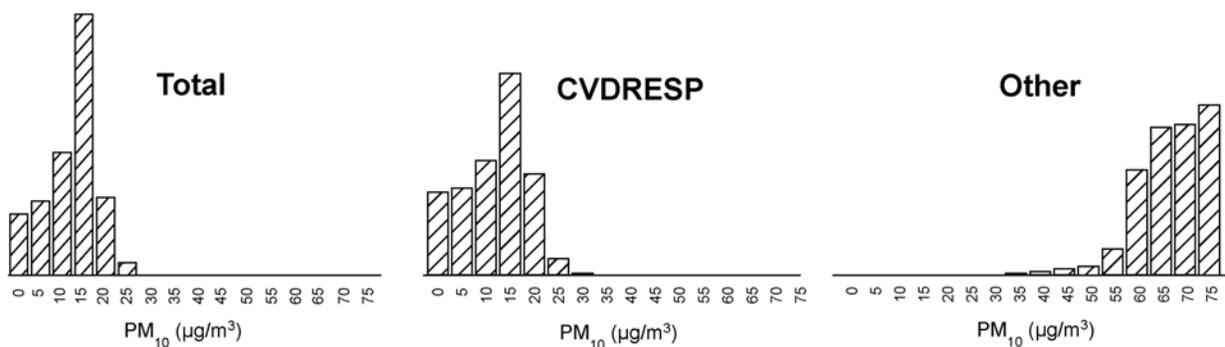


Figure 8-31. Posterior probabilities of thresholds for each cause-specific mortality and for mean PM₁₀, 20 largest U.S. cities, 1987-1994. Total = total nonaccidental mortality; CVDRESP = cardiovascular mortality and respiratory mortality; Other = mortality from other causes.

Source: Dominici et al. (2003).

1 but not with $PM_{2.5}$. In modeling possible thresholds, they applied: (1) a piecewise linear model
2 in which several possible thresholds were specified; and (2) a B-spline (spline with cubic
3 polynomials) model with 4 knots. Using the piecewise model, there was no indication that there
4 was a threshold for $PM_{10-2.5}$. However, for $PM_{2.5}$, the piecewise model resulted in suggestive
5 evidence for a threshold, around 20 to 25 $\mu\text{g}/\text{m}^3$. The B-spline results also showed no evidence
6 of threshold for $PM_{10-2.5}$, but for $PM_{2.5}$, a non-linear curve showed a change in the slope around
7 20 $\mu\text{g}/\text{m}^3$. A further Bayesian analysis for threshold selection suggested a clear peak in the
8 posterior density of $PM_{2.5}$ effects around 22 $\mu\text{g}/\text{m}^3$. These results make it difficult to evaluate the
9 relative roles of different PM components (in this case, $PM_{2.5}$ versus $PM_{10-2.5}$). However, the
10 concentration-response curve for $PM_{2.5}$ presented in this publication suggests more of a U- or
11 V-shaped relationship than the usual “hockey stick” relationship. Such a relationship is, unlike
12 the temperature-mortality relationship, difficult to interpret biologically. Because the sample
13 size of this data (3 years) is relatively small, further investigation of this issue using similar
14 methods but a larger data set is warranted. Other studies evaluate non-linear relationships using
15 a multi-city meta-smoothing approach based on non- or semi-parametric smoothers rather than
16 on linear parametric models.

17 In summary, the results from large multi-city studies suggest that there is no strong
18 evidence of a clear threshold for PM mortality effect. Some single-city studies provide some
19 suggestive hints for possible thresholds, but not in a statistically clear manner. More data need
20 to be examined with alternative approaches (e.g., Smith et al.’s parametric model); but, in the
21 meantime, the use of linear PM effect models appears to be appropriate.

22 23 **8.4.8 The Question of Heterogeneity of Particulate Matter Effects Estimates**

24 Approximately 35 then-available acute PM exposure community epidemiologic studies
25 were assessed in the 1996 PM AQCD as collectively demonstrating increased risks of mortality
26 being associated with short-term (24-h) PM exposures indexed by various ambient PM
27 measurement indices (e.g., PM_{10} , $PM_{2.5}$, BS, CoH, sulfates, etc.) in many different cities in the
28 United States and internationally. Much homogeneity appeared to exist across various
29 geographic locations, with many studies suggesting, for example, increased relative risk (RR)
30 estimates for total nonaccidental mortality mainly on the order of 1.025 to 1.05 (or 2.5 to 5.0%
31 excess deaths) per 50 $\mu\text{g}/\text{m}^3$ increase in 24-h PM_{10} , with statistically significant results extending

1 more broadly in the range of 1.5 to 8.0%. The elderly ≥ 65 yrs. old and those with preexisting
2 cardiopulmonary conditions had somewhat higher excess risks. One study, the Harvard Six City
3 Study, also provided estimates of increased RR for total mortality falling in the range of 1.02 to
4 1.056 (2.0 to 5.6% excess deaths) per $25 \mu\text{g}/\text{m}^3$ 24-h $\text{PM}_{2.5}$ increment.
5

6 **8.4.8.1 Evaluation of Heterogeneity in Time-Series Studies**

7 More than 80 new time-series PM-mortality studies assessed earlier in this chapter provide
8 extensive additional evidence which, qualitatively, largely substantiates significant ambient PM-
9 mortality relationships, based on 24-h exposures indexed by a wide variety of PM metrics in
10 many different cities of the United States, in Canada, in Mexico, and elsewhere (in South
11 America, Europe, Asia, etc.). The newly available effect size estimates from such studies are
12 reasonably consistent with the ranges derived from the earlier studies reviewed in the 1996 PM
13 AQCD. For example, newly estimated PM_{10} effects generally fall in the range of 1.0 to 8.0%
14 excess deaths per $50 \mu\text{g}/\text{m}^3$ PM_{10} increment in 24-h concentration; and new $\text{PM}_{2.5}$ excess death
15 estimates for short-term exposures generally fall in the range of 2 to 8% per $25 \mu\text{g}/\text{m}^3$ increment
16 in 24-h $\text{PM}_{2.5}$ concentration.

17 However, in contrast to the past appearance of considerable homogeneity among risk
18 estimates, somewhat greater spatial heterogeneity appears to exist across newly reported study
19 results, both with regard to PM-mortality and morbidity effects associations. The newly
20 apparent heterogeneity of findings across locations is perhaps most notable in relation to reports
21 based on multiple-city studies in which investigators used the same analytical strategies and
22 models adjusted for the same or similar co-pollutants and meteorological conditions, raising the
23 possibility of different findings reflecting real location-specific differences in exposure-response
24 relationships rather than potential differences in models used, pollutants included in the models,
25 etc. Some examples of newly reported and well-conducted multiple-city studies include: the
26 NMMAPS analyses of mortality and morbidity in 90 and 20 U.S. cities (Samet et al., 2000a,b;
27 Dominici et al., 2000a); the Schwartz (2000b,c) analyses of 10 U.S. cities; the study of eight
28 largest Canadian cities (Burnett et al., 2000); the study of hospital admissions in eight U.S.
29 counties (Schwartz, 1999); and the APHEA studies of mortality and morbidity in several
30 European cities (Katsouyanni et al., 1997; Zmirou et al., 1998).

1 The large NMMAPS studies of mortality and morbidity in U.S. cities provide important
2 information about potential U.S. within- and between-region heterogeneity. HEI (2003a), after
3 examining the NMMAPS GAM reanalyses by Dominici et al. (2002), concluded that while
4 formal tests of PM effects across cities did not indicate evidence of heterogeneity because of the
5 individual-city effects standard error being generally large, the power to assess the presence of
6 heterogeneity was low and, as such, the possibility of heterogeneity still exists.

7 Some insight into the possible extent of heterogeneity can be gained by close examination
8 of data from the NMMAPS study (Samet et al., 2000b). Data for excess risk and 95%
9 confidence intervals were plotted by EPA against the total number of effective observations,
10 measured by the number of days of PM₁₀ data times the mean number of daily deaths in the
11 community. This provides a useful measure of the weight that might be assigned to the results,
12 since the uncertainty of the RR estimate based on a Poisson mean is roughly inversely
13 proportional to this product. That is, the expected pattern should typically show less spread of
14 estimated excess risk with increasing death-days of data. A more refined weight index would
15 also include the spread in the distribution of PM concentrations. The results for NMMAPS,
16 including the GAM reanalyses results, conform to some extent to the expected pattern. That is,
17 with increasingly more mortality-days observations, the 95% confidence intervals generally
18 became narrower. However, the results for relationships between effect size estimates and
19 precision estimates for different regions vary considerably. In the Northeast, for example, there
20 is some degree of consistency of effect size for larger study-size cities, even with moderately
21 wide confidence intervals for those with log mortality-days > 8 to 9, and all clearly exceed the
22 overall nationwide grand mean. On the other hand, the smaller study-size Northeast cities (with
23 much wider confidence intervals at log mortality-days < 8) show much greater variability of
24 effect size estimates and less precision. As for the estimates derived for cities in other U.S.
25 regions, there is even less consistency between magnitude of effect size and precision of the
26 estimates, suggesting that other factors may account for differences in direction and/or size of
27 the risk estimates.

28 Burnett and Goldberg (2003) also investigated heterogeneity in effects across eight
29 Canadian cities, and concluded that there was not sufficient evidence to conclude that the PM
30 association with mortality varies across the eight cities. In the initial analyses using GAM, a
31 positive estimate of heterogeneity was reported, but in reanalyses using GLM with natural

1 splines, negative estimates were reported. The authors stated that this reflected reduced variation
2 in effect size estimates across cities along with increased within-city estimation error in the
3 reanalysis results. In addition, as discussed in Section 8.2.2.3.3, in the initial analyses using data
4 from the APHEA cohort, some apparent heterogeneity was found between results for western
5 and eastern European cities; however, in reanalyses of these results, the distinctions between the
6 western and eastern cities were less clear. Variables that may potentially influence heterogeneity
7 of effects were further investigated in the APHEA2 analyses for 29 European cities, with mean
8 NO₂ concentration in the cities (indicator of traffic-related pollution), warmer climate and low
9 overall mortality rate being associated with increased PM-mortality associations.

10 Further closer reexamination of results for different areas in the U.S. or elsewhere may
11 reveal interesting new insights into what factors may account for apparent differences among the
12 cities within a given region or across regions. Some potential factors include differences in PM
13 sources or composition, differences in population exposures across cities, and differences in
14 potentially susceptible groups (e.g., % of population ≥ 65 yr old). The NMMAPS investigators
15 reported no substantial differences in PM₁₀-mortality associations based on PM_{2.5} / PM₁₀ ratios or
16 socioeconomic indicators for the various cities; however, no statistically significant evidence of
17 heterogeneity was reported for that study. As stated previously, European investigators
18 discussed several factors that may have influenced heterogeneity in PM-mortality associations
19 across 29 European cities. These included variations in presence of an indicator of traffic-related
20 pollution, warmer climate (postulated to be related to better estimation of exposures since people
21 were more likely to open windows) and low mortality rate (which the authors suggested was due
22 to the larger number of potentially susceptible people in cities with lower mortality rates). These
23 findings are consistent with those reported by Janssen et al. (2002, reanalyzed in Schwartz et al.,
24 2003), where PM₁₀-hospitalization associations were greater in areas with less use of central air
25 conditioning and with greater contributions of PM₁₀ emissions from vehicle emissions and oil
26 combustion.

1 **8.4.8.2 Comparison of Spatial Relationships in the NMMAPS and Cohort** 2 **Reanalyses Studies**

3 Both the NMMAPS and HEI Cohort Reanalyses studies had a sufficiently large number of
4 U.S. cities to allow considerable resolution of regional PM effects within the “lower 48” states,
5 but an attempt was made to take this approach to a much more detailed level in the Cohort
6 Reanalysis studies than in NMMAPS. There were: 88 cities with PM₁₀ effect size estimates in
7 NMMAPS; 50 cities with PM_{2.5} and 151 cities with sulfates in the original Pope et al. (1995)
8 ACS analyses and in the HEI reanalyses using the original data; and 63 cities with PM_{2.5} data
9 and 144 cities with sulfate data in the additional analyses done by the HEI Cohort Reanalysis
10 team. The relatively large number of data points utilized in the HEI reanalyses effort and
11 additional analyses allowed estimation of surfaces for elevated long-term concentrations of
12 PM_{2.5}, sulfates, and SO₂ with resolution on a scale of a few tens to hundreds of kilometers.

13 The patterns for PM_{2.5} and sulfates are similar, but not identical. In particular, the modeled
14 PM_{2.5} surface (Krewski et al., 2000; Figure 18) had peak levels around Chicago - Gary, in the
15 eastern Kentucky - Cleveland region, and around Birmingham AL, with elevated but lower PM_{2.5}
16 almost everywhere east of the Mississippi, as well as southern California. This is similar to the
17 modeled sulfate surface (Krewski et al., 2000; Figure 16), with the absence of a peak in
18 Birmingham and an emerging sulfate peak in Atlanta. The only area with markedly elevated
19 SO₂ concentrations was the Cleveland - Pittsburgh region. Secondary sulfates in particles
20 derived from local SO₂ appeared more likely to be important in the industrial midwest, south
21 from the Chicago - Gary region into Ohio, northeastern Kentucky, West Virginia, and southwest
22 Pennsylvania, possibly related to combustion of high-sulfur fuels.

23 The overlay of mortality with air pollution patterns is also of much interest. The spatial
24 overlay of long-term PM_{2.5} and mortality (Krewski et al., 2000; Figure 21) was highest from
25 southern Ohio to northeastern Kentucky/West Virginia, but also included a significant
26 association over most of the industrial midwest. This was reflected, in diminished form, by the
27 sulfates and SO₂ maps (Krewski et al., 2000; Figures 19 and 20), where there appeared to be a
28 somewhat tighter focus of elevated risk in the upper Ohio River Valley area. This suggests that,
29 while SO₂ was an important precursor of sulfates in this region, there may also have been some
30 other (non-sulfur) contributors to associations between PM_{2.5} and long-term mortality,
31 encompassing a wide area of the North Central Midwest and non-coastal Mid-Atlantic region.

1 The apparent differences in PM₁₀ and/or PM_{2.5} effect sizes across different regions should
2 not be attributed merely to possible variations in measurement error or other statistical
3 artifact(s). Some of these differences may reflect: real regional differences in particle
4 composition or co-pollutant mix; differences in relative human exposures to ambient particles or
5 other gaseous pollutants; sociodemographic differences (e.g., percent of infants or elderly in
6 regional population); or other important, as of yet unidentified PM effect modifiers.

8 **8.4.9 Age-Related Differences in PM Effect Estimates**

9 Numerous epidemiological studies have reported health responses to PM and other
10 pollutants for one or another specific age group. For example, in the U.S., data on hospital
11 admissions for older people (aged 65 years and older) are available through a national data
12 system maintained by the Health Care Financing Administration; and, thus, many U.S. hospital
13 admissions studies have focused on health responses in this age group. Other studies, such as
14 panel studies for asthma symptoms, have evaluated groups of schoolchildren. In general, such
15 studies have indicated that both the elderly and children are likely susceptible subpopulations for
16 PM-related effects (see Sections 8.3.1.4 and 8.3.2.5).

17 Though less commonly done, possible age-related differences in ambient PM health effects
18 have been evaluated in certain recently published epidemiological studies that assessed health
19 responses to air pollution by means of stratified analyses for different age groups within the
20 population studied. For example, a number of studies have assessed relationships between PM
21 and total mortality across all ages, then evaluated possible differences in risk for the subset of
22 older adults (50+ or 65+ years); and some of these have reported slightly larger effect estimates
23 for the older age group (e.g., Schwartz et al., 1996a; Styer et al., 1995; Borja-Aburto et al.,
24 1998), whereas others have found associations that are similar in magnitude or even slightly
25 smaller for the older age group (e.g., Ostro et al., 1999a, 1995; Castillejos et al., 2000). Also,
26 Chock et al. (2000) reported associations between PM and total mortality that were not
27 substantially different for age groups of 0-74 and 75+ years.

28 In other studies of hospital admissions or medical visits for asthma or respiratory disease,
29 some studies have reported larger effect estimates for children than for adults (e.g., Anderson
30 et al., 1998; Medina et al., 1997), whereas others have reported effect estimates of generally
31 similar size across young and adult age groups (e.g., Atkinson et al., 1999b; Hajat et al., 1999;

1 Wong et al., 1999a) and some studies of respiratory hospital admissions have shown larger effect
2 sizes for adults (e.g., Prescott et al., 1998). For hospital admissions or medical visits for
3 cardiovascular diseases, most studies (but not all -- e.g., Atkinson et al., 1999), have reported
4 somewhat larger effect estimate sizes for older adults (65+ years) than adults in younger age
5 categories (e.g., Le Tertre et al., 2003; Wong et al., 1999a; Prescott et al., 1998; Morgan et al.,
6 1998).

7 The above rather small group of studies does not show striking differences in effect
8 estimates from analyses across age group strata, but they do tend to support previous findings
9 that, depending on the specific type of effect under study, older adults and children may be more
10 susceptible to certain PM- related effects. More specifically, older adults (aged 65+ yrs) appear
11 to be most clearly at somewhat higher risk for PM exacerbation of cardiovascular-related disease
12 effects and , perhaps, tend to experience higher PM-related total (non-accidental) mortality risk,
13 as well . On the other hand, more limited evidence points toward children possibly being at
14 somewhat higher risk for respiratory-related (especially asthma) PM effects than adults.
15

16 **8.4.10 Implications of Airborne Particle Mortality Effects**

17 The public health burden of mortality associated with exposure to ambient PM depends not
18 only on the increased risk of death, but also on the amount of life shortening that is attributable
19 to those deaths. The 1996 PM AQCD concluded that confident quantitative determination of years
20 of life lost to ambient PM exposure was not yet possible and life shortening may range from
21 days to years (U.S. Environmental Protection Agency, 1996a). Now, some newly available
22 analyses provide further interesting insights with regard to potential life-shortening associated
23 with ambient PM exposures.
24

25 **8.4.10.1 Short-Term Exposure and Mortality Displacement**

26 A few studies have investigated the question of “harvesting,” a phenomenon in which a
27 deficit in mortality occurs following days with (pollution-caused) elevated mortality, due to
28 depletion of the susceptible population pool. This issue is very important in interpreting the
29 public health implication of the reported short-term PM mortality effects. The 1996 PM AQCD
30 discussed suggestive evidence observed by Spix et al. (1993) during a period when air pollution

1 levels were relatively high. Recent studies, however, generally used data from areas with lower,
2 non-episodic pollution levels.

3 Schwartz (2000c; reanalysis 2003a) separated time-series air pollution, weather, and
4 mortality data from Boston, MA, into three components: (1) seasonal and longer fluctuations;
5 (2) “intermediate” fluctuations; (3) “short-term” fluctuations. By varying the cut-off between
6 the intermediate and short term, evidence of harvesting was sought. The idea is, for example, if
7 the extent of harvesting were a matter of a few days, associations between weekly average values
8 of mortality and air pollution (controlling for seasonal cycles) would not be seen. Schwartz’s
9 reanalysis using natural splines reported reductions in COPD mortality $PM_{2.5}$ risk estimates for
10 longer time scale, suggesting that most of the COPD mortality was only displaced by a few
11 weeks. However, for pneumonia, ischemic heart disease, and all cause mortality, the effect size
12 increased, as longer time scales were included. For example, the percent increase in non -
13 accidental deaths associated with a $25 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ increased from 5.8% (95% CI:
14 4.5, 7.3) for the 15-day window to 9.7% (95% CI: 8.2, 11.2) for the 60-day window. Note,
15 however, that the 60-day time scale window is in the range of influenza epidemics. Some
16 caution is therefore needed in interpreting risk estimates in this range.

17 Zanobetti et al. (2000b) used what they termed “generalized additive distributed lag
18 models” (penalized splines using an algorithm that did not require back-fitting were used for all
19 the smoothing terms) to help quantify mortality displacement in Milan, Italy, 1980-1989. Non-
20 accidental total deaths were regressed on smooth functions of TSP distributed over the same day
21 and the previous 45 days using penalized splines for the smooth terms and seasonal cycles,
22 temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality
23 displacement was modeled as the initial positive increase, negative rebound (due to depletion),
24 followed by another positive coefficients period, and the sum of the three phases were
25 considered as the total cumulative effect. TSP was positively associated with mortality up to
26 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by
27 smaller but positive coefficients up to the 45 th day (maximum examined). The sum of these
28 coefficients was over three times larger than that for the single-day estimate.

29 Zanobetti et al. (2000a; reanalysis by Zanobetti and Schwartz, 2003b) also applied the
30 same concept described above (up to 41 lag days) to 10 cities from APHEA2 to estimate
31 distributed lag PM_{10} mortality risks. They applied the covariate adjustment in a GAM model

1 used in APHEA2 (Katsouyanni et al., 2001) and in reanalysis (Zanobetti and Schwartz, 2003b),
2 they also used penalized splines in addition to the GAM model with stringent convergence
3 criteria. The resulting city specific coefficients were pooled in the second-stage model, taking
4 into account heterogeneity across cities. The estimated shape of the distributed lag pooled across
5 10 cities showed a similar pattern to that from Milan data described above, with the second
6 “hump” of smaller but positive coefficients between approximately 20 to 35 days. The results
7 indicated that, compared to PM₁₀ risk estimates obtained for the average of lag 0 and 1 days, the
8 distributed lag estimates up to 40 days were about twice larger in both GAM and penalized
9 splines models. For example, the combined distributed lag estimates for the 10 cities using
10 penalized splines was 5.6% (95% CI: 1.5, 9.8), as compared to 2.9% (95% CI: 1.4, 4.4).
11 It should be noted, however, that the results for individual cities varied. For example, the
12 estimates for average of lag 0 and 1 days and the distributed lag model were comparable in
13 Tel Aviv, whereas it was nearly seven times bigger for distributed lag model in Lodz. Thus,
14 while these results do support the lack of mortality displacement up to 40-45 day period, the
15 pattern of lagged associations may vary from city to city.

16 Two new studies conducted very different analyses, beginning with the assumption that
17 harvesting is occurring. Both research groups used models to estimate the size of the frail
18 populations. In one study, as part of their analysis of PM₁₀-mortality association in Birmingham,
19 AL and Cook County, IL, Smith et al. (1999) used a latent variable structure fitted through
20 Bayesian techniques using Monte Carlo sampling. The resulting posterior mean for the size of
21 the frail population in Chicago was 765 (posterior s.d. = 189). The mean numbers of days lost
22 per person as a result of 10 µg/m³ increase in PM₁₀ was estimated to be 0.079 day (posterior
23 s.d. = 0.032). In the other study, Murray and Nelson (2000) used Kalman filtering to estimate a
24 hazard function of TSP in a state space model in the Philadelphia mortality data during
25 1973-1990. The model framework, which assumes an harvesting effect, allows estimation of
26 at-risk population and the effect of changes in air quality on the life expectancy of the at-risk
27 population. Combinations of TSP, linear temperature, squared temperature, and interaction of
28 TSP and temperature were considered in six models. The size of at-risk (or frail) population
29 estimated was about 500 people. Life expectancy was estimated to be reduced by about 2.5 days
30 with TSP exposure for the roughly 500 at-risk frail individuals in Philadelphia suggesting that
31 the hazard causing agent makes a difference of only 2.5 days in the at-risk frail population.

1 In both cases, the estimated size of the frail population is very small with short life expectancy.
2 In these cases, based on the assumption that harvesting is occurring and only small frail
3 populations are at risk, life shortening due to PM exposures is estimated to be on the order of just
4 a few days.

5 Zeger et al. (1999) first illustrated, through simulation, the implication of harvesting for
6 PM regression coefficients (i.e., mortality relative risk) as observed in a frequency domain.
7 Three levels of harvesting (3 days, 30 days, and 300 days) were simulated. As expected, the
8 shorter the harvesting, the larger the PM coefficient in the higher frequency range. However, in
9 the analysis (and reanalysis by Dominici et al., 2003a) of real data from Philadelphia, regression
10 coefficients increased toward the lower frequency range, suggesting that the extent of harvesting,
11 if it exists, is not in the short-term range. Zeger suggested that “harvesting-resistant” regression
12 coefficients could be obtained by excluding coefficients in the very high frequency range (to
13 eliminate short-term harvesting) and in the very low frequency range (to eliminate seasonal
14 confounding). Since the observed frequency domain coefficients in the very high frequency
15 range were smaller than those in the mid frequency range, eliminating the “short-term
16 harvesting” effects would only increase the average of those coefficients in the rest of the
17 frequency range.

18 Frequency domain analyses are rarely performed in air pollution health effects studies,
19 except perhaps for spectral analysis (variance decomposition by frequency) to identify seasonal
20 cycles. Examinations of the correlation by frequency (*coherence*) and the regression coefficients
21 by frequency (*gain*) may be useful in evaluating the potential frequency-dependent relationships
22 among multiple time series. A few past examples in air pollution health effects studies include:
23 (1) Shumway et al.’s (1983) analysis of London mortality analysis, in which they observed that
24 significant coherence occurred beyond two week periodicity (they interpreted this as “pollution
25 has to persist to affect mortality”); (2) Shumway et al.’s (1988) analysis of Los Angeles
26 mortality data, in which they also found larger coherence in the lower frequency; (3) Ito’s (1990)
27 analysis of London mortality data in which he observed relatively constant gain (regression
28 coefficient) for pollutants across the frequency range, except the annual cycle. These results also
29 suggest that associations and effect size, at least, are not concentrated in the very high frequency
30 range.

1 Dominici et al. (2003b) also explored associations between air pollution and mortality
2 using data from the four cities included in NMMAPS that had every-day PM₁₀ measurements,
3 Chicago, Minneapolis, Pittsburgh, and Seattle. The authors first used discrete Fourier
4 transformation to decompose the air pollution time series into distinct component series:
5 < 3.5, 3.5-6, 7-13, 14-29, 30-59, and ≥ 60 days. They then calculated associations without
6 decomposition and with each of the timescale components, with the expectation that under a
7 short-term mortality displacement scenario, mortality would be mainly associated with air
8 pollution at the short timescales. For both individual cities and the four cities overall, a pattern
9 was found of larger effects at the longer timescales and smaller effects at the shorter timescales.
10 For a 1-day lag, the 4-city overall relative risk of 0.22% increase in cardiovascular and
11 respiratory mortality per 10 µg/m³ PM₁₀ (95% CI -0.02, 0.46) was comparable to that found in
12 the 90-city analyses (Dominici, 2003). At the ≥ 60 day timescale, the authors report relative
13 risks of 1.35% (95% CI 0.52, 2.17) per 10 µg/m³ PM₁₀ for total mortality, and 1.87% (95% CI
14 0.75, 2.99) per 10 µg/m³ PM₁₀ for cardiovascular and respiratory mortality. The authors also
15 investigated the sensitivity of their findings to alternative lag period choice (optimal lags from
16 0-6 days selected), adjustment for long-term trends and seasonality (ranging from 3.5 to
17 14 degrees of freedom per year for time), and alternative assumptions of heterogeneity in effects
18 between cities. For all, the authors report that the overall pattern of results remains similar,
19 though the confidence intervals widened considerably with greater heterogeneity. The authors
20 conclude that the results are inconsistent with the short-term mortality displacement hypothesis.

21 In a commentary on the previous analyses, Smith (2003) conducted further analyses using
22 the software developed by Dominici et al. (2003b) and TSP data from Philadelphia. Results are
23 presented for models including alternative timescales for meteorological factors in the analyses,
24 with a consistent pattern of results showing larger effect estimates with longer timescales. Smith
25 (2003) also used the frequency decomposition software with a simulated data set that had an
26 assumed association between TSP and mortality (1% increase per 10 µg/m³ TSP). From these
27 results, the author concluded that it was more difficult to determine time-scale dependency in
28 response, particularly for the results of the simulated harvesting model, where the effect estimate
29 appears to be consistent in size across all time scales but the longest (≥ 60 days). In addition, the
30 author conducted a simpler analysis using multi-day averaged TSP concentrations, up to a 30-
31 day average, with the results of different models indicating a peak in the time-dependent TSP

1 effect at approximately 15 days but with different patterns for longer time scales. The author
2 concluded that interpretation of results from these models remained as difficult as ever. In
3 response, Dominici et al. (2004b) agreed that careful interpretation of air pollution-mortality
4 models and consideration of assumptions is needed. The authors discuss further their results of
5 analyses using data from the four NMMAPS cities, observing that their “harvesting-resistant”
6 effect estimates are larger than the “harvesting-prone” estimates, and that these results are
7 consistent with air pollution effects on all people, not simply the very frail.

8 Schwartz (2000c), Zanobetti et al. (2000b), Zanobetti et al., (2000a); reanalysis by
9 Zanobetti and Schwartz, (2003b) and Zeger et al.’s analysis (1999); reanalysis by Dominici et al.
10 (2003a, 2003b) all suggest that the extent of harvesting, if any, is not a matter of only a few days.
11 Other past studies that used frequency domain analyses are also at least qualitatively in
12 agreement with the evidence against the short-term only harvesting. Since long wave cycles
13 (> 6 months) need to be controlled in time-series analyses to avoid seasonal confounding, the
14 extent of harvesting beyond 6 months periodicity is not possible in time-series study design.
15 Also, influenza epidemics can possibly confound the PM-mortality associations in the 1 to
16 3 month periodicity ranges. Therefore, interpreting PM risk estimates in these “intermediate”
17 time scale also requires cautions.

18 In contrast to this group of studies, Smith et al. (1999) and Murray and Nelson (2000)
19 suggest that the frail population is very small and its life expectancy short, such that PM or any
20 external stress cannot have more than a few days of life-shortening impacts on this specific
21 subpopulation. This may, in part, reflect the limitation of the model itself when applied only to a
22 small frail subpopulation. Thus, there appears to be consistency in results within the similar
23 models but not across different types of models. Clearly, more research is needed in this area
24 both in terms of development of a conceptual framework that can be tested with real data, and
25 applications of these models to more data sets. However, at least in the models that extend the
26 common time-series modeling, there appears to be no strong evidence to suggest that PM is
27 shortening life by only a few days.

1 **8.4.10.2 Life-Shortening Estimates Based on Prospective Cohort Study Results**

2 Brunekreef (1997) reviewed available evidence for long-term PM exposure effects on
3 mortality and, using life table methods, derived a rough preliminary estimate of the reduction in
4 life expectancy implied by those effect estimates. Based on the results of Dockery et al. (1993)
5 and Pope et al. (1995), a relative risk of 1.1 per 10 $\mu\text{g}/\text{m}^3$ exposure over 15 years was assumed
6 for the effect of PM air pollution on men 25-75 years of age. A 1992 life table for men in the
7 Netherlands was developed for 10 successive five-year categories that make up the 25-75 year
8 old age range. Life expectancy of a 25 year old was then calculated for this base case and
9 compared with the calculated life expectancy for the PM-exposed case, in which the death rates
10 were increased in each age group by a factor of 1.1. A difference of 1.11 years was estimated
11 between the “exposed” and “clean air” cohorts’ overall life expectancy at age 25. Looked at
12 another way, this implies that the expected lifespan for persons who actually died from air
13 pollution would be reduced by more than 10 years, because they represent a small percentage of
14 the entire cohort population. A similar calculation by present EPA authors, based on the 1969-
15 71 life table for U.S. white males, yielded a larger estimated reduction of 1.31 years for the
16 entire U.S. population’s life expectancy at age 25. Thus, these calculations imply that relatively
17 small differences in long-term exposure to ambient PM may have substantial effects on life
18 expectancy. However, these “back of the envelope” calculations have not been verified by
19 others and can only be viewed as providing very rough “ballpark” estimates of potential life-
20 shortening effects of PM. They depend heavily on the specific PM risk estimates used and, for
21 example, would likely have to be adjusted downward to reflect the newer (presumably more
22 credible) lower RR estimates derived from the Pope et al. (2002) ACS extension study.

23 **8.4.10.3 Potential Effects of Infant Mortality on Life-Shortening Estimates**

24 Deaths among children would logically have the greatest influence on a population’s
25 overall life expectancy, but the Brunekreef (1997) life table calculations did not consider any
26 possible long-term air pollution exposure effects on the population aged < 25 years. Thus, any
27 premature mortality that may occur among children due to PM exposure would logically be
28 likely to increase significantly any overall population life shortening over and above that
29 estimated by Brunekreef (1997) for long-term PM exposure of adults aged ≥ 25 years. However,
30 as discussed earlier, only a few older cross-sectional studies and a few more recent studies
31

1 provide very limited evidence bearing on the extent to which infants may be among
2 subpopulations affected by long-term PM exposure. Thus, much more definitive future research
3 is needed before infant mortality can be considered in generating estimates of potential PM-
4 related life shortening in the U.S. population.

7 **8.5 SUMMARY OF KEY FINDINGS AND CONCLUSIONS DERIVED** 8 **FROM PARTICULATE MATTER EPIDEMIOLOGY STUDIES**

9 Important types of additions to the epidemiologic database beyond that assessed in the
10 1996 PM AQCD, as evaluated above in this chapter, include:

- 11 • Several new multi-city studies of mortality and morbidity effects which provide more
precise estimates of PM effect sizes than most smaller-scale individual city studies;
- 12 • A large number of new studies of various health endpoints using mass-based indicators
of thoracic particles (e.g., PM₁₀); fine-fraction particles (e.g., PM_{2.5} and/or components
such as sulfates, nitrates, H⁺, and ultrafine particles [PM_{1.0} and smaller]); and, to a lesser
extent, coarse-fraction particles (e.g., PM_{10-2.5} and components such as crustal particles).
- 13 • Many new studies that reflect consideration of ambient PM as a component of complex
air pollution mixtures and which evaluate the sensitivity of estimated PM effects to the
inclusion of gaseous co-pollutants (e.g., O₃, CO, NO₂, SO₂) and/or various different PM
indicators / components in analytical models;
- 14 • New and reanalyzed studies that provide insight into the sensitivity of PM effects to the
use of alternative statistical models and model specifications for addressing weather and
other temporal variables;
- 15 • New studies providing insight into various key issues such as alternative lag structures
(e.g., single-day and distributed lags), concentration-response relationships, spatial
heterogeneity of PM effects, measurement error effects (e.g., differential error across
various PM components and/or gaseous co-pollutants);
- 16 • Initial studies using new approaches to evaluate the effects of combinations of air
pollutant or mixtures including PM components, based on empirical combinations (e.g.,
factor analysis or source profiles);
- 17 • New evidence from “found experiments,” or so-called “intervention studies” that
evaluate associations between reduced air pollution levels and improvements in health
endpoints;

- 1 • Numerous new studies of cardiovascular endpoints, with particular emphasis on
assessment of cardiovascular risk factors as well as symptoms;
- 2 • Additional new studies on asthma and other respiratory conditions potentially
exacerbated by ambient PM exposure;
- 3 • New and extended studies of long-term PM exposure effects, notably including analyses
of lung cancer associations with long-term exposures to ambient PM;
- 4 • New studies of infants and children as a potentially susceptible population; and
- 5 • New studies providing insights into the public health impacts of ambient PM
associations with mortality, as well as with other health indices (e.g., physician visits).

6 Evaluation of the new epidemiologic studies, in conjunction with previously existing ones
7 involves consideration of several salient aspects of the evidence so as to reach conclusions as to
8 the likely causal significance of observed associations between ambient PM indicators and
9 various health endpoints. As discussed in Section 8.1.4, these aspects include what can be
10 generally characterized as the strength and consistency of the epidemiologic evidence, as well as
11 broader aspects of plausibility and coherence that reflect an integration of the epidemiologic
12 evidence with information derived from other types of studies (e.g., exposure, dosimetry,
13 toxicology, etc.). Evaluation of the evidence involves an objective appraisal of these salient
14 aspects, recognizing that they do not lend themselves to the application of simple formulas for
15 reaching conclusions with a known degree of certainty, but rather involve an exercise in reaching
16 scientific judgments, taking into account the broad range of views held by the scientific experts
17 engaged in this review. Conclusions derived from such an appraisal of the epidemiologic
18 evidence are presented below, with a broader, more integrative synthesis of all relevant
19 information being presented in Chapter 9.

- 20 (1) Thoracic Particles. An extensive body of epidemiology evidence, confirming earlier-
reported associations between short- and long-term exposures (inferred from stationary
air monitor measures) to ambient thoracic particles (typically indexed by PM₁₀) and
mortality/morbidity effects, supports the general conclusion that ambient thoracic
particles, acting alone and/or in combination with gaseous co-pollutants, are likely
causally related to various human health endpoints.

1 The strength of the evidence across such endpoints includes especially strong evidence
2 for PM₁₀ associations with total (non-accidental) mortality. A large majority of relevant
3 mortality studies show positive PM₁₀ effect estimates, with most all (especially the relatively
4 more precise) estimates being statistically significant. In particular, several multi-city studies
5 in the U.S., Canada, and Europe provide strong support for this conclusion, reporting
6 statistically significant associations with total mortality effect estimates ranging from ~ 1.0 to
7 3.5% (per 50 µg/m³ 24-h PM₁₀ increment). These estimates are generally within (but toward
8 the lower end of) the range of PM₁₀ estimates previously reported in the 1996 PM AQCD.
9 It is notable that the effect estimates from the largest of the multi-city studies (for the 90
10 largest U.S. cities) have also been shown to be robust to the inclusion of gaseous co-
11 pollutants, and the significance of the effect estimates has been shown to be robust to the use
12 of alternative statistical models. The multi-city estimates as well as total mortality risk
13 estimates from many individual-city studies, generally falling in the range of ~ 1.0 to 8.0%
14 per 50 µg/m³ 24-h PM₁₀ increment, also comport well with results of numerous new studies
15 reporting increased cause-specific cardiovascular- and respiratory-related mortality (most
16 statistically significant) and/or cardiovascular and respiratory-related (most statistically
17 significant) morbidity effects.

18 (2) Fine-fraction particles. A growing body of epidemiologic evidence both (a) confirms
associations between short- and long-term ambient exposures (inferred from stationary
air monitor measures) to fine-fraction particles (generally indexed by PM_{2.5}) and
various mortality or morbidity endpoint effects and (b) supports the general conclusion
that PM_{2.5} (or one or more PM_{2.5} components), acting alone and/or in combination with
gaseous co-pollutants, are likely causally related to observed ambient fine particle-
associated health effects.

19 The strength of the evidence varies across such endpoints, with relatively stronger
20 evidence of associations with cardiovascular than respiratory endpoints. As seen in the PM₁₀
21 studies, a large majority of studies of fine-fraction particles show positive effects estimates,
22 with most all of the relatively more precise estimates being statistically significant. In
23 addition, mortality associations with long-term exposures to PM_{2.5}, in conjunction with
24 evidence of associations with short-term exposures, provide strong evidence in support of a

1 casual inference. This conclusion is also supported by studies showing associations with
2 ultrafine particles and other fine-particle components (e.g. sulfates), and by studies showing
3 associations with air pollution factors linked to key sources of fine-fraction particles (e.g.,
4 motor vehicles, other oil and/or coal combustion sources, etc).

5 (3) Coarse-fraction particles. A much more limited body of evidence is suggestive of
associations between short-term (but not long-term) exposures (inferred from stationary
air monitor measures) to ambient coarse-fraction thoracic particles (generally indexed
by $PM_{10-2.5}$) and various mortality and morbidity effects observed at times in some
locations. This suggests that $PM_{10-2.5}$, or some constituent component(s) of $PM_{10-2.5}$,
may contribute under some circumstances to increased human health risks.

6 The strength of the evidence varies across endpoints, with somewhat stronger evidence
7 for coarse-fraction particle associations with morbidity (especially respiratory) endpoints than
8 for mortality. Reasons for differences among findings on coarse-particle health effects
9 reported for different cities are still poorly understood, but several of the locations where
10 significant $PM_{10-2.5}$ effects have been observed (e.g., Phoenix, Mexico City, Santiago) tend to
11 be in drier climates and may have contributions to observed effects due to higher levels of
12 organic particles from biogenic processes (e.g., endotoxins, fungi, etc.) during warm months.
13 Other studies suggest that particles of crustal origin are generally unlikely to exert notable
14 health effects under most ambient exposure conditions. Some exceptions may include
15 situations where crustal particles have come to be heavily contaminated by metals originally
16 emitted as fine particles from smelting operations but deposited over many years on soils
17 around smelters, steel mills, etc. (see Item 10, below). Also, in some U.S. cities (especially in
18 the NW and the SW) where $PM_{10-2.5}$ tends to be a large fraction of PM_{10} , measurements, coarse
19 thoracic particles from woodburning are often an important source during at least some
20 seasons. In such situations, the relationship between hospital admissions and PM_{10} may be an
21 indicator of response to coarse thoracic particles from wood burning.

22 (4) Co-pollutant confounding and effects modification. Much progress has been made in
sorting out contributions of ambient PM_{10} and its components to observed health effects
relative to other co-pollutants; and, despite continuing uncertainties, the evidence
overall tends to support the above conclusions that ambient PM_{10} and $PM_{2.5}$ are most

clearly associated with mortality/morbidity effects, acting either alone or in combination with other covarying gaseous pollutants, with more limited support with regard to PM_{10-2.5}.

23 A major methodological issue affecting epidemiology studies of both short-term and
24 long-term PM exposure effects relates to use of appropriate approaches for evaluating the
25 extent to which other air pollutants correlated with ambient PM, including gaseous criteria
26 pollutants (e.g, O₃, NO₂, SO₂, CO), air toxics, and/or bioaerosols, may confound or modify
27 PM-related effects estimates. A variety of statistical methods for assessing potential
28 confounding arising from these associations have been employed. However, no clear
29 consensus yet exists as to what methods may be most appropriate or adequate for many
30 specific cases. The inclusion of multiple pollutants often produces statistically unstable
31 estimates (for PM, at times, and/or for other gaseous copollutants), such that this commonly
32 applied approach has inherent limitations in disentangling the effects of highly correlated
33 pollutants. Omission of other well correlated, potentially-contributing pollutants, on the other
34 hand, may incorrectly attribute some of their independent effects to PM or obscure possible
35 modifying of PM effects by them. Still, progress has been made in evaluating effects of
36 ambient PM and those of other co-pollutants; and, overall, the new evidence tends to
37 substantiate that observed PM effects are at least partly due to ambient PM acting alone or in
38 the presence of other covarying gaseous pollutants.

39 (5) Alternative Model Specifications for Meteorological Variables. The results of available
epidemiologic studies, using a variety of approaches to control for weather effects,
appear to demonstrate increased PM-related mortality and morbidity risks beyond those
attributable to weather influences alone. However, there is no clear consensus at this
time with regard to what constitutes appropriate or adequate model specifications to
control for possible weather contributions to those human mortality/morbidity effects
attributed to PM exposure and/or on how best to characterize possible joint (interactive)
effects of weather and ambient PM or other air pollutants.

40 A wide variety of statistical approaches have been used in attempting to control for
41 weather effects. Temperature extremes (hot or cold) are well known to cause increased
42 morbidity and mortality, leading some investigations to simply characterize cities as “hot” or

1 “cold” (based on annual mean temperatures) and to compare PM effect estimates across such
2 categories. Others have included temperature and/or humidity as continuous linear variables
3 in models and then tested for PM or gaseous pollutant effects on remaining risk residuals.
4 Others have used widely varying model specifications for non-linear temperature-response
5 curves, with varying numbers of knot points, types of splines (natural, penalized, etc.), and
6 numbers of degrees of freedom used in certain models (e.g. GAM). Still others have argued
7 for and made at least preliminary attempts to use “synoptic weather categories” that define
8 daily combinations of temperature, humidity, and/or other weather variables as constituting
9 “offensive weather patterns” associated with increased risk of morbidity/mortality in a given
10 city, with such “offensive” synoptic patterns varying from city to city in different regions.
11 Higher temperatures and/or humidity combinations, for example, are required in certain
12 southern U.S. cities (e.g. New Orleans, Miami, Atlanta, etc.) to reach “heat index” levels
13 associated with increased risk of heat stroke and/or heat-related deaths than in northern U.S.
14 cities (e.g. St. Louis, Chicago, New York, etc.). One study tested a large number of
15 parametric and non-parametric models with different model specifications for weather
16 variables and found very consistent PM effect size estimates (all statistically significant), even
17 for those models using synoptic weather patterns in several of the models. It is not clear,
18 however, as to what extent the PM effect estimates would be reduced in reanalyses of any of
19 the original GAM-related model runs in that study. New evidence is also emerging for
20 possible weather-related modification of air pollution effects (or vice versa), such as results
21 indicative of more deaths occurring on high temperature/humidity days that also have elevated
22 PM or O₃ levels present than on high heat index days with cleaner air.

23 (6) Measurement Error. Newly available statistical simulation studies highlight the
importance of considering differential measurement error in assessing and interpreting
epidemiologic findings concerning the magnitude and precision of PM effect estimates,
especially in relation to comparison of the relative strength or robustness of effect
estimates attributed to one or another PM indicator (e.g., PM₁₀, PM_{2.5}, PM_{10-2.5}, etc.) or
comparison of such to gaseous co-pollutant (e.g., O₃, NO₂, SO₂, CO) effect estimates.

24 The simulation studies indicate that the greater the measurement error associated with
25 exposure estimates for a given pollutant or indicator, then the less precise the effect size

1 estimate and the less robust it tends to be in multi-pollutant models. Of importance, directly
2 measured PM_{10} and $PM_{2.5}$ values likely have less measurement error than $PM_{10-2.5}$ values
3 derived by subtracting (differencing) between PM_{10} and $PM_{2.5}$ readings (or city-wide averages
4 of them), especially if obtained from non-collocated PM_{10} and $PM_{2.5}$ monitors at different
5 locations in a given urban area. Also, gaseous pollutant exposure estimates based on hourly or
6 daily measurements at many monitoring sites in an urban area are likely subject to less
7 measurement error than PM_{10} or $PM_{2.5}$ samples obtained on 1-in-6 day monitoring schedules at
8 fewer locations or extrapolated from measures of other PM indicators (e.g. PM_{10} from TSP
9 data) or other types of data (e.g. estimating fine particle or $PM_{2.5}$ levels based on airport
10 visibility via use of light extinction calculations). Importantly, available simulation studies
11 show that “transfer of effects”, wherein the effects of one pollutant (e.g. one or another
12 gaseous copollutant) are inappropriately attributed to another (e.g. PM_{10} or $PM_{2.5}$) in multi-
13 pollutant models, can occur only under very unusual circumstances, e.g. with simultaneously
14 very high positive or negative correlation ($r \geq .90$) between ambient PM indicators and
15 copollutant levels and high negative correlations between their respective measurement errors,
16 conditions not yet reported for real world data sets.

17 (7) Alternative Lag Structures. Different PM size components or particles with different
composition or sources may produce effects by different mechanisms manifested at
different lags, and different preexisting health conditions may lead to different delays
between exposure and effect.

18 Thus, although maximum effect sizes for PM effects have often been reported for 0-1 day
19 lags, evidence is also beginning to suggest that more consideration should be given to lags of
20 several days. It is plausible that effects linked with PM may arise from different responses or
21 PM-associated diseases with different characteristic lags, for example, that cardiovascular
22 responses may arise almost immediately after exposure, within zero or one day lags or even
23 within two hours (Peter et al., 2001a, for myocardial infarction). In contrast, a number of
24 studies on respiratory symptoms have reported finding larger effect estimates with moving
25 average lag models (for example, Mortimer et al., 2001). One would then expect to see
26 different best-fitting lags for different effects, based on potentially different biological
27 mechanisms as well as individual variability in responses. If various health effects are

1 substantiated by toxicological evidence as likely occurring at different lag days, so that the
2 risks for each lag day should be additive, then higher overall risks may exist than are
3 implied by maximum estimates for any given single day lag. In that case, multi-day averages
4 or distributed lag models should be used to project more fully any potential PM-related public
5 health risks..

- 6 (8) Cardiovascular Endpoints. Numerous time series studies indicate that increased
cardiovascular-related mortality and/or morbidity risks are associated with short-term
(≤ 24 -h) exposure to ambient particles (especially PM_{10} and/or $PM_{2.5}$).

7 Cardiovascular mortality risks appear to be increased most strongly (especially for those
8 ≥ 65 yrs. old) with $PM_{2.5}$ and occur within short lag times (0-1 day). Morbidity measures, e.g.,
9 cardiovascular hospital admissions and emergency department visits are also positively (but
10 not as statistically significantly) related to short-term (24-h) $PM_{2.5}$ exposures. Several
11 different panel studies (but not all) that evaluated temporal associations between PM
12 exposures and measures of heart beat rhythm in elderly subjects found results suggestive of
13 ambient PM exposure being associated with changes in electrocardiographic (ECG) markers
14 of cardiac function, e.g., altered heart rate variability (HRV), shown in other studies to be
15 indicators of increased risk for serious cardiovascular outcomes (e.g., heart attacks).
16 However, conflicting implications of the specific alterations in ECG patterns indicative of
17 likely predominance of sympathetic versus parasympathetic cardiac control preclude clear
18 conclusions. Other studies point toward changes in blood characteristics (e.g., alterations in
19 C-reactive protein levels, fibrinogen levels, blood viscosity, etc.) related to increased risk of
20 ischemic heart disease also being associated with ambient PM exposures. However, these
21 heart rhythm and blood chemistry findings should currently be viewed as providing only very
22 limited suggestive evidence indicative of potential pathophysiologic alterations contributing to
23 serious PM-related cardiovascular effects (e.g. myocardial infarction, stroke, death).

- 24 (9) Respiratory Endpoints. Notable new evidence now exists which substantiates positive
associations between ambient PM concentrations and (a) increased respiratory-related
hospital admissions, emergency department, and other medical visits; (b) increased
incidence of asthma and other respiratory symptoms; and (c) decrements in pulmonary
functions.

1 Of much interest are new findings tending to implicate not only fine particle components
2 but also coarse thoracic (e.g., PM_{10-2.5}) particles as likely contributing to exacerbation of
3 various respiratory conditions (e.g., asthma). Also of much interest are emerging new
4 findings indicative of likely increased occurrence of chronic bronchitis in association with
5 (especially chronic) PM exposure. New reanalyses or extensions of earlier prospective cohort
6 studies of long-term ambient PM exposure effects also show substantial evidence for
7 increased lung cancer risk being associated with such PM exposures, especially exposure to
8 fine PM or specific fine particles subcomponents (e.g., sulfates) and/or associated precursors
9 (e.g., SO₂).

10 (10) Spatial Heterogeneity of PM Effects. There appears to be greater spatial heterogeneity
in city-specific excess risk estimates for relationships between short-term ambient PM₁₀
concentrations and acute health effects than was previously evident.

11 The reasons for such variation in effects estimates are not well understood. Factors likely
12 contributing to the apparent heterogeneity include geographic differences in air pollution
13 mixtures, composition of ambient PM components, and personal and sociodemographic
14 factors potentially affecting PM exposure (such as use of air conditioning), as well as
15 differences in PM mass concentration. For example, the Utah Valley studies showed that
16 PM₁₀ particles, known to be richer in metals during exposure periods while the steel mill was
17 operating, were more highly associated with adverse health effects than was PM₁₀ during the
18 PM exposure reduction while the steel mill was closed. In contrast, when PM₁₀ and PM_{2.5}
19 samples were relatively higher in crustal particles during windblown dust episodes in Spokane
20 and at three central Utah sites than at other times, they were not associated with higher total
21 mortality during those periods. These differences require more research that may become
22 more feasible as the PM_{2.5} sampling network produces air quality data related to speciated
23 samples.

24 Certain classes of ambient particles appear to be distinctly less toxic than others and are
25 unlikely to exert human health effects at typical ambient exposure concentrations (or perhaps
26 only under special circumstances). For example, particles of crustal origin, which are
27 predominately in the coarse fraction, are relatively non-toxic under most circumstances,
28 compared to combustion-related particles (such as from coal and oil combustion, wood

1 burning, etc.) However, under some conditions, crustal particles may be sufficiently toxic to
2 cause human health effects. For example, resuspended crustal particles may be contaminated
3 with toxic trace elements and other components from previously deposited fine PM, e.g.,
4 metals from smelters (Phoenix) or steel mills (Steubenville, Utah Valley), PAH's from
5 automobile exhaust, or pesticides from agricultural lands. Fine particles of differing
6 composition from different sources may also vary in toxic potency and in associated health
7 risks. More research is needed to identify conditions under which one or another class of
8 particles may cause little or no adverse health effects, as well as conditions under which
9 particles may cause notable effects.

10 The above reasons suggest that it is inadvisable to pool epidemiology studies involving
11 different locations, different time periods, different population sub-groups, or different health
12 endpoints, without assessing potential causes and the consequences of these differences.
13 However, multi-city analyses using common data bases, measurement devices, analytical
14 strategies, and extensive independent external review (as carried out in the NMMAPS and
15 APHEA studies) are useful. Quantitative meta-analyses of more diverse collections of
16 independent studies of different cities, varying in methodologies used and/or in data quality or
17 representativeness, are likely less credible.

18 (11) Effects of Long-term PM Exposure. Long-term PM exposure durations, on the order of
months to years, are statistically associated with human health effects (indexed by
mortality, development of chronic respiratory disease, and changes in lung function).

19 Notable uncertainties remain regarding the magnitude of and mechanisms underlying
20 chronic health effects of long-term PM exposures and relationships between chronic exposure
21 effects and acute responses to short-term exposures. Prospective cohort studies providing
22 mortality risk estimates likely most representative of the general U.S. population report higher
23 PM effect estimates for mortality associations with chronic long term exposures to PM_{2.5}
24 and/or sulfates than with acute short-term exposures to these fine particle indicators. Also, the
25 most recent extension of the ACS study, more than doubling the original followup time,
26 provides the strongest evidence to date for increased lung cancer mortality risk being
27 significantly associated with long-term fine particle exposures. Studies that combine the
28 features of cross-sectional and cohort studies provide some of the best evidence for non-
29 cancer morbidity effects of chronic PM exposure.

1 (12) Intervention Studies. Certain epidemiology evidence suggests that relatively sharp
2 reductions in ambient PM concentrations may reduce a variety of health effects on a
3 time scale from a few days to a few months.

4 This has been observed in epidemiology studies of “natural or “found experiments,” such
5 as in the Utah Valley, and by supporting toxicology studies using particle extracts from
6 ambient community PM₁₀ sampling filters from the Utah Valley. Another study in Dublin,
7 Ireland also provides evidence for reductions in ambient PM air pollution (measured as British
8 smoke) being associated with reductions in mortality rates. Other “found experiments” also
9 provide evidence for decreases in mortality and/or morbidity being associated with notable
10 declines in PM (and/or gases such as SO₂) as the result of interventions aimed at reducing air
11 pollution.

12 (13) Concentration-Response Functions. The results from large multi-city studies suggest
13 that there is no strong evidence of a clear threshold for PM mortality effects. Some
14 single city studies suggest a hint of a threshold, but not in a statistically clear manner.
15 More data may need to be examined with alternative approaches (e.g., Smith et al.’s
16 parametric model), but meanwhile, the use of a linear PM effect models appears to be
17 appropriate.

18 Certain statistical simulation analyses have shown that increasing measurement error
19 tends to flatten PM concentration-response curves somewhat and to increase uncertainty
20 associated with estimates of potential thresholds (especially under extreme error scenarios).
21 Nevertheless, it has been concluded that if thresholds exist, standard statistical analyses should
22 be able to detect them. Newly available evaluations of the shape of PM-related
23 concentrations-response relationships provide very limited results suggestive of possible
24 threshold(s) for health effects associated with low ambient PM concentrations (e.g., at
25 $\leq 15\text{-}20\ \mu\text{g}/\text{m}^3$ for 24-h PM₁₀ or $\leq 20\text{-}25\ \mu\text{g}/\text{m}^3$ 24-h PM_{2.5} levels). However, formal statistical
26 tests comparing linear (no threshold) models versus various non-linear or threshold models
27 have not shown statistically significant distinctions between them or clear preference of one
28 over the other. Results of analyses of NMMAPS data for the 20 largest U.S. cities, that
29 compared a linear model for PM₁₀, a natural cubic spline model of PM₁₀ with knots at 30 and
30 $60\ \mu\text{g}/\text{m}^3$, and a threshold model with grid search in $5\ \mu\text{g}/\text{m}^3$ increments across 5 to $200\ \mu\text{g}/\text{m}^3$

1 PM₁₀ suggested possible thresholds for daily total or cardiorespiratory mortality at PM₁₀ levels
2 below ~15-20 µg/m³, but essentially zero probability of a threshold above ~25 µg/m³.
3 However, comparing AIC values across the models suggested that the linear (no-threshold)
4 model would be preferred over the others. Other single-city analyses were suggestive of
5 possible threshold change points in Birmingham and Chicago at 80 and ≥ 100 µg/m³ PM₁₀ but
6 not statistically significantly so. In another single-city (Phoenix) study using a piecewise
7 linear model or a B-spline model with 4 knots, some evidence was found to suggest a possible
8 daily total mortality threshold(s) in the range of 20-25 µg/m³ PM_{2.5}, but no evidence was
9 found for threshold(s) for total mortality associations with PM_{10-2.5} (perhaps reflecting greater
10 measurement error for PM_{10-2.5} exposure estimates in the analysis).

- 11 (14) Public Health Implications. Progress has been made in advancing our understanding of
public health implications of PM mortality and morbidity effects, both in terms of
(a) potential life shortening due to PM exposures and (b) a broader array of morbidity
effects shown to be associated with ambient PM exposures.

12 Long-term exposures (on the order of years or decades) to thoracic particles in general
13 and fine-fraction particles in particular appear to be associated with life shortening well
14 beyond that accounted for by the simple accumulation of the more acute “harvesting” of
15 effects of short-term PM exposures (on the order of a few days). Investigations of the public
16 health implications of such long-term PM exposure-mortality effect estimates have been
17 attempted. For example, preliminary life table calculations using risk estimates from long-
18 term PM_{2.5} exposure studies suggest that relatively small differences in long-term exposure to
19 ambient PM can have substantial effects on life expectancy. To illustrate, based on the initial
20 1995 ACS study PM-mortality risk estimates, a U.S. EPA calculation for the 1969-71 life
21 table for U.S. white males projected that a chronic exposure increase of 10 µg/m³ PM_{2.5} could
22 be associated with a reduction of 1.31 years for the entire U.S. population’s life expectancy at
23 age 25. However, such projections must be viewed with caution given their dependence on
24 the specific PM effect-size estimates used in the calculations. The 1.31 year life expectancy
25 reduction estimate, as an example, would need to be recalculated to a lower value based on
26 lower (and presumably more credible) PM mortality risk estimates from the more recent Pope
27 et al. (2002) extension of the ACS study.

1 PM-related health effects in infants and children are emerging as an area of more concern
2 than in the 1996 PM AQCD; and ultimately, such health effects could have very substantial
3 implications for life expectancy calculations. However, only very limited evidence currently
4 exists about potential ambient PM relationships with some of the more serious pertinent health
5 endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital
6 admissions, and mortality in older children). Also, little is yet known about involvement of
7 PM exposure in the progression from less serious childhood conditions, such as asthma and
8 respiratory symptoms, to more serious disease endpoints later in life. This is an important
9 health issue, because childhood illness or death may cost a very large number of productive
10 life-years.

11 Lastly, new epidemiologic studies of a broader array of health endpoints indicate ambient
12 PM associations with increased non-hospital medical visits (physician visits) and asthma
13 effects. Such new findings suggest likely much larger health impacts and costs to society due
14 to ambient PM than just those indexed either by just hospital admissions/visits and/or
15 mortality.

1 REFERENCES

- 2 Abbey, D. E.; Mills, P. K.; Petersen, F. F.; Beeson, W. L. (1991) Long-term ambient concentrations of total
3 suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day
4 Adventists. *Environ. Health Perspect.* 94: 43-50.
- 5 Abbey, D. E.; Lebowitz, M. D.; Mills, P. K.; Petersen, F. F.; Beeson, W. L.; Burchette, R. J. (1995a) Long-term
6 ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of
7 nonsmoking California residents. In: Phalen, R. F.; Bates, D. V., eds. *Proceedings of the colloquium on*
8 *particulate air pollution and human mortality and morbidity*; January 1994; Irvine, CA. *Inhalation Toxicol.*
9 7: 19-34.
- 10 Abbey, D. E.; Ostro, B. E.; Fraser, G.; Vancuren, T.; Burchette, R. J. (1995b) Estimating fine particulates less than
11 2.5 microns in aerodynamic diameter (PM_{2.5}) from airport visibility data in California. *J. Exposure Anal.*
12 *Environ. Epidemiol.* 5: 161-180.
- 13 Abbey, D. E.; Burchette, R. J.; Knutsen, S. F.; McDonnell, W. F.; Lebowitz, M. D.; Enright, P. L. (1998) Long-term
14 particulate and other air pollutants and lung function in nonsmokers. *Am. J. Respir. Crit. Care Med.*
15 158: 289-298.
- 16 Abbey, D. E.; Nishino, N.; McDonnell, W. F.; Burchette, R. J.; Knutsen, S. F.; Beeson, W. L.; Yang, J. X. (1999)
17 Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am. J. Respir. Crit.*
18 *Care Med.* 159: 373-382.
- 19 Ackermann-Liebrich, U.; Leuenberger, P.; Schwartz, J.; Schindler, C.; Monn, C.; Bolognini, B.; Bongard, J. P.;
20 Brändli, O.; Domenighetti, G.; Elsasser, S.; Grize, L.; Karrer, W.; Keller, R.; Keller-Wossidlo, H.; Künzli, N.;
21 Martin, B. W.; Medici, T. C.; Perruchoud, A. P.; Schöni, M. H.; Tschopp, J. M.; Villiger, B.; Wüthrich, B.;
22 Zellweger, J. P.; Zemp, E. (1997) Lung function and long term exposure to air pollutants in Switzerland.
23 *Am. J. Respir. Crit. Care Med.* 155: 122-129.
- 24 Agócs, M. M.; White, M. C.; Ursicz, G.; Olson, D. R.; Vámos, A. (1997) A longitudinal study of ambient air
25 pollutants and the lung peak expiratory flow rates among asthmatic children in Hungary. *Int. J. Epidemiol.*
26 26: 1272-1280.
- 27 Alberdi Odriozola, J. C.; Díaz Jiménez, J.; Montero Rubio, J. C.; Mirón Pérez, I. J.; Pajares Ortíz, M. S.; Ribera
28 Rodrigues, P. (1998) Air pollution and mortality in Madrid, Spain: a time-series analysis. *Int. Arch. Occup.*
29 *Environ. Health* 71: 543-549.
- 30 Anderson, H. R.; Ponce de Leon, A.; Bland, J. M.; Bower, J. S.; Strachan, D. P. (1996) Air pollution and daily
31 mortality in London: 1987-92. *Br. Med. J.* 312: 665-669.
- 32 Anderson, H. R.; Spix, C.; Medina, S.; Schouten, J. P.; Castellsague, J.; Rossi, G.; Zmirou, D.; Touloumi, G.;
33 Wojtyniak, B.; Ponka, A.; Bacharova, L.; Schwartz, J.; Katsouyanni, K. (1997) Air pollution and daily
34 admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project.
35 *Eur. Respir. J.* 10: 1064-1071.
- 36 Anderson, H. R.; Ponce de Leon, A.; Bland, J. M.; Bower, J. S.; Emberlin, J.; Strachen, D. P. (1998) Air pollution,
37 pollens, and daily admissions for asthma in London 1987-92. *Thorax* 53: 842-848.
- 38 Anderson, H. R.; Bremner, S. A.; Atkinson, R. W.; Harrison, R. M.; Walters, S. (2001) Particulate matter and daily
39 mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with
40 fine and coarse particles, black smoke and sulphate. *Occup. Environ. Med.* 58: 504-510.
- 41 Archer, V. E. (1990) Air pollution and fatal lung disease in three Utah counties. *Arch. Environ. Health* 45: 325-334.
- 42 Atkinson, R. W.; Bremner, S. A.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Ponce de Leon, A. (1999a)
43 Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease
44 and outdoor air pollution in London. *Arch. Environ. Health* 54: 398-411.
- 45 Atkinson, R. W.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Bremner, S. A.; Ponce de Leon, A. (1999b)
46 Short-term associations between outdoor air pollution and visits to accident and emergency departments in
47 London for respiratory complaints. *Eur. Respir. J.* 13: 257-265.
- 48 Atkinson, R. W.; Anderson, H. R.; Sunyer, J.; Ayres, J.; Baccini, M.; Vonk, J. M.; Boumghar, A.; Forastiere, F.;
49 Forsberg, B.; Touloumi, G.; Schwartz, J.; Katsouyanni, K. (2001) Acute effects of particulate air pollution on
50 respiratory admissions: results from APHEA 2 project. *Am. J. Respir. Crit. Care Med.* 164: 1860-1866.

- 1 Atkinson, R. W.; Anderson, H. R.; Sunyer, J.; Ayres, J.; Baccini, M.; Vonk, J. M.; Boumghar, A.; Forastiere, F.;
2 Forsberg, B.; Touloumi, G.; Schwartz, J.; Katsouyanni, K. (2003) Acute effects of particulate air pollution on
3 respiratory admissions. In: Revised analyses of time-series studies of air pollution and health. Special report.
4 Boston, MA: Health Effects Institute; pp. 81-84. Available: <http://www.healtheffects.org/news.htm> [16 May,
5 2003].
- 6 Avol, E. L.; Gauderman, W. J.; Tan, S. M.; London, S. J.; Peters, J. M. (2001) Respiratory effects of relocating to
7 areas of differing air pollution levels. *Am. J. Respir. Crit. Care Med.* 164: 2067-2072.
- 8 Awasthi, S.; Glick, H. A.; Fletcher, R. H.; Ahmed, N. (1996) Ambient air pollution & respiratory symptoms
9 complex in preschool children. *Indian J. Med. Res.* 104: 257-262.
- 10 Ayres, J. G. (2002) Chronic effects of air pollution [editorial]. *Occup. Environ. Med.* 59: 147-148.
- 11 Bailey, D. L. R.; Clayton, P. (1982) The measurement of suspended particle and total carbon concentrations in the
12 atmosphere using standard smoke shade methods. *Atmos. Environ.* 16: 2683-2690.
- 13 Baldi, I.; Tessier, J. F.; Kauffmann, F.; Jacqmin-Gadda, H.; Nejjari, C.; Salamon, R. (1999) Prevalence of asthma
14 and mean levels of air pollution: results from the French PAARC survey. *Eur. Respir. J.* 14: 132-138.
- 15 Barbone, F.; Bovenzi, M.; Cavalleri, F.; Stanta, G. (1995) Air pollution and lung cancer in Trieste, Italy. *Am. J.*
16 *Epidemiol.* 141: 1161-1169.
- 17 Barker, D. J. P.; Gluckman, P. D.; Godfrey, K. M.; Harding, J. E.; Owens, J. A.; Robinson, J. S. (1993) Fetal
18 nutrition and cardiovascular disease in adult life. *Lancet* 341: 938-941.
- 19 Basu, R.; Samet, J. M. (1999) A review of the epidemiological evidence on health effects of nitrogen dioxide
20 exposure from gas stoves. *J. Environ. Med.* 1: 173-187.
- 21 Bateson, T. F.; Schwartz, J. (1999) Control for seasonal variation and time trend in case-crossover studies of acute
22 effects of environmental exposures. *Epidemiology* 10: 539-544.
- 23 Bateson, T. F.; Schwartz, J. (2001) Selection bias and confounding in case-crossover analyses of environmental
24 time-series data. *Epidemiology* 12: 654-661.
- 25 Beckett, W. S. (2001) The air pollution detectives. *Am. J. Respir. Crit. Care Med.* 164: 515-516.
- 26 Beeson, W. L.; Abbey, D. E.; Knutsen, S. F. (1998) Long-term concentrations of ambient air pollutants and incident
27 lung cancer in California adults: results from the AHSMOG study. *Environ. Health Perspect.* 106: 813-823.
- 28 Berglund, D. J.; Abbey, D. E.; Lebowitz, M. D.; Knutsen, S. F.; McDonnell, W. F. (1999) Respiratory symptoms
29 and pulmonary function in an elderly nonsmoking population. *Chest* 115: 49-59.
- 30 Berkowitz, G. S.; Papiernik, E. (1993) Epidemiology of preterm birth. *Epidemiol. Rev.* 15: 414-443.
- 31 Beyer, U.; Franke, K.; Cyrus, J.; Peters, A.; Heinrich, J.; Wichmann, H. E.; Brunekreef, B. (1998) Air pollution and
32 respiratory health of children: the PEACE panel study in Hettstedt and Zerbst, Eastern Germany. *Eur. Respir.*
33 *Rev.* 8: 61-69.
- 34 Bobak, M.; Leon, D. A. (1992) Air pollution and infant mortality in the Czech Republic, 1986-1988.
35 *Lancet* (8826): 1010-1014.
- 36 Bobak, M.; Leon, D. A. (1999) Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the
37 Czech Republic 1986-8. *Occup. Environ. Med.* 56: 539-543.
- 38 Bobak, M.; Roberts, A. (1997) Heterogeneity of air pollution effects is related to average temperature [letter].
39 *Br. Med. J.* 315: 1161.
- 40 Boezen, M.; Schouten, J.; Rijcken, B.; Vonk, J.; Gerritsen, J.; Van Der Zee, S.; Hoek, G.; Brunekreef, B.;
41 Postma, D. (1998) Peak expiratory flow variability, bronchial responsiveness, and susceptibility to ambient
42 air pollution in adults. *Am. J. Respir. Crit. Care Med.* 158: 1848-1854.
- 43 Boezen, H. M.; Van Der Zee, S. C.; Postma, D. S.; Vonk, J. M.; Gerritsen, J.; Hoek, G.; Brunekreef, B.; Rijcken, B.;
44 Schouten, J. P. (1999) Effects of ambient air pollution on upper and lower respiratory symptoms and peak
45 expiratory flow in children. *Lancet* 353: 874-878.
- 46 Borja-Aburto, V. H.; Loomis, D. P.; Bangdiwala, S. I.; Shy, C. M.; Rascon-Pacheco, R. A. (1997) Ozone, suspended
47 particulates, and daily mortality in Mexico City. *Am. J. Epidemiol.* 145: 258-268.
- 48 Borja-Aburto, V. H.; Castillejos, M.; Gold, D. R.; Bierzwinski, S.; Loomis, D. (1998) Mortality and ambient fine
49 particles in southwest Mexico City, 1993-1995. *Environ. Health Perspect.* 106: 849-855.
- 50 Braga, A. L. F.; Conceição, G. M. S.; Pereira, L. A. A.; Kishi, H. S.; Pereira, J. C. R.; Andrade, M. F.; Gonçalves,
51 F. L. T.; Saldiva, P. H. N.; Latorre, M. R. D. O. (1999) Air pollution and pediatric respiratory hospital
52 admissions in São Paulo, Brazil. *J. Environ. Med.* 1: 95-102.
- 53 Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2000) Do respiratory epidemics confound the association between air
54 pollution and daily deaths? *Eur. Respir. J.* 16: 723-728.
- 55 Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2001a) The lag structure between particulate air pollution and
56 respiratory and cardiovascular deaths in ten U.S. cities. *J. Occup. Environ. Med.* 43: 927-933.

1 Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2001b) The time course of weather-related deaths. *Epidemiology*
2 12: 662-667.

3 Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2002) The effect of weather on respiratory and cardiovascular deaths in
4 12 U.S. cities. *Environ. Health Perspect.* 110: 859-864.

5 Brauer, M.; Ebelt, S. T.; Fisher, T. V.; Brumm, J.; Petkau, A. J.; Vedal, S. (2001) Exposure of chronic obstructive
6 pulmonary disease patients to particles: respiratory and cardiovascular health effects. *J. Exposure Anal.*
7 *Environ. Epidemiol.* 11: 490-500.

8 Braun-Fahrländer, C.; Vuille, J. C.; Sennhauser, F. H.; Neu, U.; Künzle, T.; Grize, L.; Gassner, M.; Minder, C.;
9 Schindler, C.; Varonier, H. S.; Wüthrich, B.; SCARPOL team. (1997) Respiratory health and long-term
10 exposure to air pollutants in Swiss schoolchildren. *Am. J. Respir. Crit. Care Med.* 155: 1042-1049.

11 Bremner, S. A.; Anderson, H. R.; Atkinson, R. W.; McMichael, A. J.; Strachan, D. P.; Bland, J. M.; Bower, J. S.
12 (1999) Short term associations between outdoor air pollution and mortality in London 1992-4. *Occup.*
13 *Environ. Med.* 56: 237-244.

14 Brook, J. R.; Wiebe, A. H.; Woodhouse, S. A.; Audette, C. V.; Dann, T. F.; Callaghan, S.; Piechowski, M.;
15 Dabek-Zlotorzynska, E.; Dlouhy, J. F. (1997) Temporal and spatial relationships in fine particle strong
16 acidity, sulphate, PM₁₀, and PM_{2.5} across multiple Canadian locations. *Atmos. Environ.* 31: 4223-4236.

17 Brunekreef, B. (1997) Air pollution and life expectancy: is there a relation? *Occup. Environ. Med.* 54: 781-784.

18 Buffler, P. A.; Cooper, S. P.; Stinnett, S.; Contant, C.; Shirts, S.; Hardy, R. J.; Agu, V.; Gehan, B.; Burau, K. (1988)
19 Air pollution and lung cancer mortality in Harris County, Texas, 1979-1981. *Am. J. Epidemiol.* 128: 683-699.

20 Burnett, R. T.; Goldberg, M. S. (2003) Size-fractionated particulate mass and daily mortality in eight Canadian
21 cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA:
22 Health Effects Institute; pp. 85-90. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].

23 Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.;
24 Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of
25 respiratory admissions to Ontario hospitals. *Environ. Res.* 65: 172-194.

26 Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient
27 particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. *Am. J. Epidemiol.*
28 142: 15-22.

29 Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (1997a) The role of particulate size and chemistry in the
30 association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases.
31 *Environ. Health Perspect.* 105: 614-620.

32 Burnett, R. T.; Dales, R. E.; Brook, J. R.; Raizenne, M. E.; Krewski, D. (1997b) Association between ambient
33 carbon monoxide levels and hospitalizations for congestive heart failure in the elderly in 10 Canadian cities.
34 *Epidemiology* 8: 162-167.

35 Burnett, R. T.; Brook, J. R.; Yung, W. T.; Dales, R. E.; Krewski, D. (1997c) Association between ozone and
36 hospitalization for respiratory diseases in 16 Canadian cities. *Environ. Res.* 72: 24-31.

37 Burnett, R. T.; Cakmak, S.; Brook, J. R. (1998a) The effect of the urban ambient air pollution mix on daily mortality
38 rates in 11 Canadian cities. *Can. J. Public Health* 89: 152-156.

39 Burnett, R. T.; Cakmak, S.; Raizenne, M. E.; Stieb, D.; Vincent, R.; Krewski, D.; Brook, J. R.; Philips, O.;
40 Ozkaynak, H. (1998b) The association between ambient carbon monoxide levels and daily mortality in
41 Toronto, Canada. *J. Air Waste Manage. Assoc.* 48: 689-700.

42 Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Cakmak, S.; Brook, J. R. (1999) Effects of particulate and gaseous air
43 pollution on cardiorespiratory hospitalizations. *Arch. Environ. Health* 54: 130-139.

44 Burnett, R. T.; Brook, J.; Dann, T.; Delocla, C.; Philips, O.; Cakmak, S.; Vincent, R.; Goldberg, M. S.; Krewski, D.
45 (2000) Association between particulate- and gas-phase components of urban air pollution and daily mortality
46 in eight Canadian cities. In: Grant, L. D., ed. PM2000: particulate matter and health. *Inhalation Toxicol.*
47 12(suppl. 4): 15-39.

48 Burnett, R.; Ma, R.; Jerrett, M.; Goldberg, M. S.; Cakmak, S.; Pope, C. A., III; Krewski, D. (2001a) The spatial
49 association between community air pollution and mortality: a new method of analyzing correlated geographic
50 cohort data. *Environ. Health Perspect.* 109(suppl. 3): 375-380.

51 Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Raizenne, M. E.; Brook, J. R.; Dales, R. E.; Leech, J. A.; Cakmak, S.;
52 Krewski, D. (2001b) Association between ozone and hospitalization for acute respiratory diseases in children
53 less than 2 years of age. *Am. J. Epidemiol.* 153: 444-452.

54 Cakmak, S.; Burnett, R. T.; Krewski, D. (1999) Methods for detecting and estimating population threshold
55 concentrations for air pollution-related mortality with exposure measurement error. *Risk Anal.* 19: 487-496.

- 1 Calderón-Garcidueñas, L.; Mora-Tiscareño, A.; Chung, C. J.; Valencia, G.; Fordham, L. A.; García, R.; Osnaya, N.;
2 Romero, L.; Acuña, H.; Villarreal-Calderón, A.; Devlin, R. B.; Koren, H. S. (2000) Exposure to air pollution
3 is associated with lung hyperinflation in healthy children and adolescents in southwest Mexico City: a pilot
4 study. *Inhalation Toxicol.* 12: 537-561.
- 5 Carroll, R. J.; Ruppert, D.; Stefanski, L. A. (1995) *Measurement error in nonlinear models*. London, United
6 Kingdom: Chapman & Hall. (Cox, D. R.; Hinkley, D. V.; Keiding, N.; Reid, N.; Rubin, D. B.; Silverman,
7 B. W., eds. *Monographs on statistics and applied probability*: v. 63).
- 8 Carrothers, T. J.; Evans, J. S. (2000) Assessing the impact of differential measurement error on estimates of fine
9 particle mortality. *J. Air Waste Manage. Assoc.* 50: 65-74.
- 10 Cassino, C.; Ito, K.; Bader, I.; Ciotoli, C.; Thurston, G.; Reibman, J. (1999) Cigarette smoking and ozone-associated
11 emergency department use for asthma by adults in New York City. *Am. J. Respir. Crit. Care Med.*
12 159: 1773-1779.
- 13 Castillejos, M.; Borja-Aburto, V. H.; Dockery, D. W.; Gold, D. R.; Loomis, D. (2000) Airborne coarse particles and
14 mortality. In: Phalen, R. F., ed. *Inhalation toxicology: proceedings of the third colloquium on particulate air
15 pollution and human health (first special issue)*; June, 1999; Durham, NC. *Inhalation Toxicol.*
16 12(suppl. 1): 61-72.
- 17 Checkoway, H.; Levy, D.; Sheppard, L.; Kaufman, J.; Koenig, J.; Siscovick, D. (2000) A case-crossover analysis of
18 fine particulate matter air pollution and out-of-hospital sudden cardiac arrest. Cambridge, MA: Health Effects
19 Institute; research report no. 99. Available: <http://www.healtheffects.org/pubs-recent.htm> [19 March, 2001].
- 20 Chen, C.; Chock, D. P.; Winkler, S. L. (1999) A simulation study of confounding in generalized linear models for air
21 pollution epidemiology. *Environ. Health Perspect.* 107: 217-222.
- 22 Chen, L.; Yang, W.; Jennison, B. L.; Omaye, S. T. (2000) Air particulate pollution and hospital admissions for
23 chronic obstructive pulmonary disease in Reno, Nevada. *Inhalation Toxicol.* 12: 281-298.
- 24 Chen, L.; Yang, W.; Jennison, B. L.; Goodrich, A.; Omaye, S. T. (2002) Air pollution and birth weight in northern
25 Nevada, 1991-1999. *Inhalation Toxicol.* 14: 141-157.
- 26 Chew, F. T.; Goh, D. Y. T.; Ooi, B. C.; Saharom, R.; Hui, J. K. S.; Lee, B. W. (1999) Association of ambient
27 air-pollution levels with acute asthma exacerbation among children in Singapore. *Allergy (Copenhagen)*
28 54: 320-329.
- 29 Chock, D. P.; Winkler, S.; Chen, C. (2000) A study of the association between daily mortality and ambient air
30 pollutant concentrations in Pittsburgh, Pennsylvania. *J. Air Waste Manage. Assoc.* 50: 1481-1500.
- 31 Choudhury, A. H.; Gordian, M. E.; Morris, S. S. (1997) Associations between respiratory illness and PM₁₀ air
32 pollution. *Arch. Environ. Health* 52: 113-117.
- 33 Cifuentes, L. A.; Vega, J.; Köpfer, K.; Lave, L. B. (2000) Effect of the fine fraction of particulate matter versus the
34 coarse mass and other pollutants on daily mortality in Santiago, Chile. *J. Air Waste Manage. Assoc.*
35 50: 1287-1298.
- 36 Clancy, L.; Goodman, P.; Sinclair, H.; Dockery, D. W. (2002) Effect of air pollution control on death rates in
37 Dublin, Ireland: an intervention study. *Lancet* 360: 1210-1214.
- 38 Clench-Aas, J.; Bartonova, A.; Skjærnsberg, O. H.; Leegaard, J.; Hagen, L. O.; Giæver, P.; Moseng, J.; Roemer, W.
39 (1998) Air pollution and respiratory health of children: the PEACE study in Oslo, Norway. *Eur. Respir. Rev.*
40 8: 36-43.
- 41 Clyde, M. A.; Guttorp, P.; Sullivan, E. (2000) *Effects of ambient fine and coarse particles on mortality in Phoenix,*
42 *Arizona*. Seattle, WA: University of Washington, National Research Center for Statistics and the
43 Environment; NRCSE technical report series, NRCSE-TRS no. 040. Available:
44 <http://www.nrcse.washington.edu/research/reports.html> [30 May, 2003].
- 45 Cohen, A. J. (2000) Outdoor air pollution and lung cancer. *Environ. Health Perspect.* 108(suppl. 4): 743-750.
- 46 Cohen, A. J.; Pope, C. A., III. (1995) Lung cancer and air pollution. *Environ. Health Perspect.* 103(suppl. 8):
47 219-224.
- 48 Conceição, G. M. S.; Miraglia, S. G. E. K.; Kishi, H. S.; Saldiva, P. H. N.; Singer, J. M. (2001) Air pollution and
49 child mortality: a time-series study in São Paulo, Brazil. *Environ. Health Perspect.* 109(suppl. 3): 347-350.
- 50 Cook, J. R.; Stefanski, L. A. (1994) Simulation-extrapolation estimation in parametric measurement error models.
51 *J. Am. Stat. Assoc.* 89: 1314-1328.
- 52 Coull, B. A.; Schwartz, J.; Wand, M. P. (2001) Respiratory health and air pollution: additive mixed model analyses.
53 *Biostatistics* 2: 337-349.
- 54 Coutant, R. W. (1977) Effect of environmental variables on collection of atmospheric sulfate. *Environ. Sci. Technol.*
55 11: 873-878.

- 1 Creason, J.; Neas, L.; Walsh, D.; Williams, R.; Sheldon, L.; Liao, D.; Shy, C. (2001) Particulate matter and heart
2 rate variability among elderly retirees: the Baltimore 1998 PM study. *J. Exposure Anal. Environ. Epidemiol.*
3 11: 116-122.
- 4 Cropper, M. L.; Simon, N. B.; Alberini, A.; Arora, S.; Sharma, P. K. (1997) The health benefits of air pollution
5 control in Delhi. *Am. J. Agric. Econ.* 79: 1625-1629.
- 6 Cuijpers, C. E. J.; Swaen, G. M. H.; Wesseling, G.; Wouters, E. F. M. (1994) Acute respiratory effects of summer
7 smog in primary school children. *Toxicol. Lett.* 72: 227-235.
- 8 Dab, W.; Medina, S.; Quénel, P.; Le Moullec, Y.; Le Tertre, A.; Thelot, B.; Monteil, C.; Lameloise, P.; Pirard, P.;
9 Momas, I.; Ferry, R.; Festy, B. (1996) Short term respiratory health effects of ambient air pollution: results of
10 the APHEA project in Paris. In: St Leger, S., ed. *The APHEA project. Short term effects of air pollution on*
11 *health: a European approach using epidemiological time series data.* *J. Epidemiol. Community Health*
12 50(suppl. 1): S42-S46.
- 13 Damiá, A. D.; Fabregas, M. L.; Tordera, M. P.; Torrero, L. C. (1999) Effects of air pollution and weather conditions
14 on asthma exacerbation. *Respiration* 66: 52-58.
- 15 Daniels, M.; Dominici, F.; Samet, J. M.; Zeger, S. L. (2000) Estimating particulate matter-mortality dose-response
16 curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. *Am. J. Epidemiol.*
17 152: 397-406.
- 18 Daniels, M. J.; Lee, Y.-D.; Kaiser, M. (2001) Assessing sources of variability in measurement of ambient particulate
19 matter. *Environmetrics* 12: 547-558.
- 20 Dejmek, J.; Selevan, S. G.; Beneš, I.; Solanský, I.; Šrám, R. J. (1999) Fetal growth and maternal exposure to
21 particulate matter during pregnancy. *Environ. Health Perspect.* 107: 475-480.
- 22 Dejmek, J.; Solanský, I.; Beneš, I.; Leníček, J.; Šrám, R. J. (2000) The impact of polycyclic aromatic hydrocarbons
23 and fine particles on pregnancy outcome. *Environ. Health Perspect.* 108: 1159-1164.
- 24 Delfino, R. J.; Coate, B. D.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; Koutrakis, P. (1996) Daily asthma severity in
25 relation to personal ozone exposure and outdoor fungal spores. *Am. J. Respir. Crit. Care Med.* 154: 633-641.
- 26 Delfino, R. J.; Murphy-Moulton, A. M.; Burnett, R. T.; Brook, J. R.; Becklake, M. R. (1997a) Effects of air
27 pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. *Am. J. Respir. Crit. Care*
28 *Med.* 155: 568-576.
- 29 Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; Matteucci, R. M.; Anderson, P. R.; Koutrakis, P. (1997b)
30 The effect of outdoor fungal spore concentrations on daily asthma severity. *Environ. Health Perspect.*
31 105: 622-635.
- 32 Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H. (1998a) Symptoms in pediatric asthmatics and air pollution:
33 differences in effects by symptom severity, anti-inflammatory medication use and particulate averaging time.
34 *Environ. Health Perspect.* 106: 751-761.
- 35 Delfino, R. J.; Murphy-Moulton, A. M.; Becklake, M. R. (1998b) Emergency room visits for respiratory illnesses
36 among the elderly in Montreal: association with low level ozone exposure. *Environ. Res.* 76: 67-77.
- 37 Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; McLaren, C. E. (2002) Association of asthma symptoms
38 with peak particulate air pollution and effect modification by anti-inflammatory medication use. *Environ.*
39 *Health Perspect.* 110: A607-A617.
- 40 Desqueyroux, H.; Pujet, J.-C.; Prosper, M.; Squinazi, F.; Momas, I. (2002) Short-term effects of low-level air
41 pollution on respiratory health of adults suffering from moderate to severe asthma. *Environ. Res. A* 89: 29-37.
- 42 Díaz, J.; García, R.; Ribera, P.; Alberdi, J. C.; Hernández, E.; Pajares, M. S.; Otero, A. (1999) Modeling of air
43 pollution and its relationship with mortality and morbidity in Madrid, Spain. *Int. Arch. Occup. Environ.*
44 *Health* 72: 366-376.
- 45 Divon, M. Y.; Boldes, R.; McGahan, J. P. (1994) Assessment of intrauterine growth retardation. In: McGahan, J. P.;
46 Porto, M., eds. *Diagnostic obstetrical ultrasound.* Philadelphia, PA: J. B. Lippincott; pp. 67-82.
- 47 Dockery, D. W.; Spengler, J. D. (1981) Personal exposure to respirable particulates and sulfates. *J. Air Pollut.*
48 *Control Assoc.* 31: 153-159.
- 49 Dockery, D. W.; Speizer, F. E.; Stram, D. O.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr. (1989) Effects of
50 inhalable particles on respiratory health of children. *Am. Rev. Respir. Dis.* 139: 587-594.
- 51 Dockery, D. W.; Schwartz, J.; Spengler, J. D. (1992) Air pollution and daily mortality: associations with particulates
52 and acid aerosols. *Environ. Res.* 59: 362-373.
- 53 Dockery, D. W.; Pope, C. A., III; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G., Jr.; Speizer, F. E.
54 (1993) An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med.* 329: 1753-1759.

- 1 Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.;
2 Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory
3 symptoms. *Environ. Health Perspect.* 104: 500-505.
- 4 Dockery, D. W.; Pope, C. A., III; Kanner, R. E.; Villegas, G. M.; Schwartz, J. (1999) Daily changes in oxygen
5 saturation and pulse rate associated with particulate air pollution and barometric pressure. Cambridge, MA:
6 Health Effects Institute; research report no. 83.
- 7 Dominici, F.; Samet, J. M.; Zeger, S. (2000a) Combining evidence on air pollution and daily mortality from the
8 largest 20 US cities: a hierarchical modeling strategy. *J. R. Stat. Soc. A* 163: 263-302.
- 9 Dominici, F.; Zeger, S. L.; Samet, J. (2000b) A measurement error model for time-series studies of air pollution and
10 mortality. *Biostatistics* 1: 157-175.
- 11 Dominici, F.; Daniels, M.; Zeger, S. L.; Samet, J. M. (2002) Air pollution and mortality: estimating regional and
12 national dose-response relationships. *J. Am. Stat. Assoc.* 97: 100-111.
- 13 Dominici, F.; Daniels, M.; McDermott, A.; Zeger, S. L.; Samet, J. M. (2003) Shape of the exposure-response
14 relation and mortality displacement in the NMMAPS database. In: Revised analyses of time-series studies of
15 air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 91-96. Available:
16 <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 17 Fairley, D. (1990) The relationship of daily mortality to suspended particulates in Santa Clara county, 1980-86.
18 *Environ. Health Perspect.* 89: 159-168.
- 19 Fairley, D. (1999) Daily mortality and air pollution in Santa Clara County, California: 1989-1996. *Environ. Health*
20 *Perspect.* 107: 637-641.
- 21 Fairley, D. (2003) Mortality and air pollution for Santa Clara County, California, 1989-1996. In: Revised analyses of
22 time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute;
23 pp. 97-106. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 24 Forsberg, B.; Segerstedt, B.; Stjernberg, N.; Roemer, W. (1998) Air pollution and respiratory health of children:
25 the PEACE panel study in Umeå, Sweden. *Eur. Respir. Rev.* 8: 12-19.
- 26 Friedman, M. S.; Powell, K. E.; Hutwagner, L.; Graham, L. M.; Teague, W. G. (2001) Impact of changes in
27 transportation and commuting behaviors during the 1996 summer olympic games in Atlanta on air quality and
28 childhood asthma. *JAMA J. Am. Med. Assoc.* 285: 897-905.
- 29 Frischer, T.; Studnicka, M.; Gartner, C.; Tauber, E.; Horak, F.; Veiter, A.; Spengler, J.; Kühr, J.; Urbanek, R. (1999)
30 Lung function growth and ambient ozone: a three-year population study in school children. *Am. J. Respir.*
31 *Crit. Care Med.* 160: 390-396.
- 32 Fung, K. Y.; Krewski, D. (1999) On measurement error adjustment methods in Poisson regression. *Environmetrics*
33 10: 213-224.
- 34 Fusco, D.; Forastiere, F.; Michelozzi, P.; Spadea, T.; Ostro, B.; Arca, M.; Perucci, C. A. (2001) Air pollution and
35 hospital admissions for respiratory conditions in Rome, Italy. *Eur. Respir. J.* 17: 1143-1150.
- 36 Gamble, J. L. (1998) Effects of ambient air pollution on daily mortality: a time series analysis of Dallas, Texas,
37 1990-1994. Presented at: 91st annual meeting and exhibition of the Air & Waste Management Association;
38 June; San Diego, CA. Pittsburgh, PA: Air & Waste Management Association; paper no. 98-MP26.03.
- 39 Garcia-Aymerich, J.; Tobias, A.; Anto, J. M.; Sunyer, J. (2000) Air pollution and mortality in a cohort of patients
40 with chronic obstructive pulmonary disease: a time series analysis. *J. Epidemiol. Community Health*
41 54: 73-74.
- 42 Garty, B. Z.; Kosman, E.; Ganor, E.; Berger, V.; Garty, L.; Wietzen, T.; Waisman, Y.; Mimouni, M.; Waisel, Y.
43 (1998) Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens.
44 *Ann. Allergy Asthma Immunol.* 81: 563-570.
- 45 Gauderman, W. J.; McConnell, R.; Gilliland, F.; London, S.; Thomas, D.; Avol, E.; Vora, H.; Berhane, K.;
46 Rappaport, E. B.; Lurmann, F.; Margolis, H. G.; Peters, J. (2000) Association between air pollution and lung
47 function growth in southern California children. *Am. J. Respir. Crit. Care Med.* 162: 1383-1390.
- 48 Gauderman, W. J.; Gilliland, G. F.; Vora, H.; Avol, E.; Stram, D.; McConnell, R.; Thomas, D.; Lurmann, F.;
49 Margolis, H. G.; Rappaport, E. B.; Berhane, K.; Peters, J. M. (2002) Association between air pollution and
50 lung function growth in southern California children: results from a second cohort. *Am. J. Respir. Crit. Care*
51 *Med.* 166: 76-84.
- 52 Gauvin, S.; Zmirou, D.; Pin, I.; Quentin, J.; Balducci, F.; Boudet, C.; Poizeau, D.; Brambilla, C. (1999) Short-term
53 effect of exposure to suspended particulate matter (PM10) on the respiratory function of urban asthmatic and
54 control adults. *J. Environ. Med.* 1: 71-79.

- 1 Gehring, U.; Cyrus, J.; Sedlmeir, G.; Brunekreef, B.; Bellander, T.; Fischer, P.; Bauer, C. P.; Reinhardt, D.;
2 Wichmann, H. E.; Heinrich, J. (2002) Traffic-related air pollution and respiratory health during the first 2 yrs.
3 of life. *Eur. Respir. J.* 19: 690-698.
- 4 Gherghinova, M.; Kostyanve, S.; Ivanova, M. (1989) Theoretic values of body plethysmography indices in healthy
5 children between 7 and 14 years of age. *Pediatrics* 28: 52-58.
- 6 Gielen, M. H.; Van Der Zee, S. C.; Van Wijnen, J. H.; Van Steen, C. J.; Brunekreef, B. (1997) Acute effects of
7 summer air pollution on respiratory health of asthmatic children. *Am. J. Respir. Crit. Care Med.*
8 155: 2105-2108.
- 9 Glinianaia, S. V.; Rankin, J.; Bell, R.; Pless-Mulloli, T.; Howel, D. (2004) Particulate air pollution and fetal health:
10 a systematic review of the epidemiologic evidence. *Epidemiology* 15: 36-45.
- 11 Gold, D. R.; Damokosh, A. I.; Pope, C. A., III; Dockery, D. W.; McDonnell, W. F.; Serrano, P.; Retama, A.;
12 Castillejos, M. (1999) Particulate and ozone pollutant effects on the respiratory function of children in
13 southwest Mexico City. *Epidemiology* 10: 8-16.
- 14 Gold, D. R.; Litonjua, A.; Schwartz, J.; Lovett, E.; Larson, A.; Nearing, B.; Allen, G.; Verrier, M.; Cherry, R.;
15 Verrier, R. (2000) Ambient pollution and heart rate variability. *Circulation* 101: 1267-1273.
- 16 Gold, D. R.; Schwartz, J.; Litonjua, A.; Verrier, R.; Zanobetti, A. (2003) Ambient pollution and reduced heart rate
17 variability. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA:
18 Health Effects Institute; pp. 107-112. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 19 Goldberg, M. S.; Burnett, R. T. (2003) Revised analysis of the Montreal time-series study. In: Revised analyses of
20 time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute;
21 pp. 113-132. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 22 Goldberg, M. S.; Bailar, J. C., III; Burnett, R. T.; Brook, J. R.; Tamblyn, R.; Bonvalot, Y.; Ernst, P.; Flegel, K. M.;
23 Singh, R. K.; Valois, M.-F. (2000) Identifying subgroups of the general population that may be susceptible to
24 short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. Cambridge, MA:
25 Health Effects Institute; research report 97. Available: <http://www.healtheffects.org/pubs-research.htm>
26 [15 February, 2001].
- 27 Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Brook, J.; Bonvalot, Y.; Tamblyn, R.; Singh, R.; Valois, M.-F.
28 (2001a) The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 1.
29 Nonaccidental mortality. *Environ. Res.* 86: 12-25.
- 30 Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Brook, J.; Bonvalot, Y.; Tamblyn, R.; Singh, R.; Valois, M.-F.;
31 Vincent, R. (2001b) The association between daily mortality and ambient air particle pollution in Montreal,
32 Quebec. 2. Cause-specific mortality. *Environ. Res.* 86: 26-36.
- 33 Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Tamblyn, R.; Ernst, P.; Flegel, K.; Brook, J.; Bonvalot, Y.;
34 Singh, R.; Valois, M.-F.; Vincent, R. (2001c) Identification of persons with cardiorespiratory conditions who
35 are at risk of dying from the acute effects of ambient air particles. *Environ. Health Perspect.*
36 109(suppl. 4): 487-494.
- 37 Goldberg, M. S.; Burnett, R. T.; Brook, J.; Bailar, J. C., III; Valois, M.-F.; Vincent, R. (2001d) Associations between
38 daily cause-specific mortality and concentrations of ground-level ozone in Montreal, Quebec. *Am. J.*
39 *Epidemiol.* 154: 817-826.
- 40 Goldberg, M. S.; Burnett, R. T.; Valois, M.-F.; Flegel, K.; Bailar, J. C., III; Brook, J.; Vincent, R.; Radon, K. (2003)
41 Associations between ambient air pollution and daily mortality among persons with congestive heart failure.
42 *Environ. Res.* 91: 8-20.
- 43 Gordian, M. E.; Özkaynak, H.; Xue, J.; Morris, S. S.; Spengler, J. D. (1996) Particulate air pollution and respiratory
44 disease in Anchorage, Alaska. *Environ. Health Perspect.* 104: 290-297.
- 45 Gouveia, N.; Fletcher, T. (2000) Respiratory diseases in children and outdoor air pollution in Sao Paulo, Brazil:
46 a time series analysis. *Occup. Environ. Med.* 57: 477-483.
- 47 Grievink, L.; Van der Zee, S. C.; Hoek, G.; Boezen, H. M.; Van't Veer, P.; Brunekreef, B. (1999) Modulation of the
48 acute respiratory effects of winter air pollution by serum and dietary antioxidants: a panel study. *Eur. Respir.*
49 *J.* 13: 1439-1446.
- 50 Gützel, O.; Bollag, U.; Helfenstein, U. (1996) Asthma and exacerbation of chronic bronchitis: sentinel and
51 environmental data in a time series analysis. *Zentralbl. Hyg. Umweltmed.* 198: 383-393.
- 52 Guo, Y. L.; Lin, Y.-C.; Sung, F.-C.; Huang, S.-L.; Ko, Y.-C.; Lai, J.-S.; Su, H.-J.; Shaw, C.-K.; Lin, R.-S.; Dockery,
53 D. W. (1999) Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in
54 Taiwan. *Environ. Health Perspect.* 107: 1001-1006.
- 55 Gwynn, R. C.; Thurston, G. D. (2001) The burden of air pollution: impacts among racial minorities. *Environ. Health*
56 *Perspect.* 109(suppl. 4): 501-506.

- 1 Gwynn, R. C.; Burnett, R. T.; Thurston, G. D. (2000) A time-series analysis of acidic particulate matter and daily
2 mortality and morbidity in the Buffalo, New York, region. *Environ. Health Perspect.* 108: 125-133.
- 3 Hagen, J. A.; Nafstad, P.; Skrondal, A.; Bjørkly, S.; Magnus, P. (2000) Associations between outdoor air pollutants
4 and hospitalization for respiratory diseases. *Epidemiology* 11: 136-140.
- 5 Hajat, S.; Haines, A.; Goubet, S. A.; Atkinson, R. W.; Anderson, H. R. (1999) Association of air pollution with daily
6 GP consultations for asthma and other lower respiratory conditions in London. *Thorax* 54: 597-605.
- 7 Hajat, S.; Haines, A.; Atkinson, R. W.; Bremner, S. A.; Anderson, H. R.; Emberlin, J. (2001) Association between
8 air pollution and daily consultations with general practitioners for allergic rhinitis in London, United
9 Kingdom. *Am. J. Epidemiol.* 153: 704-714.
- 10 Haluszka, J.; Pisiewicz, K.; Miczynski, J.; Roemer, W.; Tomalak, W. (1998) Air pollution and respiratory health in
11 children: the PEACE panel study in Kraków, Poland. *Eur. Respir. Rev.* 8: 94-100.
- 12 Harré, E. S. M.; Price, P. D.; Ayrey, R. B.; Toop, L. J.; Martin, I. R.; Town, G. I. (1997) Respiratory effects of air
13 pollution in chronic obstructive pulmonary disease: a three month prospective study. *Thorax* 52: 1040-1044.
- 14 Harris, R. J. (1975) A primer of multivariate statistics. New York, NY: Academic Press; pp. 155-224.
- 15 Haverkate, F.; Thompson, S. G.; Pyke, S. D. M.; Gallimore, J. R.; Papys, M. B. (1997) Production of C-reactive
16 protein and risk of coronary events in stable and unstable angina. *Lancet* 349: 462-466.
- 17 Health Effects Institute. (2000) Critique. Health Review Committee. In: Checkoway, H.; Levy, D.; Sheppard, L.;
18 Kaufman, J.; Koenig, J.; Siscovick, D. A case-crossover analysis of fine particulate matter air pollution and
19 out-of-hospital sudden cardiac arrest. Cambridge, MA: Health Effects Institute; research report no. 99;
20 pp. 29-32. Available: <http://www.healtheffects.org/pubs-recent.htm> [19 March, 2001].
- 21 Health Effects Institute. (2002) Reanalysis of National Morbidity, Mortality, and Air Pollution Study (NMMAPS)
22 [letter with attachments]. Boston, MA: May 30.
- 23 Health Effects Institute. (2003a) Revised analyses of the National Morbidity, Mortality, and Air Pollution Study
24 (NMMAPS), part II. In: Revised analyses of time-series studies of air pollution and health. Special report.
25 Boston, MA: Health Effects Institute; pp. 9-72. Available: <http://www.healtheffects.org/news.htm>
26 [16 May, 2003].
- 27 Health Effects Institute. (2003b) Revised analyses of time-series studies of air pollution and health. Boston, MA:
28 Health Effects Institute; special report. Available: Available:
29 <http://www.healtheffects.org/Pubs/TimeSeries.pdf> [27 June 2003].
- 30 Health Effects Institute. (2003c) Commentary on revised analyses of selected studies. In: Revised analyses of
31 time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute;
32 pp. 255-290. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 33 Hedley, A. J.; Wong, C.-M.; Thach, T. Q.; Ma, S.; Lam, T.-H.; Anderson, H. R. (2002) Cardiorespiratory and
34 all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *Lancet*
35 360: 1646-1652.
- 36 Hefflin, B. J.; Jalaludin, B.; McClure, E.; Cobb, N.; Johnson, C. A.; Jecha, L.; Etzel, R. A. (1994) Surveillance for
37 dust storms and respiratory diseases in Washington State, 1991. *Arch. Environ. Health* 49: 170-174.
- 38 Heinrich, J.; Hoelscher, B.; Wjst, M.; Ritz, B.; Cyrus, J.; Wichmann, H.-E. (1999) Respiratory diseases and allergies
39 in two polluted areas in East Germany. *Environ. Health Perspect.* 107: 53-62.
- 40 Heinrich, J.; Hoelscher, B.; Wichmann, H. E. (2000) Decline of ambient air pollution and respiratory symptoms in
41 children. *Am. J. Respir. Crit. Care Med.* 161: 1930-1936.
- 42 Heinrich, J.; Hoelscher, B.; Frye, C.; Meyer, I.; Pitz, M.; Cyrus, J.; Wjst, M.; Neas, L.; Wichmann, H.-E. (2002)
43 Improved air quality in reunified Germany and decreases in respiratory symptoms. *Epidemiology*
44 13: 394-401.
- 45 Henderson, B. E.; Gordon, R. J.; Menck, H.; SooHoo, J.; Martin, S. P.; Pike, M. C. (1975) Lung cancer and air
46 pollution in southcentral Los Angeles County. *Am. J. Epidemiol.* 101: 477-488.
- 47 Hill, A. B. (1965) The environment and disease: association or causation? *Proc. R. Soc. Med.* 58: 295-300.
- 48 Hiltermann, T. J. N.; de Bruijne, C. R.; Stolk, J.; Zwinderman, A. H.; Spijksma, F. Th. M.; Roemer, W.;
49 Steerenberg, P. A.; Fischer, P. H.; van Bree, L.; Hiemstra, P. S. (1997) Effects of photochemical air pollution
50 and allergen exposure on upper respiratory tract inflammation in asthmatics. *Am. J. Respir. Crit. Care Med.*
51 156: 1765-1772.
- 52 Hiltermann, T. J. N.; Stolk, J.; Van der Zee, S. C.; Brunekreef, B.; De Bruijne, C. R.; Fischer, P. H.; Ameling, C. B.;
53 Sterk, P. J.; Hiemstra, P. S.; Van Bree, L. (1998) Asthma severity and susceptibility to air pollution. *Eur.*
54 *Respir. J.* 11: 686-693.

- 1 Hoek, G. (2003) Daily mortality and air pollution in The Netherlands. In: Revised analyses of time-series studies of
2 air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 133-142. Available:
3 <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 4 Hoek, G.; Schwartz, J. D.; Groot, B.; Eilers, P. (1997) Effects of ambient particulate matter and ozone on daily
5 mortality in Rotterdam, the Netherlands. *Arch. Environ. Health* 52: 455-463.
- 6 Hoek, G.; Dockery, D. W.; Pope, A.; Neas, L.; Roemer, W.; Brunekreef, B. (1998) Association between PM₁₀ and
7 decrements in peak expiratory flow rates in children: reanalysis of data from five panel studies. *Eur. Respir. J.*
8 11: 1307-1311.
- 9 Hoek, G.; Brunekreef, B.; Verhoeff, A.; van, Wijnen, J.; Fischer, P. (2000) Daily mortality and air pollution in the
10 Netherlands. *J. Air Waste Manage. Assoc.* 50: 1380-1389.
- 11 Hoek, G.; Brunekreef, B.; Fischer, P.; Van Wijnen, J. (2001) The association between air pollution and heart failure,
12 arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study.
13 *Epidemiology* 12: 355-357.
- 14 Hoek, G.; Brunekreef, B.; Goldbohm, S.; Fischer, P.; Van den Brandt, P. A. (2002) Association between mortality
15 and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* 360: 1203-1209.
- 16 Hodgkin, J. E.; Abbey, D. E.; Euler, G. L.; Magie, A. R. (1984) COPD prevalence in nonsmokers in high and low
17 photochemical air pollution areas. *Chest* 86: 830-838.
- 18 Hong, Y.-C.; Leem, J.-H.; Ha, E.-H.; Christiani, D. C. (1999) PM₁₀ exposure, gaseous pollutants, and daily mortality
19 in Inchon, South Korea. *Environ. Health Perspect.* 107: 873-878.
- 20 Horak, F., Jr.; Studnicka, M.; Gartner, C.; Spengler, J. D.; Tauber, E.; Urbanek, R.; Veiter, A.; Frischer, T. (2002)
21 Particulate matter and lung function growth in children: a 3-yr follow-up study in Austrian schoolchildren.
22 *Eur. Respir. J.* 19: 838-845.
- 23 Howel, D.; Darnell, R.; Pless-Mulloli, T. (2001) Children's respiratory health and daily particulate levels in
24 10 nonurban communities. *Environ. Res.* 87: 1-9.
- 25 Ibaldo-Mulli, A.; Stieber, J.; Wichmann, H.-E.; Koenig, W.; Peters, A. (2001) Effects of air pollution on blood
26 pressure: a population-based approach. *Am. J. Public Health* 91: 571-577.
- 27 Ilabaca, M.; Olaeta, I.; Campos, E.; Villaire, J.; Tellez-Rojo, M. M.; Romieu, I. (1999) Association between levels
28 of fine particulate and emergency visits for pneumonia and other respiratory illnesses among children in
29 Santiago, Chile. *J. Air Waste Manage. Assoc.* 49: 154-163.
- 30 Ito, K. (1990) An examination of the role of aerosol acidity in historical London, England daily mortality
31 [dissertation]. Syracuse, NY: New York University. Available from: University Microfilms International,
32 Ann Arbor, MI; AAD91-13012.
- 33 Ito, K. (2003) Associations of particulate matter components with daily mortality and morbidity in Detroit,
34 Michigan. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA:
35 Health Effects Institute; pp. 143-156. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 36 Ito, K.; Kinney, P.; Thurston, G. D. (1995) Variations in PM-10 concentrations within two metropolitan areas and
37 their implications for health effects analyses. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the
38 colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA.
39 *Inhalation Toxicol.* 7: 735-745.
- 40 Ito, K.; Thurston, G. D.; Nádas, A.; Lippmann, M. (2001) Monitor-to-monitor temporal correlation of air pollution
41 and weather variables in the North-Central U.S. *J. Exposure Anal. Environ. Epidemiol.* 11: 21-32.
- 42 Jacobs, J.; Kreutzer, R.; Smith, D. (1997) Rice burning and asthma hospitalizations, Butte County, California,
43 1983-1992. *Environ. Health Perspect.* 105: 980-985.
- 44 Jalaludin, B. B.; Chey, T.; O'Toole, B. I.; Smith, W. T.; Capon, A. G.; Leeder, S. R. (2000) Acute effects of low
45 levels of ambient ozone on peak expiratory flow rate in a cohort of Australian children. *Int. J. Epidemiol.*
46 29: 549-557.
- 47 Jamason, P. F.; Kalkstein, L. S.; Gergen, P. J. (1997) A synoptic evaluation of asthma hospital admissions in
48 New York City. *Am. J. Respir. Crit. Care Med.* 156: 1781-1788.
- 49 Janssen, N. A. H.; Schwartz, J.; Zanobetti, A.; Suh, H. H. (2002) Air conditioning and source-specific particles as
50 modifiers of the effect of PM₁₀ on hospital admissions for heart and lung disease. *Environ. Health Perspect.*
51 110: 43-49.
- 52 Jedrychowski, W.; Flak, E. (1998) Separate and combined effects of the outdoor and indoor air quality on chronic
53 respiratory symptoms adjusted for allergy among preadolescent children. *Int. J. Occup. Med. Environ. Health*
54 11: 19-35.
- 55 Jedrychowski, W.; Becher, H.; Wahrendorf, J.; Basa-Cierpielek, Z. (1990) A case-control study of lung cancer with
56 special reference to the effect of air pollution in Poland. *J. Epidemiol. Commun. Health* 44: 114-120.

- 1 Jedrychowski, W.; Flak, E.; Mróz, E. (1999) The adverse effect of low levels of ambient air pollutants on lung
2 function growth in preadolescent children. *Environ. Health Perspect.* 107: 669-674.
- 3 Joseph, K. S.; Kramer, M. S. (1996) Review of the evidence on fetal and early childhood antecedents of adult
4 chronic disease. *Epidemiol. Rev.* 18: 158-174.
- 5 Just, J.; Ségala, C.; Sahraoui, F.; Priol, G.; Grimfeld, A.; Neukirch, F. (2002) Short-term health effects of particulate
6 and photochemical air pollution in asthmatic children. *Eur. Respir. J.* 20: 899-906.
- 7 Kalandidi, A.; Gratziou, C.; Katsouyanni, K.; Manalis, N.; Tzala, L.; Pantazopoulou, A.; Efthimiou, M.; Roussos,
8 C.; Roemer, W. (1998) Air pollution and respiratory health of children: the PEACE panel study in Athens,
9 Greece. *Eur. Respir. Rev.* 8: 117-124.
- 10 Katsouyanni, K.; Touloumi, G. (1998) Causes of regional differences in air pollution effects are being studied
11 further [letter]. *Br. Med. J.* 316: 1982.
- 12 Katsouyanni, K.; Karakatsani, A.; Messari, I.; Touloumi, G.; Hatzakis, A.; Kalandidi, A.; Trichopoulos, D. (1990)
13 Air pollution and cause specific mortality in Athens. *J. Epidemiol. Community Health* 44: 321-324.
- 14 Katsouyanni, K.; Schwartz, J.; Spix, C.; Touloumi, G.; Zmirou, D.; Zanobetti, A.; Wojtyniak, B.; Vonk, J. M.;
15 Tobias, A.; Pönkä, A.; Medina, S.; Bachárová, L.; Andersen, H. R. (1996) Short term effects of air pollution
16 on health: a European approach using epidemiology time series data: the APHEA protocol. In: St Leger, S.,
17 ed. *The APHEA project. Short term effects of air pollution on health: a European approach using*
18 *epidemiological time series data.* *J. Epidemiol. Community Health* 50(suppl. 1): S12-S18.
- 19 Katsouyanni, K.; Touloumi, G.; Spix, C.; Schwartz, J.; Balducci, F.; Medina, S.; Rossi, G.; Wojtyniak, B.;
20 Sunyer, J.; Bachárová, L.; Schouten, J. P.; Pönkä, A.; Anderson, H. R. (1997) Short term effects of ambient
21 sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from
22 the APHEA project. *Br. Med. J.* 314: 1658-1663.
- 23 Katsouyanni, K.; Touloumi, G.; Samoli, E.; Gryparis, A.; Le Tertre, A.; Monopolis, Y.; Rossi, G.; Zmirou, D.;
24 Ballester, F.; Boumghar, A.; Anderson, H. R.; Wojtyniak, B.; Paldy, A.; Braunstein, R.; Pekkanen, J.;
25 Schindler, C.; Schwartz, J. (2001) Confounding and effect modification in the short-term effects of ambient
26 particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology*
27 12: 521-531.
- 28 Katsouyanni, K.; Touloumi, G.; Samoli, E.; Petasakis, Y.; Analitis, A.; Le Tertre, A.; Rossi, G.; Zmirou, D.;
29 Ballester, F.; Boumghar, A.; Anderson, H. R.; Wojtyniak, B.; Paldy, A.; Braunstein, R.; Pekkanen, J.;
30 Schindler, C.; Schwartz, J. (2003) Sensitivity analysis of various models of short-term effects of ambient
31 particles on total mortality in 29 cities in APHEA2. In: *Revised analyses of time-series studies of air pollution*
32 *and health. Special report.* Boston, MA: Health Effects Institute; pp. 157-164. Available:
33 <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 34 Keatinge, W. R.; Donaldson, G. C. (2001) Mortality related to cold and air pollution in London after allowance for
35 effects of associated weather patterns. *Environ. Res. A* 86: 209-216.
- 36 Keles, N.; Ilicali, Ö. C.; Deger, K. (1999) Impact of air pollution on prevalence of rhinitis in Istanbul. *Arch. Environ.*
37 *Health* 54: 48-51.
- 38 Kelsall, J. E.; Samet, J. M.; Zeger, S. L.; Xu, J. (1997) Air pollution and mortality in Philadelphia, 1974-1988.
39 *Am. J. Epidemiol.* 146: 750-762.
- 40 Kinney, P. L.; Aggarwal, M.; Northridge, M. E.; Janssen, N. A. H.; Shepard, P. (2000) Airborne concentrations of
41 PM_{2.5} and diesel exhaust particles on Harlem sidewalks: a community-based pilot study. *Environ. Health*
42 *Perspect.* 108: 213-218.
- 43 Klemm, R. J.; Mason, R. M., Jr. (2000) Aerosol research and inhalation epidemiological study (ARIES): air quality
44 and daily mortality statistical modeling—interim results. *J. Air. Waste Manage. Assoc.* 50: 1433-1439.
- 45 Klemm, R. J.; Mason, R. (2003) Replication of reanalysis of Harvard Six-City mortality study. In: *Revised analyses*
46 *of time-series studies of air pollution and health. Special report.* Boston, MA: Health Effects Institute;
47 pp. 165-172. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 48 Klemm, R. J.; Mason, R. M., Jr.; Heilig, C. M.; Neas, L. M.; Dockery, D. W. (2000) Is daily mortality associated
49 specifically with fine particles? Data reconstruction and replication of analyses. *J. Air Waste Manage. Assoc.*
50 50: 1215-1222.
- 51 Koenig, J. Q.; Larson, T. V.; Hanley, Q. S.; Rebollo, V.; Dumler, K.; Checkoway, H.; Wang, S.-Z.; Lin, D.;
52 Pierson, W. E. (1993) Pulmonary function changes in children associated with fine particulate matter.
53 *Environ. Res.* 63: 26-38.
- 54 Kontos, A. S.; Fassois, S. D.; Deli, M. F. (1999) Short-term effects of air pollution on childhood respiratory illness
55 in Piraeus, Greece, 1987-1992: nonparametric stochastic dynamic analysis. *Environ. Res.* 81: 275-296.
- 56 Koren, H. S.; Utell, M. J. (1997) Asthma and the environment. *Environ. Health Perspect.* 105: 534-537.

- 1 Korrick, S. A.; Neas, L. M.; Dockery, D. W.; Gold, D. R.; Allen, G. A.; Hill, L. B.; Kimball, K. D.; Rosner, B. A.;
2 Speizer, F. E. (1998) Effects of ozone and other pollutants on the pulmonary function of adult hikers.
3 *Environ. Health Perspect.* 106: 93-99.
- 4 Kostianev, S.; Gerginova, M.; Ivanova, M. (1994) Reference values of lung function parameters in Bulgarian girls
5 aged 7 to 14 years. *Pediatrics* 33: 30-33.
- 6 Kotěšovec, F.; Vitnerova, N.; Leixner, M.; Benes, I.; Skorkovský, J.; Roemer, W. (1998) Air pollution and
7 respiratory health of children: the PEACE panel study in Teplice, Czech Republic. *Eur. Respir. Rev.* 8: 70-77.
- 8 Kotěšovec, F.; Skorkovský, J.; Brynda, J.; Peters, A.; Heinrich, J. (2000) Daily mortality and air pollution in
9 northern Bohemia; different effects for men and women. *Cent. Eur. J. Public Health* 8: 120-127.
- 10 Kramer, M. S. (1987) Intrauterine growth and gestational duration determinants. *Pediatrics* 80: 502-511.
- 11 Krämer, U.; Behrendt, H.; Dolgner, R.; Ranft, U.; Ring, J.; Willer, H.; Schlipkötter, H.-W. (1999) Airway diseases
12 and allergies in East and West German children during the first 5 years after reunification: time trends and the
13 impact of sulphur dioxide and total suspended particles. *Int. J. Epidemiol.* 28: 865-873.
- 14 Krewski, D.; Burnett, R. T.; Goldberg, M. S.; Hoover, K.; Siemiatycki, J.; Jerrett, M.; Abrahamowicz, M.; White,
15 W. H. (2000) Reanalysis of the Harvard Six Cities study and the American Cancer Society study of
16 particulate air pollution and mortality. A special report of the Institute's Particle Epidemiology Reanalysis
17 Project. Cambridge, MA: Health Effects Institute.
- 18 Künzli, N.; Tager, I. B. (1997) The semi-individual study in air pollution epidemiology: a valid design as compared
19 to ecologic studies. *Environ. Health Perspect.* 105: 1078-1083.
- 20 Künzli, N.; Ackermann-Liebrich, U.; Brändli, O.; Tschopp, J. M.; Schindler, C.; Leuenberger, P.; SAPALDIA
21 Team. (2000) Clinically "small" effects of air pollution on FVC have a large public health impact. *Eur.*
22 *Respir. J.* 15: 131-136.
- 23 Kwon, H.-J.; Cho, S.-H.; Nyberg, F.; Pershagen, G. (2001) Effects of ambient air pollution on daily mortality in a
24 cohort of patients with congestive heart failure. *Epidemiology* 12: 413-419.
- 25 Laden, F.; Neas, L. M.; Dockery, D. W.; Schwartz, J. (2000) Association of fine particulate matter from different
26 sources with daily mortality in six U.S. cities. *Environ. Health Perspect.* 108: 941-947.
- 27 Lave, L. B.; Seskin, E. P. (1977) Air pollution and human health. Baltimore, MD: The Johns Hopkins University
28 Press.
- 29 Le Tertre, A.; Medina, S.; Samoli, E.; Forsberg, B.; Michelozzi, P.; Boumghar, A.; Vonk, J. M.; Bellini, A.;
30 Atkinson, R.; Ayres, J. G.; Sunyer, J.; Schwartz, J.; Katsouyanni, K. (2002) Short term effects of particulate
31 air pollution on cardiovascular diseases in eight European cities. *J. Epidemiol. Community Health*
32 56: 773-779.
- 33 Le Tertre, A.; Medina, S.; Samoli, E.; Forsberg, B.; Michelozzi, P.; Boumghar, A.; Vonk, J. M.; Bellini, A.;
34 Atkinson, R.; Ayres, J. G.; Sunyer, J.; Schwartz, J.; Katsouyanni, K. (2003) Short-term effects of particulate
35 air pollution on cardiovascular diseases in eight European cities. In: Revised analyses of time-series studies of
36 air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 173-176. Available:
37 <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 38 Lebowitz, M. D.; Collins, L.; Holberg, C. J. (1987) Time series analyses of respiratory responses to indoor and
39 outdoor environmental phenomena. *Environ. Res.* 43: 332-341.
- 40 Lee, J.-T.; Schwartz, J. (1999) Reanalysis of the effects of air pollution on daily mortality in Seoul, Korea:
41 a case-crossover design. *Environ. Health Perspect.* 107: 633-636.
- 42 Lee, J.-T.; Shy, C. M. (1999) Respiratory function as measured by peak expiratory flow rate and PM₁₀:
43 six communities study. *J. Exposure Anal. Environ. Epidemiol.* 9: 293-299.
- 44 Lee, R. E., Jr.; Caldwell, J. S.; Morgan, G. B. (1972) The evaluation of methods for measuring suspended
45 particulates in air. *Atmos. Environ.* 6: 593-622.
- 46 Lee, J.-T.; Shin, D.; Chung, Y. (1999) Air pollution and daily mortality in Seoul and Ulsan, Korea. *Environ. Health*
47 *Perspect.* 107: 149-154.
- 48 Lee, J.-T.; Kim, H.; Hong, Y.-C.; Kwon, H.-J.; Schwartz, J.; Christiani, D. C. (2000) Air pollution and daily
49 mortality in seven major cities of Korea, 1991-1997. *Environ. Res.* 84: 247-254.
- 50 Leonardi, G. S.; Houthuijs, D.; Steerenberg, P. A.; Fletcher, T.; Armstrong, B.; Antova, T. (2000) Immune
51 biomarkers in relation to exposure to particulate matter: a cross-sectional survey in 17 cities of central
52 Europe. In: Grant, L. D., ed. PM2000: particulate matter and health. *Inhalation Toxicol.* 12(suppl. 4): 1-14.
- 53 Levy, D. (1998) Fine particulate air pollution and out-of-hospital mortality in King County, Washington. In: Vostal,
54 J. J., ed. Health effects of particulate matter in ambient air. Proceedings of an international conference; 1997;
55 Prague, Czech Republic. Pittsburgh, PA: Air & Waste Management Association; pp. 262-271. (A&WMA
56 publication VIP-80).

- 1 Levy, J. I.; Hammitt, J. K.; Spengler, J. D. (2000) Estimating the mortality impacts of particulate matter: what can be
2 learned from between-study variability? *Environ. Health Perspect.* 108: 109-117.
- 3 Levy, D.; Sheppard, L.; Checkoway, H.; Kaufman, J.; Lumley, T.; Koenig, J.; Siscovick, D. (2001) A case-crossover
4 analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. *Epidemiology* 12:
5 193-199.
- 6 Lewis, P. R.; Hensley, M. J.; Wlodarczyk, J.; Toneguzzi, R. C.; Westley-Wise, V. J.; Dunn, T.; Calvert, D. (1998)
7 Outdoor air pollution and children's respiratory symptoms in the steel cities of New South Wales. *Med. J.*
8 *Aust.* 169: 459-463.
- 9 Lewis, S. A.; Corden, J. M.; Forster, G. E.; Newlands, M. (2000) Combined effects of aerobiological pollutants,
10 chemical pollutants and meteorological conditions on asthma admissions and A & E attendances in
11 Derbyshire UK, 1993-96. *Clin. Exp. Allergy* 30: 1724-1732.
- 12 Liao, D.; Creason, J.; Shy, C.; Williams, R.; Watts, R.; Zweidinger, R. (1999) Daily variation of particulate air
13 pollution and poor cardiac autonomic control in the elderly. *Environ. Health Perspect.* 107: 521-525.
- 14 Lin, C. A.; Martins, M. A.; Farhat, S. C. L.; Pope, C. A., III; Conceição, G. M. S.; Anastácio, V. M.; Hatanaka, M.;
15 Andrade, W. C.; Hamaue, W. R.; Böhm, G. M.; Saldiva, P. H. N. (1999) Air pollution and respiratory illness
16 of children in São Paulo, Brazil. *Paediatr. Perinat. Epidemiol.* 13: 475-488.
- 17 Lin, M.; Chen, Y.; Burnett, R. T.; Villeneuve, P. J.; Krewski, D. (2002) The influence of ambient coarse particulate
18 matter on asthma hospitalization in children: case-crossover and time-series analyses. *Environ. Health*
19 *Perspect.* 110: 575-581.
- 20 Linn, W. S.; Shamoo, D. A.; Anderson, K. R.; Peng, R.-C.; Avol, E. L.; Hackney, J. D.; Gong, H., Jr. (1996)
21 Short-term air pollution exposures and responses in Los Angeles area schoolchildren. *J. Exposure Anal.*
22 *Environ. Epidemiol.* 6: 449-472.
- 23 Linn, W. S.; Gong, H., Jr.; Clark, K. W.; Anderson, K. R. (1999) Day-to-day particulate exposures and health
24 changes in Los Angeles area residents with severe lung disease. *J. Air Waste Manage. Assoc.*
25 49: PM108-PM115.
- 26 Linn, W. S.; Szlachcic, Y.; Gong, H., Jr.; Kinney, P. L.; Berhane, K. T. (2000) Air pollution and daily hospital
27 admissions in metropolitan Los Angeles. *Environ. Health Perspect.* 108: 427-434.
- 28 Lipfert, F. W. (2000) The use and misuse of surrogate variables in environmental epidemiology. *J. Environ. Med.*
29 1: 267-278.
- 30 Lipfert, F. W.; Morris, S. C. (2002) Temporal and spacial relationships between age-specific mortality and ambient
31 air quality in the United States: preliminary results for counties, 1960-97. *Occup. Environ. Med.* 59: 156-174.
- 32 Lipfert, F. W.; Wyzga, R. E. (1996) The effects of exposure error on environmental epidemiology. In: Phalen, R. F.;
33 Mannix, R. C.; Tonini, M. C., eds. *The second colloquium on particulate air pollution & human mortality &*
34 *morbidity: report to the California Air Resources Board; May; Park City, UT. Sacramento, CA: State of*
35 *California, Air Resources Board; pp. 4-295--4-302; ARB contract no. 95-323. (University of California Air*
36 *Pollution Health Effects Laboratory report no. 96-02). Available:*
37 *http://www.arb.ca.gov/research/abstracts/95-323.htm#Ch95-323 (24 September 2002).*
- 38 Lipfert, F. W.; Wyzga, R. E. (1997) Air pollution and mortality: the implications of uncertainties in regression
39 modeling and exposure measurement. *J. Air Waste Manage. Assoc.* 47: 517-523.
- 40 Lipfert, F. W.; Morris, S. C.; Wyzga, R. E. (2000a) Daily mortality in the Philadelphia metropolitan area and
41 size-classified particulate matter. *J. Air Waste Manage. Assoc.*: 1501-1513.
- 42 Lipfert, F. W.; Perry, H. M., Jr.; Miller, J. P.; Baty, J. D.; Wyzga, R. E.; Carmody, S. E. (2000b) The Washington
43 University-EPRI veterans' cohort mortality study: preliminary results. In: Grant, L. D., ed. *PM2000:*
44 *particulate matter and health. Inhalation Toxicol.* 12(suppl. 4): 41-73.
- 45 Lipfert, F. W.; Zhang, J.; Wyzga, R. E. (2000c) Infant mortality and air pollution: a comprehensive analysis of U.S.
46 data for 1990. *J. Air Waste Manage. Assoc.* 50: 1350-1366.
- 47 Lipfert, F. W.; Perry, H. M., Jr.; Miller, J. P.; Baty, J. D.; Wyzga, R. E.; Carmody, S. E. (2003) Air pollution, blood
48 pressure, and their long-term associations with mortality. *Inhalation Toxicol.* 15: 493-512.
- 49 Lippmann, M.; Thurston, G. D. (1996) Sulfate concentrations as an indicator of ambient particulate matter air
50 pollution for health risk evaluations. *J. Exposure Anal. Environ. Epidemiol.* 6: 123-146.
- 51 Lippmann, M.; Liroy, P.J.; Leikauf, G.; Green, K.B.; Baxter, D.; Morandi, M.; Pasternack, B.S.; Fife, D.; Speizer,
52 F.E. (1983) Effects of ozone on the pulmonary function of children. In: Lee, S.D.; Mustafa, M.G.; Mehlman,
53 M.A., eds. *International symposium on the biomedical effects of ozone and related photochemical oxidants;*
54 *March 1982; Pinehurst, NC. Princeton, NJ: Princeton Scientific Publishers, Inc.; pp. 423-446. (Advances in*
55 *modern environmental toxicology: v.5).*

- 1 Lippmann, M.; Ito, K.; Nádas, A.; Burnett, R. T. (2000) Association of particulate matter components with daily
2 mortality and morbidity in urban populations. Cambridge, MA: Health Effects Institute; research report no.
3 95.
- 4 Lipsett, M.; Hurley, S.; Ostro, B. (1997) Air pollution and emergency room visits for asthma in Santa Clara County,
5 California. *Environ. Health Perspect.* 105: 216-222.
- 6 Long, W.; Tate, R. B.; Neuman, M.; Manfreda, J.; Becker, A. B.; Anthonisen, N. R. (1998) Respiratory symptoms in
7 a susceptible population due to burning of agricultural residue. *Chest* 113: 351-357.
- 8 Loomis, D.; Castillejos, M.; Gold, D. R.; McDonnell, W.; Borja-Aburto, V. H. (1999) Air pollution and infant
9 mortality in Mexico City. *Epidemiology* 10: 118-123.
- 10 Lumley, T.; Heagerty, P. (1999) Weighted empirical adaptive variance estimators for correlated data regression.
11 *J. R. Stat. Soc. B* 61(part 2): 459-477.
- 12 Lumley, T.; Sheppard, L. (2000) Assessing seasonal confounding and model selection bias in air pollution
13 epidemiology using positive and negative control analyses. *Environmetrics* 11: 705-717.
- 14 Magari, S. R.; Hauser, R.; Schwartz, J.; Williams, P. L.; Smith, T. J.; Christiani, D. C. (2001) Association of heart
15 rate variability with occupational and environmental exposure to particulate air pollution. *Circulation*
16 104: 986-991.
- 17 Magari, S. R.; Schwartz, J.; Williams, P. L.; Hauser, R.; Smith, T. J.; Christiani, D. C. (2002) The association
18 between personal measurements of environmental exposure to particulates and heart rate variability.
19 *Epidemiology* 13: 305-310.
- 20 Mage, D.; Wilson, W.; Hasselblad, V.; Grant, L. (1999) Assessment of human exposure to ambient particulate
21 matter. *J. Air Waste Manage. Assoc.* 49: 174-185.
- 22 Maisonet, M.; Bush, T. J.; Correa, A.; Jaakkola, J. J. K. (2001) Relation between ambient air pollution and low birth
23 weight in the northeastern United States. *Environ. Health Perspect.* 109(suppl. 3): 351-356.
- 24 Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in
25 Phoenix, 1995-1997. *Environ. Health Perspect.* 108: 347-353.
- 26 Mar, T. F.; Norris, G. A.; Larson, T. V.; Wilson, W. E.; Koenig, J. Q. (2003) Air pollution and cardiovascular
27 mortality in Phoenix, 1995-1997. In: Revised analyses of time-series studies of air pollution and health.
28 Special report. Boston, MA: Health Effects Institute; pp. 177-182. Available:
29 <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 30 Marcus, A. H.; Chapman, R. (1998) Estimating the health effects of fine particles from epidemiology studies: how
31 serious are problems of measurement error, correlation, and confounding? In: Chow, J.; Koutrakis, P., eds.
32 *PM_{2.5}: a fine particle standard. Volume II: proceedings of an international specialty conference.*; January;
33 Long Beach, CA. Pittsburgh, PA: Air & Waste Management Association; pp. 899-919.
- 34 McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Vora, H.; Avol, E.; Gauderman, W. J.; Margolis, H. G.;
35 Lurmann, F.; Thomas, D. C.; Peters, J. M. (1999) Air pollution and bronchitic symptoms in southern
36 California children with asthma. *Environ. Health Perspect.* 107: 757-760.
- 37 McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Islam, T.; Gauderman, W. J.; Avol, E.; Margolis, H. G.;
38 Peters, J. M. (2002) Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 359: 386-391.
- 39 McDonnell, W. F.; Nishino-Ishikawa, N.; Petersen, F. F.; Chen, L. H.; Abbey, D. E. (2000) Relationships of
40 mortality with the fine and coarse fractions of long-term ambient PM₁₀ concentrations in nonsmokers.
41 *J. Exposure Anal. Environ. Epidemiol.* 10: 427-436.
- 42 McGregor, G. R.; Walters, S.; Wordley, J. (1999) Daily hospital respiratory admissions and winter air mass types,
43 Birmingham, UK. *Int. J. Biometeorol.* 43: 21-30.
- 44 McMahan, B.; Pugh, T. F. (1970) *Epidemiology: principles and methods.* Boston, MA: Little, Brown and Company.
- 45 Medina, S.; Le Tertre, A.; Quénel, P.; Le Moullec, Y.; Lameloise, P.; Guzzo, J. C.; Festy, B.; Ferry, R.; Dab, W.
46 (1997) Air pollution and doctors' house calls: results from the ERPURS system for monitoring the effects of
47 air pollution on public health in greater Paris, France, 1991-1995. *Environ. Res.* 75: 73-84.
- 48 Metzger, K. B.; Tolbert, P. E.; Klein, M.; Peel, J. L.; Flanders, W. D.; Todd, K. H.; Mulholland, J. A.; Ryan, P. B.;
49 Frumkin, H. (2004) Ambient air pollution and cardiovascular emergency department visits. *Epidemiology*
50 15: 46-56.
- 51 Michelozzi, P.; Forastiere, F.; Fusco, D.; Perucci, C. A.; Ostro, B.; Ancona, C.; Pallotti, G. (1998) Air pollution and
52 daily mortality in Rome, Italy. *Occup. Environ. Med.* 55: 605-610.
- 53 Miller, J. P.; Perry, H. M., Jr.; Rossiter, J. E.; Baty, J. D.; Carmody, S. E.; Sambhi, M. P. (1994) Regional
54 differences in mortality during 15-year follow-up of 11,936 hypertensive veterans. *Hypertension* 23: 431-438.
- 55 Mills, P. K.; Abbey, D.; Beeson, W. L.; Petersen, F. (1991) Ambient air pollution and cancer in California
56 Seventh-day Adventists. *Arch. Environ. Health* 46: 271-280.

- 1 Monn, C. (2001) Exposure assessment of air pollutants: a review on spatial heterogeneity and
2 indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. *Atmos.*
3 *Environ.* 35: 1-32.
- 4 Monn, Ch.; Carabias, V.; Junker, M.; Waeber, R.; Karrer, M.; Wanner, H. U. (1997) Small-scale spatial variability
5 of particulate matter <10 μm (PM_{10}) and nitrogen dioxide. *Atmos. Environ.* 31: 2243-2247.
- 6 Moolgavkar, S. H. (2000a) Air Pollution and Mortality in Three U.S. Counties. *Environ. Health Perspect.*
7 108: 777-784.
- 8 Moolgavkar, S. H. (2000b) Air pollution and hospital admissions for diseases of the circulatory system in three U.S.
9 metropolitan areas. *J. Air Waste Manage Assoc.* 50: 1199-1206.
- 10 Moolgavkar, S. H. (2000c) Air pollution and hospital admissions for chronic obstructive pulmonary disease in three
11 metropolitan areas in the United States. In: Grant, L. D., ed. *PM2000: particulate matter and health. Inhalation*
12 *Toxicol.* 12(suppl. 4): 75-90.
- 13 Moolgavkar, S. H. (2003) Air pollution and daily deaths and hospital admissions in Los Angeles and Cook counties.
14 In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health
15 Effects Institute; pp. 183-198. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 16 Moolgavkar, S. H.; Luebeck, E. G. (1996) A critical review of the evidence on particulate air pollution and
17 mortality. *Epidemiology* 7: 420-428.
- 18 Moolgavkar, S. H.; Luebeck, E. G.; Anderson, E. L. (1997) Air pollution and hospital admissions for respiratory
19 causes in Minneapolis-St. Paul and Birmingham. *Epidemiology* 8: 364-370.
- 20 Moolgavkar, S. H.; Hazelton, W.; Luebeck, G.; Levy, D.; Sheppard, L. (2000) Air pollution, pollens, and admissions
21 for chronic respiratory disease in King County, Washington. In: *Inhalation toxicology: proceedings of the*
22 *third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicol.*
23 12(suppl. 1): 157-171.
- 24 Morgan, G.; Corbett, S.; Wlodarczyk, J.; Lewis, P. (1998) Air pollution and daily mortality in Sydney, Australia,
25 1989 through 1993. *Am. J. Public Health* 88: 759-764.
- 26 Morris, R. D. (2001) Airborne particulates and hospital admissions for cardiovascular disease: a quantitative review
27 of the evidence. *Environ. Health Perspect.* 109(suppl. 4): 495-500.
- 28 Morris, R. D.; Naumova, E. N. (1998) Carbon monoxide and hospital admissions for congestive heart failure:
29 evidence of an increased effect at low temperatures. *Environ. Health Perspect.* 106: 649-653.
- 30 Morris, R. D.; Naumova, E. N.; Munasinghe, R. L. (1995) Ambient air pollution and hospitalization for congestive
31 heart failure among elderly people in seven large US cities. *Am. J. Public Health* 85: 1361-1365.
- 32 Mortimer, K. M.; Neas, L. M.; Dockery, D. W.; Redline, S.; Tager, I. B. (2002) The effect of air pollution on
33 inner-city children with asthma. *Eur. Respir. J.* 19: 699-705.
- 34 Murray, C. J.; Nelson, C. R. (2000) State-space modeling of the relationship between air quality and mortality. *J. Air*
35 *Waste Manage. Assoc.* 50: 1075-1080.
- 36 Naeher, L. P.; Holford, T. R.; Beckett, W. S.; Belanger, K.; Triche, E. W.; Bracken, M. B.; Leaderer, B. P. (1999)
37 Healthy women's PEF variations with ambient summer concentrations of PM_{10} , $\text{PM}_{2.5}$, SO_4^{2-} , H^+ , and O_3 .
38 *Am. J. Respir. Crit. Care Med.* 160: 117-125.
- 39 Nauenberg, E.; Basu, K. (1999) Effect of insurance coverage on the relationship between asthma hospitalizations
40 and exposure to air pollution. *Public Health Rep.* 114: 135-148.
- 41 Neas, L. M.; Dockery, D. W.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr.; Speizer, F. E. (1994) Concentration of
42 indoor particulate matter as a determinant of respiratory health in children. *Am. J. Epidemiol.*
43 139: 1088-1099.
- 44 Neas, L. M.; Dockery, D. W.; Koutrakis, P.; Tollerud, D. J.; Speizer, F. E. (1995) The association of ambient air
45 pollution with twice daily peak expiratory flow rate measurements in children. *Am. J. Epidemiol.*
46 141: 111-122.
- 47 Neas, L. M.; Dockery, D. W.; Burge, H.; Koutrakis, P.; Speizer, F. E. (1996) Fungus spores, air pollutants, and other
48 determinants of peak expiratory flow rate in children. *Am. J. Epidemiol.* 143: 797-807.
- 49 Neas, L. M.; Schwartz, J.; Dockery, D. (1999) A case-crossover analysis of air pollution and mortality in
50 Philadelphia. *Environ. Health Perspect.* 107: 629-631.
- 51 Neukirch, F.; Ségala, C.; Le Moullec, Y.; Korobaef, M.; Aubier, M. (1998) Short-term effects of low-level winter
52 pollution on respiratory health of asthmatic adults. *Arch. Environ. Health* 53: 320-328.
- 53 Norris, G.; Young-Pong, S. N.; Koenig, J. Q.; Larson, T. V.; Sheppard, L.; Stout, J. W. (1999) An association
54 between fine particles and asthma emergency department visits for children in Seattle. *Environ. Health*
55 *Perspect.* 107: 489-493.

- 1 Norris, G.; Larson, T.; Koenig, J.; Claiborn, C.; Sheppard, L.; Finn, D. (2000) Asthma aggravation, combustion, and
2 stagnant air. *Thorax* 55: 466-470.
- 3 Nyberg, F.; Gustavsson, P.; Järup, L.; Bellander, T.; Berglind, N.; Jakobsson, R.; Pershagen, G. (2000) Urban air
4 pollution and lung cancer in Stockholm. *Epidemiology* 11: 487-495.
- 5 Ostro, B. (1995) Fine particulate air pollution and mortality in two Southern California counties. *Environ. Res.*
6 70: 98-104.
- 7 Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols.
8 *Am. J. Public Health* 81: 694-702.
- 9 Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma
10 exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds.
11 Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II;
12 January 1994; Irvine, CA. *Inhalation Toxicol.* 7: 711-722.
- 13 Ostro, B.; Chestnut, L.; Vichit-Vadakan, N.; Laixuthai, A. (1998) The impact of fine particulate matter in Bangkok,
14 Thailand. In: Chow, J.; Koutrakis, P., eds. *PM2.5: a fine particle standard. Volume II: proceedings of an*
15 *international specialty conference; January; Long Beach, CA. Pittsburgh, PA: Air & Waste Management*
16 *Association; pp. 939-949. (A&WMA publication VIP-81).*
- 17 Ostro, B. D.; Hurley, S.; Lipsett, M. J. (1999a) Air pollution and daily mortality in the Coachella Valley, California:
18 a study of PM₁₀ dominated by coarse particles. *Environ. Res.* 81: 231-238.
- 19 Ostro, B. D.; Eskeland, G. S.; Sanchez, J. M.; Feyzioglu, T. (1999b) Air pollution and health effects: a study of
20 medical visits among children in Santiago, Chile. *Environ. Health Perspect.* 107: 69-73.
- 21 Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2000) Coarse and fine particles and daily mortality in the Coachella
22 Valley, CA: a follow-up study. *J. Exposure Anal. Environ. Epidemiol.* 10: 412-419.
- 23 Ostro, B.; Lipsett, M.; Mann, J.; Braxton-Owens, H.; White, M. (2001) Air pollution and exacerbation of asthma in
24 African-American children in Los Angeles. *Epidemiology* 12: 200-208.
- 25 Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2003) Coarse particles and daily mortality in Coachella Valley,
26 California. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA:
27 Health Effects Institute; pp. 199-204. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 28 Osunsanya, T.; Prescott, G.; Seaton, A. (2001) Acute respiratory effects of particles: mass or number? *Occup.*
29 *Environ. Med.* 58: 154-159.
- 30 Ott, W.; Wallace, L.; Mage, D. (2000) Predicting particulate (PM₁₀) personal exposure distributions using a random
31 component superposition statistical model. *J. Air Waste Manage. Assoc.* 50: 1390-1406.
- 32 Pantazopoulou, A.; Katsouyanni, K.; Kourea-Kremastinou, J.; Trichopoulos, D. (1995) Short-term effects of air
33 pollution on hospital emergency outpatient visits and admissions in the greater Athens, Greece area. *Environ.*
34 *Res.* 69: 31-36.
- 35 Pekkanen, J.; Timonen, K. L.; Ruuskanen, J.; Reponen, A.; Mirme, A. (1997) Effects of ultrafine and fine particles
36 in urban air on peak expiratory flow among children with asthmatic symptoms. *Environ. Res.* 74: 24-33.
- 37 Pekkanen, J.; Brunner, E. J.; Anderson, H. R.; Tiittanen, P.; Atkinson, R. W. (2000) Daily concentrations of air
38 pollution and plasma fibrinogen in London. *Occup. Environ. Med.* 57: 818-822.
- 39 Penttinen, P.; Timonen, K. L.; Tiittanen, P.; Mirme, A.; Ruuskanen, J.; Pekkanen, J. (2001) Number concentration
40 and size of particles in urban air: effects on spirometric lung function in adult asthmatic subjects. *Environ.*
41 *Health Perspect.* 109: 319-323.
- 42 Pereira, L. A. A.; Loomis, D.; Conceição, G. M. S.; Braga, A. L. F.; Arcas, R. M.; Kishi, H. S.; Singer, J. M.; Böhm,
43 G. M.; Saldiva, P. H. N. (1998) Association between air pollution and intrauterine mortality in São Paulo,
44 Brazil. *Environ. Health Perspect.* 106: 325-329.
- 45 Perry, H. M., Jr.; Schnaper, H. W.; Meyer, G.; Swatzell, R. (1982) Clinical program for screening and treatment of
46 hypertension in veterans. *J. Natl. Med. Assoc.* 74: 433-444.
- 47 Peters, A.; Goldstein, I. F.; Beyer, U.; Franke, K.; Heinrich, J.; Dockery, D. W.; Spengler, J. D.; Wichmann, H.-E.
48 (1996) Acute health effects of exposure to high levels of air pollution in eastern Europe. *Am. J. Epidemiol.*
49 144: 570-581.
- 50 Peters, A.; Doring, A.; Wichmann, H.-E.; Koenig, W. (1997a) Increased plasma viscosity during an air pollution
51 episode: a link to mortality? *Lancet* 349: 1582-1587.
- 52 Peters, A.; Wichmann, H. E.; Tuch, T.; Heinrich, J.; Heyder, J. (1997b) Respiratory effects are associated with the
53 number of ultrafine particles. *Am. J. Respir. Crit. Care Med.* 155: 1376-1383.
- 54 Peters, A.; Dockery, D. W.; Heinrich, J.; Wichmann, H. E. (1997c) Short-term effects of particulate air pollution on
55 respiratory morbidity in asthmatic children. *Eur. Respir. J.* 10: 872-879.

- 1 Peters, A.; Kotesovec, F.; Skorkovsky, J.; Brynda, J.; Heinrich, J. (1999a) Akute Auswirkung der
2 Schwebstaubkonzentrationen in der Außenluft auf die Mortalität - Vergleichsstudie Nordost-Bayern /
3 Nordböhmen. Abschlußbericht [Acute effects of suspended particle concentrations in the atmosphere on
4 mortality - a study comparing northeast Bavaria and north Bohemia. Final report]. Bavaria, Federal Republic
5 of Germany: Institut für Epidemiologie; report no. GSF-EP S 1/99.
- 6 Peters, J. M.; Avol, E.; Navidi, W.; London, S. J.; Gauderman, W. J.; Lurmann, F.; Linn, W. S.; Margolis, H.;
7 Rappaport, E.; Gong, H., Jr.; Thomas, D. C. (1999b) A study of twelve southern California communities with
8 differing levels and types of air pollution. I. Prevalence of respiratory morbidity. *Am. J. Respir. Crit. Care*
9 *Med.* 159: 760-767.
- 10 Peters, J. M.; Avol, E.; Gauderman, W. J.; Linn, W. S.; Navidi, W.; London, S. J.; Margolis, H.; Rappaport, E.;
11 Vora, H.; Gong, H., Jr.; Thomas, D. C. (1999c) A study of twelve southern California communities with
12 differing levels and types of air pollution. II. Effects on pulmonary function. *Am. J. Respir. Crit. Care Med.*
13 159: 768-775.
- 14 Peters, A.; Liu, E.; Verrier, R. L.; Schwartz, J.; Gold, D. R.; Mittleman, M.; Baliff, J.; Oh, J. A.; Allen, G.;
15 Monahan, K.; Dockery, D. W. (2000a) Air pollution and incidence of cardiac arrhythmia. *Epidemiology*
16 11: 11-17.
- 17 Peters, A.; Skorkovsky, J.; Kotesovec, F.; Brynda, J.; Spix, C.; Wichmann, H. E.; Heinrich, J. (2000b) Associations
18 between mortality and air pollution in central Europe. *Environ. Health Perspect.* 108: 283-287.
- 19 Peters, A.; Dockery, D. W.; Muller, J. E.; Mittleman, M. A. (2001a) Increased particulate air pollution and the
20 triggering of myocardial infarction. *Circulation* 103: 2810-2815.
- 21 Peters, A.; Fröhlich, M.; Döring, A.; Immervoll, T.; Wichmann, H.-E.; Hutchinson, W. L.; Pepys, M. B.; Koenig, W.
22 (2001b) Particulate air pollution is associated with an acute phase response in men: results from the
23 MONICA-Augsburg Study. *Eur. Heart J.* 22: 1198-1204.
- 24 Petroschevsky, A.; Simpson, R. W.; Thalib, L.; Rutherford, S. (2001) Associations between outdoor air pollution
25 and hospital admissions in Brisbane, Australia. *Arch. Environ. Health* 56: 37-52.
- 26 Pike, M. C.; Jing, J. S.; Rosario, I. P.; Henderson, B. E.; Menck, H. R. (1979) Occupation: "explanation" of an
27 apparent air pollution related localized excess of lung cancer in Los Angeles County. In: Breslow, N. E.;
28 Whitmore, A. S., eds. *Energy and Health: proceedings of a conference sponsored by Siam Institute for*
29 *Mathematics and Society; 1978; Alta, Utah. [SIAM-SIMS conference series 6].*
- 30 Pless-Mullooli, T.; Howel, D.; King, A.; Stone, I.; Merefield, J.; Bessell, J.; Darnell, R. (2000) Living near opencast
31 coal mining sites and children's respiratory health. *Occup. Environ. Med.* 57: 145-151.
- 32 Ponce de Leon, A.; Anderson, H. R.; Bland, J. M.; Strachan, D. P.; Bower, J. (1996) Effects of air pollution on daily
33 hospital admissions for respiratory disease in London between 1987-88 and 1991-92. In: St Leger, S., ed.
34 *The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological*
35 *time series data. J. Epidemiol. Community Health* 50(suppl. 1): S63-S70.
- 36 Pönkä, A.; Savela, M.; Virtanen, M. (1998) Mortality and air pollution in Helsinki. *Arch. Environ. Health*
37 53: 281-286.
- 38 Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley.
39 *Am. J. Public Health* 79: 623-628.
- 40 Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM₁₀ pollution in Utah, Salt Lake, and
41 Cache Valleys. *Arch. Environ. Health* 46: 90-97.
- 42 Pope, C. A., III; Kalkstein, L. S. (1996) Synoptic weather modeling and estimates of the exposure-response
43 relationship between daily mortality and particulate air pollution. *Environ. Health Perspect.* 104: 414-420.
- 44 Pope, C. A., III; Dockery, D. W.; Spengler, J. D.; Raizenne, M. E. (1991) Respiratory health and PM₁₀ pollution:
45 a daily time series analysis. *Am. Rev. Respir. Dis.* 144: 668-674.
- 46 Pope, C. A., III; Schwartz, J.; Ransom, M. R. (1992) Daily mortality and PM₁₀ pollution in Utah valley.
47 *Arch. Environ. Health* 47: 211-217.
- 48 Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr.
49 (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am. J. Respir.*
50 *Crit. Care Med.* 151: 669-674.
- 51 Pope, C. A., III; Hill, R. W.; Villegas, G. M. (1999a) Particulate air pollution and daily mortality on Utah's Wasatch
52 Front. *Environ. Health Perspect.* 107: 567-573.
- 53 Pope, C. A., III; Dockery, D. W.; Kanner, R. E.; Vollegas, G. M.; Schwartz, J. (1999b) Oxygen saturation, pulse
54 rate, and particulate air pollution: a daily time-series panel study. *Am. J. Respir. Crit. Care Med.*
55 159: 365-372.

- 1 Pope, C. A., III; Verrier, R. L.; Lovett, E. G.; Larson, A. C.; Raizenne, M. E.; Kanner, R. E.; Schwartz, J.; Villegas,
2 G. M.; Gold, D. R.; Dockery, D. W. (1999c) Heart rate variability associated with particulate air pollution.
3 *Am. Heart J.* 138: 890-899.
- 4 Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. (2002) Lung cancer,
5 cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA J. Am. Med.*
6 *Assoc.* 287: 1132-1141.
- 7 Prescott, G. J.; Cohen, G. R.; Elton, R. A.; Fowkes, F. G. R.; Agius, R. M. (1998) Urban air pollution and
8 cardiopulmonary ill health: a 14.5 year time series study. *Occup. Environ. Med.* 55: 697-704.
- 9 Prescott, G. J.; Lee, R. J.; Cohen, G. R.; Elton, R. A.; Lee, A. J.; Fowkes, F. G. R.; Agius, R. M. (2000)
10 Investigation of factors which might indicate susceptibility to particulate air pollution. *Occup. Environ. Med.*
11 57: 53-57.
- 12 Qian, Z. Chapman, R. S.; Tian, Q.; Chen, Y.; Liyo, P. J.; Zhang, J. (2000) Effects of air pollution on children's
13 respiratory health in three Chinese cities. *Arch. Environ. Health* 55: 126-133.
- 14 Rahlenbeck, S. I.; Kahl, H. (1996) Air pollution and mortality in East Berlin during the winters of 1981-1989. *Int. J.*
15 *Epidemiol.* 25: 1220-1226.
- 16 Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer,
17 F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. *Environ. Health*
18 *Perspect.* 104: 506-514.
- 19 Ritz, B.; Yu, F.; Chapa, G.; Fruin, S. (2000) Effect of air pollution on preterm birth among children born in
20 Southern California between 1989 and 1993. *Epidemiology* 11: 502-511.
- 21 Roemer, W. H.; Van Wijnen, J. H. (2001) Daily mortality and air pollution along busy streets in Amsterdam,
22 1987-1998. *Epidemiology* 12: 649-653.
- 23 Roemer, W.; Hoek, G.; Brunekreef, B. (1993) Effect of ambient winter air pollution on respiratory health of children
24 with chronic respiratory symptoms. *Am. Rev. Respir. Dis.* 147: 118-124.
- 25 Roemer, W.; Hoek, G.; Brunekreef, B.; Haluszka, J.; Kalandidi, A.; Pekkanen, J. (1998) Daily variations in air
26 pollution and respiratory health in a multicentre study: the PEACE project. *Eur. Respir. J.* 12: 1354-1361.
- 27 Roemer, W.; Hoek, G.; Brunekreef, B.; Clench-Aas, J.; Forsberg, B.; Pekkanen, J.; Schutz, A. (2000) PM₁₀
28 elemental composition and acute respiratory health effects in European children (PEACE project). *Eur.*
29 *Respir. J.* 15: 553-559.
- 30 Rogers, J. F.; Thompson, S. J.; Addy, C. L.; McKeown, R. E.; Cowen, D. J.; Decouflé, P. (2000) Association of very
31 low birth weight with exposures to environmental sulfur dioxide and total suspended particulates. *Am. J.*
32 *Epidemiol.* 151: 602-613.
- 33 Romieu, I.; Meneses, F.; Ruiz, S.; Sienna, J. J.; Huerta, J.; White, M. C.; Etzel, R. A. (1996) Effects of air pollution
34 on the respiratory health of asthmatic children living in Mexico City. *Am. J. Respir. Crit. Care Med.*
35 154: 300-307.
- 36 Romieu, I.; Meneses, F.; Ruiz, S.; Huerta, J.; Sienna, J. J.; White, M.; Etzel, R.; Hernandez, M. (1997) Effects of
37 intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in
38 Mexico City. *Arch. Environ. Health* 52: 368-376.
- 39 Rooney, C.; McMichael, A. J.; Kovats, R. S.; Coleman, M. P. (1998) Excess mortality in England and Wales, and in
40 greater London, during the 1995 heatwave. *J. Epidemiol. Community Health* 52: 482-486.
- 41 Rosas, I.; McCartney, H. A.; Payne, R. W.; Calderon, C.; Lacey, J.; Chapela, R.; Ruiz-Velazco, S. (1998) Analysis
42 of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma
43 emergency admissions to a hospital in Mexico City. *Allergy (Copenhagen)* 53: 394-401.
- 44 Rossi, G.; Vigotti, M. A.; Zanobetti, A.; Repetto, F.; Gianelle, V.; and Schwartz, J. (1999) Air pollution and
45 cause-specific mortality in Milan, Italy, 1980-1989. *Arch. Environ. Health* 54: 158-164.
- 46 Rothman, K. J.; Greenland, S., eds. (1998) *Modern epidemiology*. 2nd ed. Philadelphia, PA: Lippincott-Raven
47 Publishers.
- 48 Rutherford, S.; Clark, E.; McTainsh, G.; Simpson, R.; Mitchell, C. (1999) Characteristics of rural dust events shown
49 to impact on asthma severity in Brisbane, Australia. *Int. J. Biometeorol.* 42: 217-225.
- 50 Samet, J. M. (2000) What properties of particulate matter are responsible for health effects? In: *Inhalation*
51 *Toxicology: proceedings of the third colloquium on particulate air pollution and human health*; June, 1999;
52 Durham, NC. *Inhalation Toxicol.* 12(suppl. 1): 19-21.
- 53 Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J.; Kalkstein, L. S. (1996) *Weather, air pollution and mortality in*
54 *Philadelphia, 1973-1980, report to the Health Effects Institute on phase IB, Particle Epidemiology Evaluation*
55 *Project*. Cambridge, MA: Health Effects Institute; review draft.

- 1 Samet, J. M.; Zeger, S. L.; Dominici, F.; Curriero, F.; Coursac, I.; Dockery, D. W.; Schwartz, J.; Zanobetti, A.
2 (2000a) The national morbidity, mortality, and air pollution study. Part II: morbidity, mortality, and air
3 pollution in the United States. Cambridge, MA: Health Effects Institute; research report no. 94.
- 4 Samet, J. M.; Dominici, F.; Zeger, S. L.; Schwartz, J.; Dockery, D. W. (2000b) National morbidity, mortality, and
5 air pollution study. Part I: methods and methodologic issues. Cambridge, MA: Health Effects Institute;
6 research report no. 94.
- 7 Samet, J. M.; Dominici, F.; Curriero, F. C.; Coursac, I.; Zeger, S. L. (2000c) Fine particulate air pollution and
8 mortality in 20 U.S. cities, 1987-1994. *N. Engl. J. Med.* 343: 1742-1749.
- 9 Samoli, E.; Schwartz, J.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina, S.; Rossi, G.; Sunyer, J.;
10 Bacharova, L.; Anderson, H. R.; Katsouyanni, K. (2001) Investigating regional differences in short-term
11 effects of air pollution on daily mortality in the APHEA project: a sensitivity analysis for controlling
12 long-term trends and seasonality. *Environ. Health Perspect.* 109: 349-353.
- 13 Samoli, E.; Schwartz, J.; Analitis, A.; Petasakis, Y.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina,
14 S.; Rossi, G.; Sunyer, J.; Anderson, H. R.; Katsouyanni, K. (2003) Sensitivity analyses of regional differences
15 in short-term effects of air pollution on daily mortality in APHEA cities. In: Revised analyses of time-series
16 studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 205-210.
17 Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 18 Sarnat, J. A.; Koutrakis, P.; Suh, H. H. (2000) Assessing the relationship between personal particulate and gaseous
19 exposures of senior citizens living in Baltimore, MD. *J. Air Waste Manage. Assoc.* 50: 1184-1198.
- 20 Sarnat, J. A.; Schwartz, J.; Catalano, P. J.; Suh, H. H. (2001) Gaseous pollutants in particulate matter epidemiology:
21 confounders or surrogates? *Environ. Health Perspect.* 109: 1053-1061.
- 22 Scarlett, J. F.; Abbott, K. J.; Peacock, J. L.; Strachan, D. P.; Anderson, H. R. (1996) Acute effects of summer air
23 pollution on respiratory function in primary school children in southern England. *Thorax* 51: 1109-1114.
- 24 Schouten, J. P.; Vonk, J. M.; de Graaf, A. (1996) Short term effects of air pollution on emergency hospital
25 admissions for respiratory disease: results of the APHEA project in two major cities in The Netherlands,
26 1977-89. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European
27 approach using epidemiological time series data. *J. Epidemiol. Community Health* 50(suppl. 1): S22-S29.
- 28 Schwartz, J. (1991) Particulate air pollution and daily mortality in Detroit. *Environ. Res.* 56: 204-213.
- 29 Schwartz, J. (1994) PM₁₀, ozone, and hospital admissions for the elderly in Minneapolis, MN. *Arch. Environ. Health*
30 49: 366-374.
- 31 Schwartz, J. (1997) Air pollution and hospital admissions for cardiovascular disease in Tucson. *Epidemiology*
32 8: 371-377.
- 33 Schwartz, J. (1999) Air pollution and hospital admissions for heart disease in eight U.S. counties. *Epidemiology*
34 10: 17-22.
- 35 Schwartz, J. (2000a) Assessing confounding, effect modification, and thresholds in the association between ambient
36 particles and daily deaths. *Environ. Health Perspect.* 108: 563-568.
- 37 Schwartz, J. (2000b) The distributed lag between air pollution and daily deaths. *Epidemiology* 11: 320-326.
- 38 Schwartz, J. (2000c) Harvesting and long term exposure effects in the relation between air pollution and mortality.
39 *Am. J. Epidemiol.* 151: 440-448.
- 40 Schwartz, J. (2000d) Daily deaths are associated with combustion particles rather than SO₂ in Philadelphia.
41 *Occup. Environ. Med.* 57: 692-697.
- 42 Schwartz, J. (2001) Air pollution and blood markers of cardiovascular risk. *Environ. Health Perspect.*
43 109(suppl. 3): 405-409.
- 44 Schwartz, J. (2003a) Daily deaths associated with air pollution in six US cities and short-term mortality
45 displacement in Boston. In: Revised analyses of time-series studies of air pollution and health. Special report.
46 Boston, MA: Health Effects Institute; pp. 219-226. Available: <http://www.healtheffects.org/news.htm>
47 [16 May, 2003].
- 48 Schwartz, J. (2003b) Airborne particles and daily deaths in 10 US cities. In: Revised analyses of time-series studies
49 of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 211-218. Available:
50 <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 51 Schwartz, J.; Marcus, A. (1990) Mortality and air pollution in London: a time series analysis. *Am. J. Epidemiol.*
52 131: 185-194.
- 53 Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit,
54 Michigan. *Am. J. Epidemiol.* 142: 23-35.
- 55 Schwartz, J.; Neas, L. M. (2000) Fine particles are more strongly associated than coarse particles with acute
56 respiratory health effects in schoolchildren. *Epidemiology.* 11: 6-10.

- 1 Schwartz, J.; Zanobetti, A. (2000) Using meta-smoothing to estimate dose-response trends across multiple studies,
2 with application to air pollution and daily death. *Epidemiology* 11: 666-672.
- 3 Schwartz, J.; Dockery, D. W.; Neas, L. M.; Wypij, D.; Ware, J. H.; Spengler, J. D.; Koutrakis, P.; Speizer, F. E.;
4 Ferris, B. G., Jr. (1994) Acute effects of summer air pollution on respiratory symptom reporting in children.
5 *Am. J. Respir. Crit. Care Med.* 150: 1234-1242.
- 6 Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996a) Is daily mortality associated specifically with fine particles?
7 *J. Air Waste Manage. Assoc.* 46: 927-939.
- 8 Schwartz, J.; Spix, C.; Touloumi, G.; Bacharova, L.; Barumamdzadeh, T.; le Tertre, A.; Piekarksi, T.; Ponce de
9 Leon, A.; Ponka, A.; Rossi, G.; Saez, M.; Schouten, J. P. (1996b) Methodological issues in studies of air
10 pollution and daily counts of deaths or hospital admissions. In: St Leger, S., ed. *The APHEA project. Short*
11 *term effects of air pollution on health: a European approach using epidemiological time series data.*
12 *J. Epidemiol. Community Health* 50(suppl. 1): S3-S11.
- 13 Schwartz, J.; Norris, G.; Larson, T.; Sheppard, L.; Claiborne, C.; Koenig, J. (1999) Episodes of high coarse particle
14 concentrations are not associated with increased mortality. *Environ. Health Perspect.* 107: 339-342.
- 15 Seaton, A.; Soutar, A.; Crawford, V.; Elton, R.; McNerlan, S.; Cherrie, J.; Watt, M.; Agius, R.; Stout, R. (1999)
16 Particulate air pollution and the blood. *Thorax* 54: 1027-1032.
- 17 Segala, C.; Fauroux, B.; Just, J.; Pascual, L.; Grimfeld, A.; Neukirch, F. (1998) Short-term effect of winter air
18 pollution on respiratory health of asthmatic children in Paris. *Eur. Respir. J.* 11: 677-685.
- 19 Sheppard, L. (2003) Ambient air pollution and nonelderly asthma hospital admissions in Seattle, Washington,
20 1987-1994. In: *Revised analyses of time-series studies of air pollution and health. Special report.* Boston,
21 MA: Health Effects Institute; pp. 227-230. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 22 Sheppard, L.; Damian, D. (2000) Estimating short-term PM effects accounting for surrogate exposure measurements
23 from ambient monitors. *Environmetrics* 11: 675-687.
- 24 Sheppard, L.; Levy, D.; Norris, G.; Larson, T. V.; Koenig, J. Q. (1999) Effects of ambient air pollution on
25 nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. *Epidemiology* 10: 23-30.
- 26 Sheppard, L.; Levy, D.; Checkoway, H. (2001) Correcting for the effects of location and atmospheric conditions on
27 air pollution exposures in a case-crossover study. *J. Exposure Anal. Environ. Epidemiol.* 11: 86-96.
- 28 Shumway, R. H.; Tai, R. Y.; Tai, L. P.; Pawitan, Y. (1983) Statistical analysis of daily London mortality and
29 associated weather and pollution effects. Sacramento, CA: California Air Resources Board; contract no.
30 A1-154-33.
- 31 Shumway, R. H.; Azari, A. S.; Pawitan, Y. (1988) Modeling mortality fluctuations in Los Angeles as functions of
32 pollution and weather effects. *Environ. Res.* 45: 224-241.
- 33 Simpson, R. W.; Williams, G.; Petroeshevsky, A.; Morgan, G.; Rutherford, S. (1997) Associations between outdoor
34 air pollution and daily mortality in Brisbane, Australia. *Arch. Environ. Health* 52: 442-454.
- 35 Smith, M. A.; Jalaludin, B.; Byles, J. E.; Lim, L.; Leeder, S. R. (1996) Asthma presentations to emergency
36 departments in western Sydney during the January 2194 bushfires. *Int. J. Epidemiol.* 25: 1227-1236.
- 37 Smith, R. L.; Davis, J. M.; Speckman, P. (1999) Assessing the human health risk of atmospheric particles. In:
38 *Environmental Statistics: Analysing Data for Environmental Policy: proceedings of a Novartis Foundation*
39 *Symposium; May 1998; London, England.* New York, NY: Wiley. [Novartis Foundation Symposium 220,
40 pp. 59-79].
- 41 Smith, R. L.; Spitzner, D.; Kim, Y.; Fuentes, M. (2000) Threshold dependence of mortality effects for fine and
42 coarse particles in Phoenix, Arizona. *J. Air Waste Manage. Assoc.* 50: 1367-1379.
- 43 Smoyer, K. E.; Rainham, D. G. C.; Hewko, J. N. (2000a) Heat-stress-related mortality in five cities in southern
44 Ontario: 1980-1996. *Int. J. Biometeorol.* 44: 190-197.
- 45 Smoyer, K. E.; Kalkstein, L. S.; Greene, J. S.; Ye, H. (2000b) The impacts of weather and pollution on human
46 mortality in Birmingham, Alabama and Philadelphia, Pennsylvania. *Int. J. Climatol.* 20: 881-897.
- 47 Spinillo, A.; Capuzzo, E.; Egbe, T. O.; Fazzi, E.; Colonna, L.; Nicola, S. (1995) Pregnancies complicated by
48 idiopathic intrauterine growth retardation: severity of growth failure, neonatal morbidity and two-year infant
49 neurodevelopmental outcome. *J. Reprod. Med.* 40: 209-215.
- 50 Spix, C.; Heinrich, J.; Dockery, D.; Schwartz, J.; Volksch, G.; Schwinkowski, K.; Collen, C.; Wichmann, H. E.
51 (1993) Air pollution and daily mortality in Erfurt, East Germany, 1980-1989. *Environ. Health Perspect.*
52 101: 518-526.
- 53 Spix, C.; Anderson, H. R.; Schwartz, J.; Vigotti, M. A.; LeTertre, A.; Vonk, J. M.; Touloumi, G.; Balducci, F.;
54 Piekarski, T.; Bacharova, L.; Tobias, A.; Pönkä, A.; Katsouyanni, K. (1998) Short-term effects of air
55 pollution on hospital admissions of respiratory diseases in Europe: a quantitative summary of APHEA study
56 results. *Arch. Environ. Health* 53: 54-64.

- 1 Stieb, D. M.; Burnett, R. T.; Beveridge, R. C.; Brook, J. R. (1996) Association between ozone and asthma
2 emergency department visits in Saint John, New Brunswick, Canada. *Environ. Health Perspect.*
3 104: 1354-1360.
- 4 Stieb, D. M.; Beveridge, R. C.; Rowe, B. H.; Walter, S. D.; Judek, S. (1998a) Assessing diagnostic classification in
5 an emergency department: implications for daily time series studies of air pollution. *Am. J. Epidemiol.*
6 148: 666-670.
- 7 Stieb, D. M.; Brook, J. R.; Broder, I.; Judek, S.; Burnett, R. T.; Beveridge, R. C. (1998b) Personal exposure of adults
8 with cardiorespiratory disease to particulate acid and sulfate in Saint John, New Brunswick, Canada. *Appl.*
9 *Occup. Environ. Hyg.* 13: 461-468.
- 10 Stieb, D. M.; Beveridge, R. C.; Brook, J. R.; Smith-Doiron, M.; Burnett, R. T.; Dales, R. E.; Beaulieu, S.; Judek, S.;
11 Mamedov, A. (2000) Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint
12 John, Canada. *J. Exposure Anal. Environ. Epidemiol.* 10: 461-477.
- 13 Stölzel, M.; Peters, A.; Wichmann, H.-E. (2003) Daily mortality and fine and ultrafine particles in Erfurt, Germany.
14 In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health
15 Effects Institute; pp. 231-240. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 16 Styer, P.; McMillan, N.; Gao, F.; Davis, J.; Sacks, J. (1995) Effect of outdoor airborne particulate matter on daily
17 death counts. *Environ. Health Perspect.* 103: 490-497.
- 18 Sunyer, J.; Basagaña, X. (2001) Particles, and not gases, are associated with the risk of death in patients with chronic
19 obstructive pulmonary disease. *Int. J. Epidemiol.* 30: 1138-1140.
- 20 Sunyer, J.; Spix, C.; Quénel, P.; Ponce-de-León, A.; Pönka, A.; Barumandzadeh, T.; Touloumi, G.; Bacharova, L.;
21 Wojtyniak, B.; Vonk, J.; Bisanti, L.; Schwartz, J.; Katsouyanni, K. (1997) Urban air pollution and emergency
22 admissions for asthma in four European cities: the APHEA project. *Thorax* 52: 760-765.
- 23 Sunyer, J.; Schwartz, J.; Tobias, A.; Macfarlane, D.; Garcia, J.; Anto, J. M. (2000) Patients with chronic obstructive
24 pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover
25 analysis. *Am. J. Epidemiol.* 151: 50-56.
- 26 Taggart, S. C. O.; Custovic, A.; Francis, H. C.; Faragher, E. B.; Yates, C. J.; Higgins, B. G.; Woodcock, A. (1996)
27 Asthmatic bronchial hyperresponsiveness varies with ambient levels of summertime air pollution. *Eur.*
28 *Respir. J.* 9: 1146-1154.
- 29 Tan, W. C.; Qiu, D.; Liam, B. L.; Ng, T. P.; Lee, S. H.; Van Eeden, S. F.; D'Yachkova, Y.; Hogg, J. C. (2000) The
30 human bone marrow response to acute air pollution caused by forest fires. *Am. J. Respir. Crit. Care Med.*
31 161: 1213-1217.
- 32 Tanaka, H.; Honma, S.; Nishi, M.; Igarashi, T.; Teramoto, S.; Nishio, F.; Abe, S. (1998) Acid fog and hospital visits
33 for asthma: an epidemiological study. *Eur. Respir. J.* 11: 1301-1306.
- 34 Téllez-Rojo, M. M.; Romieu, I.; Ruiz-Velasco, S.; Lezana, M.-A.; Hernández-Avila, M. M. (2000) Daily respiratory
35 mortality and PM10 pollution in Mexico City: importance of considering place of death. *Eur. Respir. J.*
36 16: 391-396.
- 37 Tenías, J. M.; Ballester, F.; Rivera, M. L. (1998) Association between hospital emergency visits for asthma and air
38 pollution in Valencia, Spain. *Occup. Environ. Med.* 55: 541-547.
- 39 Thompson, S. G.; Kienast, J.; Pyke, S. D. M.; Haverkate, F.; Van De Loo, J. C. W. (1995) Hemostatic factors and
40 the risk of myocardial infarction or sudden death in patients with angina pectoris. *N. Engl. J. Med.* 332:
41 635-641.
- 42 Thompson, A. J.; Shields, M. D.; Patterson, C. C. (2001) Acute asthma exacerbations and air pollutants in children
43 living in Belfast, Northern Ireland. *Arch. Environ. Health* 56: 234-241.
- 44 Thurston, G. D.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994) Respiratory hospital admissions and
45 summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. *Environ. Res.*
46 65: 271-290.
- 47 Thurston, G. D.; Lippmann, M.; Scott, M. B.; Fine, J. M. (1997) Summertime haze air pollution and children with
48 asthma. *Am. J. Respir. Crit. Care Med.* 155: 654-660.
- 49 Tiittanen, P.; Timonen, K. L.; Ruuskanen, J.; Mirme, A.; Pekkanen, J. (1999) Fine particulate air pollution,
50 resuspended road dust and respiratory health among symptomatic children. *Eur. Respir. J.* 13: 266-273.
- 51 Timonen, K. L.; Pekkanen, J. (1997) Air pollution and respiratory health among children with asthmatic or cough
52 symptoms. *Am. J. Respir. Crit. Care Med.* 156: 546-552.
- 53 Tobias, A.; Campbell, M. J. (1999) Modelling influenza epidemics in the relation between black smoke and total
54 mortality. A sensitivity analysis. *J. Epidemiol. Community Health* 53: 583-584.

- 1 Tolbert, P. E.; Klein, M.; Metzger, K. B.; Flanders, W. D.; Todd, K.; Mulholland, J. A.; Ryan, P. B.; Frumkin, H.
2 (2000a) Interim results of the study of particulates and health in Atlanta (SOPHIA). *J. Exposure Anal.*
3 *Environ. Epidemiol.* 10: 446-460.
- 4 Tolbert, P. E.; Mulholland, J. A.; MacIntosh, D. L.; Xu, F.; Daniels, D.; Devine, O. J.; Carlin, B. P.; Klein, M.;
5 Dorley, J.; Butler, A. J.; Nordenberg, D. F.; Frumkin, H.; Ryan, P. B.; White, M. C. (2000b) Air quality and
6 pediatric emergency room visits for asthma in Atlanta, Georgia. *Am. J. Epidemiol.* 151: 798-810.
- 7 Touloumi, G.; Katsouyanni, K.; Zmirou, D.; Schwartz, J.; Spix, C.; Ponce de Leon, A.; Tobias, A.; Quennel, P.;
8 Rabczenko, D.; Bacharova, L.; Bisanti, L.; Vonk, J. M.; Ponka, A. (1997) Short-term effects of ambient
9 oxidant exposure on mortality: a combined analysis within the APHEA project. *Am. J. Epidemiol.*
10 146: 177-185.
- 11 Tsai, F. C.; Apte, M. G.; Daisey, J. M. (1999) An exploratory analysis of the relationship between mortality and the
12 chemical composition of airborne particulate matter. Berkeley, CA: Lawrence Berkeley National Laboratory,
13 Environmental Energy Technologies Division; report no. LBNL-43583.
- 14 Tsai, F. C.; Apte, M. G.; Daisey, J. M. (2000) An exploratory analysis of the relationship between mortality and the
15 chemical composition of airborne particulate matter. *Inhalation Toxicol.* 12(suppl.): 121-135.
- 16 Turnovska, T.; Kostianev, S. (1999) Effects of reduced air pollution on children's pulmonary function. *Cent. Eur. J.*
17 *Public Health* 7: 77-79.
- 18 U.S. Census Bureau. (1995) American housing survey for the United States in 1993. Washington, DC: U.S.
19 Department of Commerce; current housing reports H150/93. Available:
20 <http://www.census.gov/hhes/www/housing/ahs/nationaldata.html> [29 April, 2002].
- 21 U.S. Census Bureau. (2003) Internal migration of the older population: 1995 to 2000. Washington, DC: U.S.
22 Department of Commerce. Available: <http://www.census.gov/prod/2003pubs/censr-10.pdf> [26 April, 2004].
- 23 U.S. Environmental Protection Agency. (1982) Air quality criteria for particulate matter and sulfur oxides. Research
24 Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment
25 Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.
- 26 U.S. Environmental Protection Agency. (1986) Second addendum to air quality criteria for particulate matter and
27 sulfur oxides (1982): assessment of newly available health effects information. Research Triangle Park, NC:
28 Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report
29 no. EPA-600/8-86-020F. Available from: NTIS, Springfield, VA; PB87-176574.
- 30 U.S. Environmental Protection Agency. (1993) Air quality criteria for oxides of nitrogen. Research Triangle Park,
31 NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report
32 nos. EPA/600/8-91/049aF-cF. 3v. Available from: NTIS, Springfield, VA; PB95-124533, PB95-124525, and
33 PB95-124517.
- 34 U.S. Environmental Protection Agency. (1996a) Air quality criteria for particulate matter. Research Triangle Park,
35 NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v.
- 36 U.S. Environmental Protection Agency. (1996b) Air quality criteria for ozone and related photochemical oxidants.
37 Research Triangle Park, NC: Office of Research and Development; report nos. EPA/600/AP-93/004aF-cF. 3v.
38 Available from: NTIS, Springfield, VA; PB96-185582, PB96-185590, and PB96-185608. Available online at:
39 www.epa.gov/ncea/ozone.htm.
- 40 U.S. Environmental Protection Agency. (2000a) Emissions and air quality data. Washington, DC: Technology
41 Transfer Network. Available: <http://www.epa.gov/ttn/naaqs/ozone/areas/> [20 May, 2003].
- 42 U.S. Environmental Protection Agency. (2000b) Air quality criteria for carbon monoxide. Research Triangle Park,
43 NC: National Center for Environmental Assessment; report no. EPA/600/P-99/001F. Available:
44 www.epa.gov/ncea/co/ [2000, October 6].
- 45 U.S. Environmental Protection Agency. (2002) Health assessment document for diesel engine exhaust. Washington,
46 DC: Office of Research and Development, National Center for Environmental Assessment; report no.
47 EPA/600/8-90/057F. Available: <http://cfpub.epa.gov/ncea/> [22 May, 2003].
- 48 Van Der Zee, S. C.; Hoek, G.; Boezen, H. M.; Schouten, J. P.; Van Wijnen, J. H.; Brunekreef, B. (1999) Acute
49 effects of urban air pollution on respiratory health of children with and without chronic respiratory symptoms.
50 *Occup. Environ. Med.* 56: 802-813.
- 51 Van Der Zee, S. C.; Hoek, G.; Boezen, M. H.; Schouten, J. P.; Van Wijnen, J. H.; Brunekreef, B. (2000) Acute
52 effects of air pollution on respiratory health of 50-70 yr old adults. *Eur. Respir. J.* 15: 700-709.
- 53 Vasan, R. S.; Larson, M. G.; Leip, E. P.; Kannel, W. B.; Levy, D. (2001) Assessment of frequency of progression to
54 hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. *Lancet*
55 358: 1682-1686.

- 1 Vedal, S.; Petkau, J.; White, R.; Blair, J. (1998) Acute effects of ambient inhalable particles in asthmatic and
2 nonasthmatic children. *Am. J. Respir. Crit. Care Med.* 157: 1034-1043.
- 3 Vena, J. E. (1982) Air pollution as a risk factor in lung cancer. *Am. J. Epidemiol.* 116: 42-56.
- 4 Veterans Administration Cooperative Study Group on Antihypertensive Agents. (1967) Effects of treatment on
5 morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm
6 Hg. *JAMA J. Am. Med. Assoc.* 202: 1028-1034.
- 7 Veterans Administration Cooperative Study Group on Antihypertensive Agents. (1970) Effects of treatment on
8 morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm
9 Hg. *JAMA J. Am. Med. Assoc.* 213: 1143-1152.
- 10 Vigotti, M. A.; Rossi, G.; Bisanti, L.; Zanobetti, A.; Schwartz, J. (1996) Short term effects of urban air pollution on
11 respiratory health in Milan, Italy, 1980-89. In: Leger, S., ed. *The APHEA project. Short term effects of air
12 pollution on health: a European approach using epidemiological time series data.* *J. Epidemiol. Community
13 Health* 50(suppl. 1): S71-S75.
- 14 Villeneuve, P. J.; Goldberg, M. S.; Krewski, D.; Burnett, R. T.; Chen, Y. (2002) Fine particulate air pollution and
15 all-cause mortality within the Harvard six-cities study: variations in risk by period of exposure. *Ann.
16 Epidemiol.* 12: 568-576.
- 17 Von Klot, S.; Wölke, G.; Tuch, T.; Heinrich, J.; Dockery, D. W.; Schwartz, J.; Kreyling, W. G.; Wichmann, H. E.;
18 Peters, A. (2002) Increased asthma medication use in association with ambient fine and ultrafine particles.
19 *Eur. Respir. J.* 20: 691-702.
- 20 Wallace, L. (2000) Real-time monitoring of particles, PAH, and CO in an occupied townhouse. *Appl. Occup.
21 Environ. Hyg.* 15: 39-47.
- 22 Wang, B.; Peng, Z.; Zhang, X.; Xu, Y.; Wang, H.; Allen, G.; Wang, L.; Xu, X. (1999) Particulate matter, sulfur
23 dioxide, and pulmonary function in never-smoking adults in Chongqing, China. *Int. J. Occup. Environ. Health*
24 5: 14-19.
- 25 Ward, D. J.; Miller, M. R.; Walters, S.; Harrison, R. M.; Ayres, J. G. (2000) Impact of correcting peak flow for
26 nonlinear errors on air pollutant effect estimates from a panel study. *Eur. Respir. J.* 15: 137-140.
- 27 Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of
28 ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. *Am. Rev.
29 Respir. Dis.* 133: 834-842.
- 30 Wichmann, H.-E.; Spix, C.; Tuch, T.; Wolke, G.; Peters, A.; Heinrich, J.; Kreyling, W. G.; Heyder, J. (2000) Daily
31 mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass.
32 Cambridge, MA: Health Effects Institute; Research Report no. 98.
- 33 Wilson, W. E.; Suh, H. H. (1997) Fine particles and coarse particles: concentration relationships relevant to
34 epidemiologic studies. *J. Air Waste Manage. Assoc.* 47: 1238-1249.
- 35 Wilson, W. E.; Mage, D. T.; Grant, L. D. (2000) Estimating separately personal exposure to ambient and
36 nonambient particulate matter for epidemiology and risk assessment: why and how. *J. Air Waste Manage.
37 Assoc.* 50: 1167-1183.
- 38 Wjst, M.; Reitmeir, P.; Dold, S.; Wulff, A.; Nicolai, T.; Von Loeffelholz-Colberg, E. F.; Von Mutius, E. (1993)
39 Road traffic and adverse effects on respiratory health in children. *Br. Med. J.* 307: 596-600.
- 40 Wolff, G. T.; Stroup, C. M.; Stroup, D. P. (1983) The coefficient of haze as a measure of particulate elemental
41 carbon. *J. Air Pollut. Control Assoc.* 33: 746-750.
- 42 Wong, T. W.; Lau, T. S.; Yu, T. S.; Neller, A.; Wong, S. L.; Tam, W.; Pang, S. W. (1999a) Air pollution and
43 hospital admissions for respiratory and cardiovascular diseases in Hong Kong. *Occup. Environ. Med.*
44 56: 679-683.
- 45 Wong, C. M.; Hu, Z. G.; Lam, T. H.; Hedley, A. J.; Peters, J. (1999b) Effects of ambient air pollution and
46 environmental tobacco smoke on respiratory health of non-smoking women in Hong Kong. *Int. J. Epidemiol.*
47 28: 859-864.
- 48 Woodhouse, P. R.; Khaw, K. T.; Plummer, M.; Foley, A.; Meade, T. W. (1994) Seasonal variations of plasma
49 fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease.
50 *Lancet* 343: 435-439.
- 51 Woodruff, T. J.; Grillo, J.; Schoendorf, K. C. (1997) The relationship between selected causes of postneonatal infant
52 mortality and particulate air pollution in the United States. *Environ. Health Perspect.* 105: 608-612.
- 53 Wordley, J.; Walters, S.; Ayres, J. G. (1997) Short term variations in hospital admissions and mortality and
54 particulate air pollution. *Occup. Environ. Med.* 54: 108-116.
- 55 Xu, Z.; Yu, D.; Jing, L.; Xu, X. (2000) Air pollution and daily mortality in Shenyang, China. *Arch. Environ. Health*
56 55: 115-120.

- 1 Yang, W.; Jennison, B. L.; Omaye, S. T. (1997) Air pollution and asthma emergency room visits in Reno, Nevada.
2 *Inhalation Toxicol.* 9: 15-29.
- 3 Ye, F.; Piver, W. T.; Ando, M.; Portier, C. J. (2001) Effects of temperature and air pollutants on cardiovascular and
4 respiratory diseases for males and females older than 65 years of age in Tokyo, July and August 1980-1995.
5 *Environ. Health Perspect.* 109: 355-359.
- 6 Yu, O.; Sheppard, L.; Lumley, T.; Koenig, J. Q.; Shapiro, G. G. (2000) Effects of ambient air pollution on symptoms
7 of asthma in Seattle-area children enrolled in the CAMP study. *Environ. Health Perspect.* 108: 1209-1214.
- 8 Zanobetti, A.; Schwartz, J. (2000) Race, gender, and social status as modifiers of the effects of PM₁₀ on mortality.
9 *J. Occup. Environ. Med.* 42: 469-474.
- 10 Zanobetti, A.; Schwartz, J. (2001) Are diabetics more susceptible to the health effects of airborne particles? *Am. J.*
11 *Respir. Crit. Care Med.* 164: 831-833.
- 12 Zanobetti, A.; Schwartz, J. (2003a) Airborne particles and hospital admissions for heart and lung disease. In:
13 Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects
14 Institute; pp. 241-248. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 15 Zanobetti, A.; Schwartz, J. (2003b) Multicity assessment of mortality displacement within the APHEA2 project. In:
16 Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects
17 Institute; pp. 249-254. Available: <http://www.healtheffects.org/news.htm> [16 May, 2003].
- 18 Zanobetti, A.; Schwartz, J.; Dockery, D. W. (2000a) Airborne particles are a risk factor for hospital admissions for
19 heart and lung disease. *Environ. Health Perspect.* 108: 1071-1077.
- 20 Zanobetti, A.; Wand, M. P.; Schwartz, J.; Ryan, L. M. (2000b) Generalized additive distributed lag models:
21 quantifying mortality displacement. *Biostatistics* 1: 279-292.
- 22 Zanobetti, A.; Schwartz, J.; Samoli, E.; Gryparis, A.; Touloumi, G.; Peacock, J.; Anderson, R. H.; Le Tertre, A.;
23 Bobros, J.; Celko, M.; Goren, A.; Forsberg, B.; Michelozzi, P.; Rabczenko, D.; Hoyos, S. P.; Wichmann,
24 H. E.; Katsouyanni, K. (2003) The temporal pattern of respiratory and heart disease mortality in response to
25 air pollution. *Environ. Health Perspect.* 111: 1188-1193.
- 26 Zeger, S. L.; Dominici, F.; Samet, J. (1999) Harvesting-resistant estimates of air pollution effects on mortality.
27 *Epidemiology* 10: 171-175.
- 28 Zeger, S. L.; Thomas, D.; Dominici, F.; Samet, J. M.; Schwartz, J.; Dockery, D.; Cohen, A. (2000) Exposure
29 measurement error in time-series studies of air pollution: concepts and consequences. *Environ. Health*
30 *Perspect.* 108: 419-426.
- 31 Zeghnoun, A.; Beaudou, P.; Carrat, F.; Delmas, V.; Boudhabhay, O.; Gayon, F.; Guincetre, D.; Czernichow, P.
32 (1999) Air pollution and respiratory drug sales in the city of Le Havre, France, 1993-1996. *Environ. Res.*
33 81: 224-230.
- 34 Zeghnoun, A.; Czernichow, P.; Beaudou, P.; Hautemanière, A.; Froment, L.; Le Tertre, A.; Quénel, P. (2001)
35 Short-term effects of air pollution on mortality in the cities of Rouen and Le Havre, France, 1990-1995.
36 *Arch. Environ. Health* 56: 327-335.
- 37 Zemp, E.; Elsasser, S.; Schindler, C.; Künzli, N.; Perruchoud, A. P.; Domenighetti, G.; Medici, T.;
38 Ackermann-Liebrich, U.; Leuenberger, P.; Monn, C.; Bolognini, G.; Bongard, J.-P.; Brändli, O.; Karrer, W.;
39 Keller, R.; Schöni, M. H.; Tschopp, J.-M.; Villiger, B.; Zellweger, J.-P.; SAPALDIA Team. (1999)
40 Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). *Am. J. Respir. Crit.*
41 *Care Med.* 159: 1257-1266.
- 42 Zhang, J.; Qian, Z.; Kong, L.; Zhou, L.; Yan, L.; Chapman, R. S. (1999) Effects of air pollution on respiratory health
43 of adults in three Chinese cities. *Arch. Environ. Health* 54: 373-381.
- 44 Zhang, H.; Triche, E.; Leaderer, B. (2000) Model for the analysis of binary time series of respiratory symptoms.
45 *Am. J. Epidemiol.* 151: 1206-1215.
- 46 Zidek, J. V.; Wong, H.; Le, N. D.; Burnett, R. (1996) Causality, measurement error and multicollinearity in
47 epidemiology. *Environmetrics* 7: 441-451.
- 48 Zmirou, D.; Schwartz, J.; Saez, M.; Zanobetti, A.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Ponce de León, A.;
49 Le Moulec, Y.; Bacharova, L.; Schouten, J.; Pönkä, A.; Katsouyanni, K. (1998) Time-series analysis of air
50 pollution and cause-specific mortality. *Epidemiology* 9: 495-503.

51