PERSPECTIVES ON TIMING OF EXPOSURE IN AN EPIDEMIOLOGIC STUDY OF ARSENIC: TEMPORAL MEASURES, EXPOSURE LIFELINES, EXPOSURE ERROR, AND UNCERTAINTY

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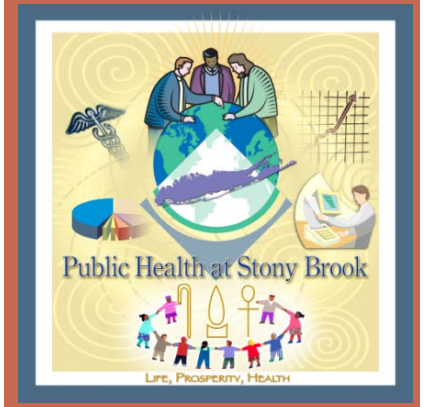

EPA Temporal Exposures Workshop, Jan 2016

OUTLINE

- Lifetime Exposure to Arsenic in Drinking Water in a Bladder Cancer Case-Control Study
  - Typical Presentation of Results: Summary Measures of Exposure
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LIFETIME EXPOSURE TO ARSENIC IN DRINKING WATER

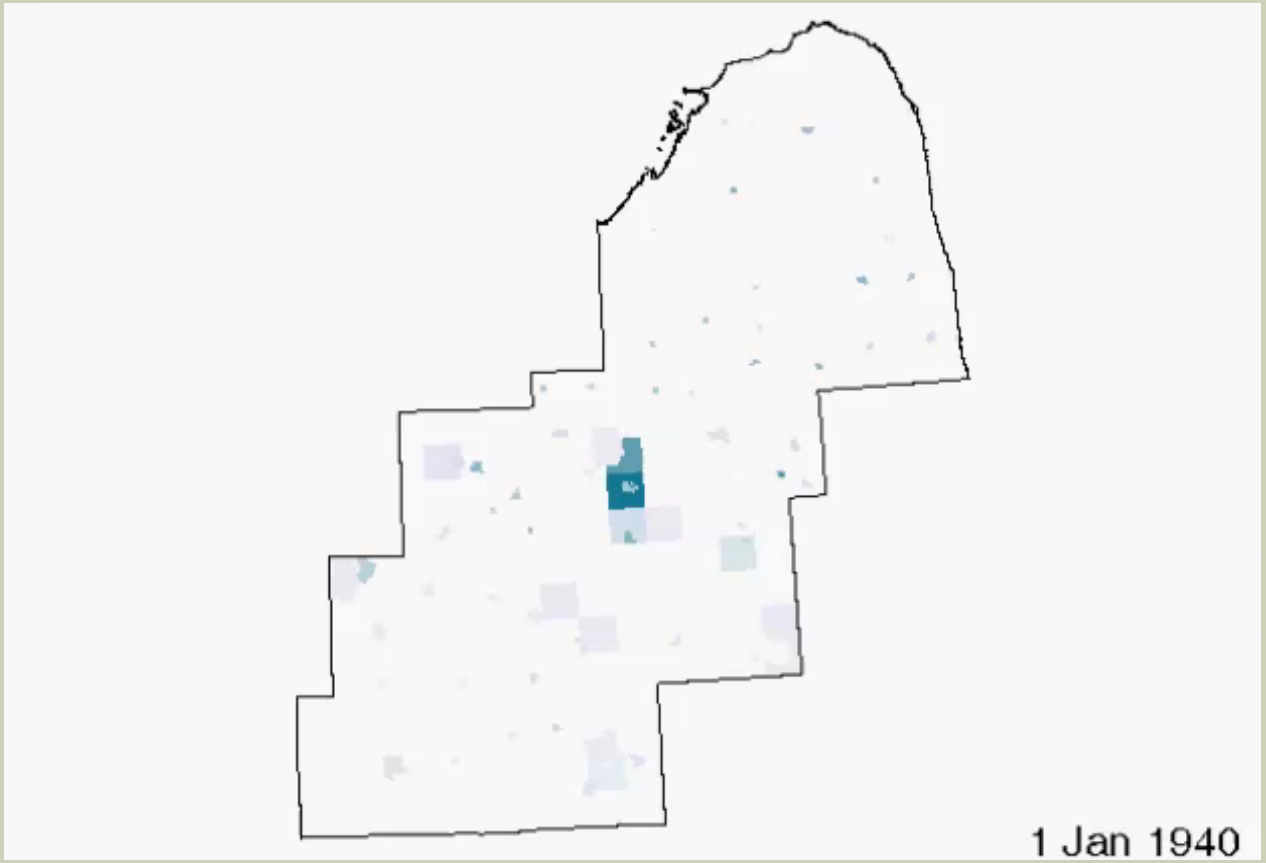
- Bladder cancer case-control study in 11 county study area of southeastern Michigan

- Public water supplies
- Private wells
- Residential mobility (and occupational mobility)
- Water supplies outside of study area

- Monte Carlo simulation analysis and biomarker analyses suggests drinking water most important route in this part of Michigan

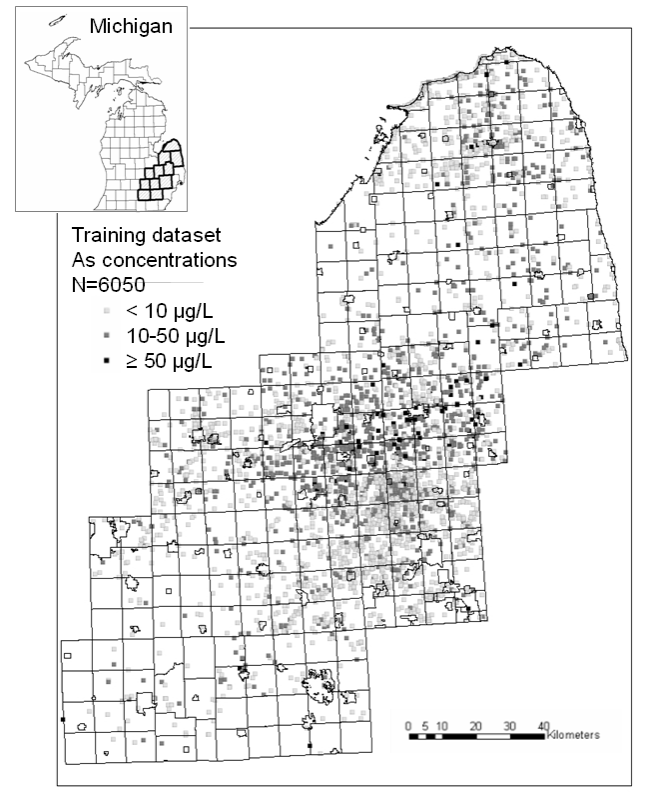
Meliker et al., 2010, Cancer Causes and Control 21: 745-757.
Meliker et al., 2007, Intl Arch Occup & Env Health 80: 184-197.
Meliker et al., 2006, Intl J Hygiene & Env Health 209: 399-411.

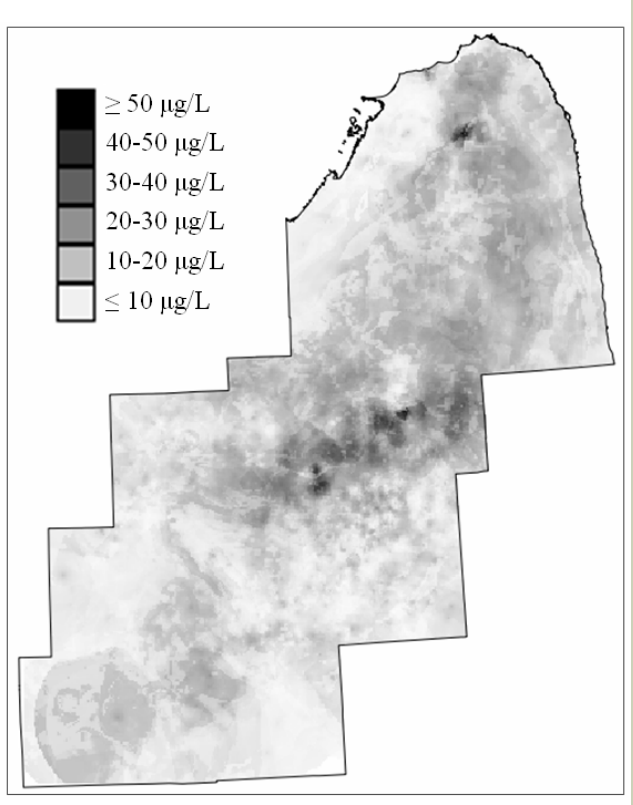
HISTORICAL ARSENIC IN PUBLIC WATER SUPPLIES



PAST PRIVATE WELLS

- One of the principal challenges in reconstructing historical arsenic exposure
  - Geostatistical model (Meliker et al., 2008, Env Research 106: 42-50; Goovaerts et al., 2005, Water Resources Research 41: W07013.

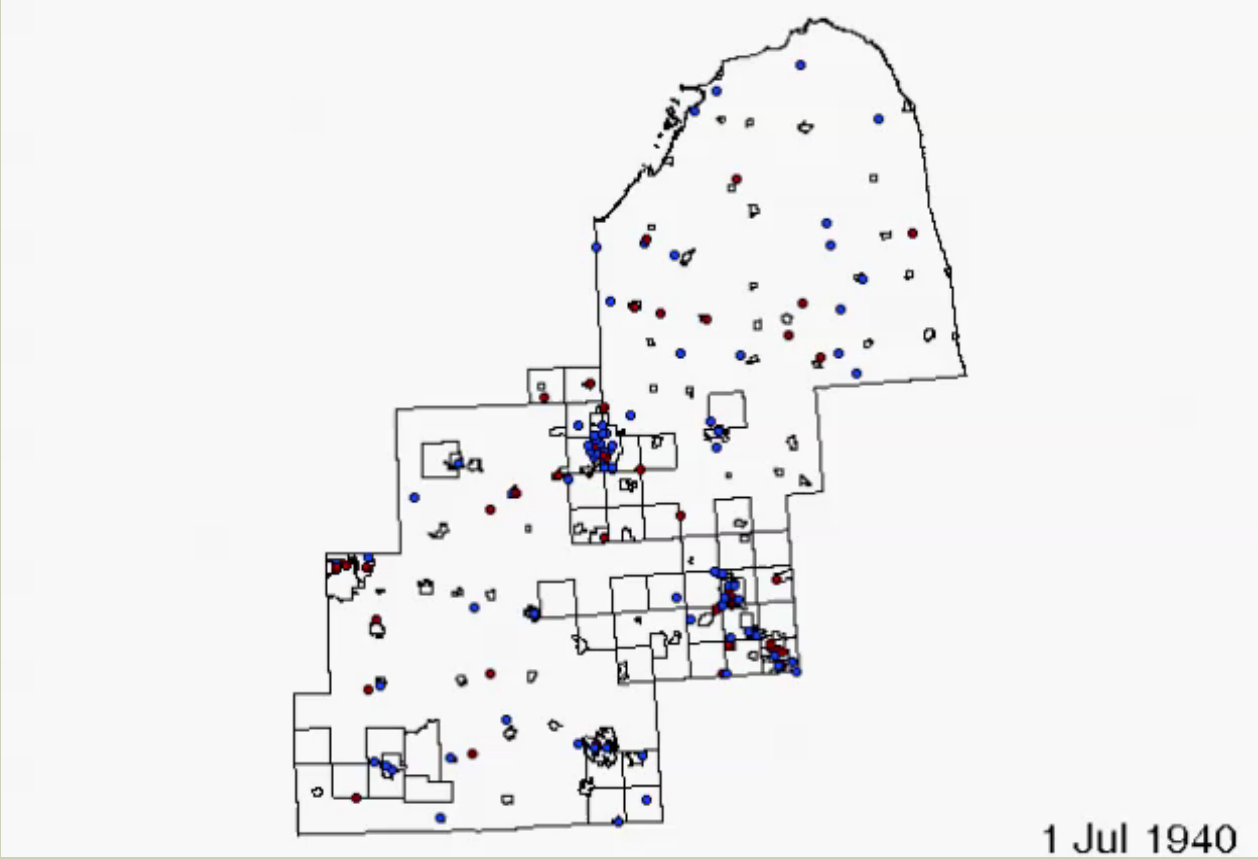




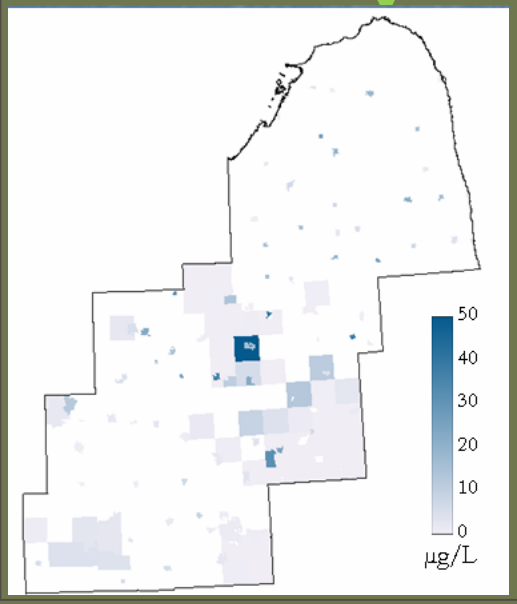
INDIVIDUAL MOBILITY HISTORIES

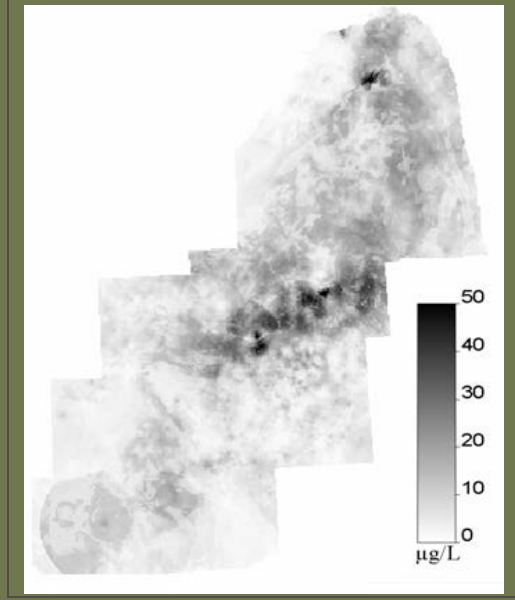
99% of person-years reported for both cases and controls

64,040 person-years



Residential History Dataset							
Participant ID	Year In	Year Out	Address	City	Geographic Coordinates	Water Source	Arsenic Concentration Estimate
2	1930	1940	XX Main St.	Bad Axe	X,Y	Community Supply	Retrieve from Public Supply Dataset
2	1940	1983	XX State St.	Montrose	X,Y	Community Supply	Retrieve from Public Supply Dataset
2	1983	1987	XX Genesee Rd.	Grand Blanc	X,Y	Private Well	Retrieve from Geostatistical Model
2	1987	2004	XX Liberty St.	Jackson	X,Y	Community Supply	1.75 µg/L
3	1942	1966	XX Lapeer Rd.	Lapeer	X,Y	Private Well	Retrieve from Geostatistical Model
3	1966	2004	XX Williams St.	Lapeer	X,Y	Community Supply	0.31 µg/L





Arsenic Concentration Estimates at Residences in the Study Area				
ID	Year In	Year Out	Arsenic Estimate	Data Source
2	1930	1940	14.12 µg/L	Public Supply Data
2	1940	1979	12.58 µg/L	Public Supply Data
2	1979	1983	0.30 µg/L	Public Supply Data
2	1983	1987	8.50 µg/L	Geostatistical Model
2	1987	2004	1.75 µg/L	Analyzed by Staff
3	1942	1966	7.50 µg/L	Geostatistical Model
3	1966	2004	0.31 µg/L	Analyzed by Staff

Public Water Supply History Arsenic Data			
Town Name	Year In	Year Out	Arsenic Estimate
Bad Axe	1920	2000	14.12 µg/L
Montrose	1920	1979	12.58 µg/L
Montrose	1979	2000	0.30 µg/L

Arsenic Estimates from Geostatistical Model			
Geographic Coordinates	Year In	Year Out	Arsenic Estimate
X, Y	1983	1987	8.50 µg/L
X, Y	1942	1966	7.50 µg/L

ESTIMATES OF EXPOSURE AND ERROR OVER THE LIFE-COURSE

ID	Year In	Year Out	Arsenic Estimate	Error Estimate	Data Source
2	1930	1940	14.12 µg/L	3.51 µg/L	Public Supply Data
2	1940	1979	12.58 µg/L	2.31 µg/L	Public Supply Data
2	1979	1983	0.30 µg/L	0.04 µg/L	Public Supply Data
2	1983	1987	8.50 µg/L	10.43 µg/L	Geostatistical Model
2	1987	2004	1.75 µg/L	0.30 µg/L	Analyzed by Staff
3	1942	1966	7.50 µg/L	5.23 µg/L	Geostatistical Model
3	1966	2004	0.31 µg/L	0.25 µg/L	Analyzed by Staff

Measurement error (measured values)

SD (public supply data + geostatistical model)

Meliker et al., 2010, Annals of Epi 20: 750-758.

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MULTIVARIATE-ADJUSTED[a] ORs AND 95% CIs FOR LIFETIME AVERAGE ARSENIC IN DRINKING WATER AND BLADDER CANCER

	Cases[b] (no.)	Controls[b] (no.)	OR	95% CI
Arsenic Concentration in Water (TWA)				
Continuous (per 5 µg/L increase)	407	564	1.07	0.94, 1.22
Categorical				
<1 µg/L	187	264	1.00	
1-10 µg/L	182	180	0.88	0.67, 1.17
>10 µg/L	38	37	1.19	0.71, 1.99
Arsenic Intake from Water (TWA)[c]				
Continuous (per 5 µg/day increase)	394	534	1.03	0.93, 1.14
Categorical				
<1 µg/day	189	252	1.00	
1-10 µg/day	162	234	0.86	0.64, 1.14
>10 µg/day	43	48	1.07	0.66, 1.72

[a]Adjusted for cigarette smoking history, education, history of employment in high-risk occupation, family history of bladder cancer, age, race, and sex.

Little impact from adjustment.

MULTIVARIATE-ADJUSTED ORs AND 95% CIs, STRATIFIED FOR FLUID CONSUMPTION

	Home Water Consumption Above 1 L/day			
	Cases (no.)	Controls (no.)	OR	95% CI
Arsenic Concentration in Water (TWA)				
Continuous (per 5 μg/L increase)	202	262	1.23	1.00, 1.52
Categorical				
<1 μg/L	79	123	1.00	
1-10 μg/L	104	124	1.15	0.76, 1.74
>10 μg/L	19	15	1.88	0.85, 4.17

	Home Water Consumption Above 1 L/day and Above Median Percentage of Fluids that Contain Water from Home			
	Cases (no.)	Controls (no.)	OR	95% CI
Arsenic Concentration in Water (TWA)				
Continuous (per 5 μg/L increase)	101	120	1.33	1.00, 1.76
Categorical				
<1 μg/L	36	58	1.00	
1-10 μg/L	52	55	1.48	0.80, 2.74
>10 μg/L	13	7	3.71	1.20, 11.42

MIGHT ALSO CONSIDER TIME WINDOWS OF EXPOSURE

Metric 1: Arsenic Concentration in Water at Home	No. of Cases	No. of Controls	Unadjusted Model OR (95%CI)	Adjusted* Model OR (95%CI)
Age 20-29				
<5 µg/L	171	363	1.00	1.00
5-10 µg/L	32	34	**2.00 (1.19, 3.34)**	1.60 (0.92, 2.76)
>10 µg/L	15	35	0.91 (0.48, 1.71)	0.63 (0.33, 1.24)
			p^b=0.37	p^b=0.63
Age 30-39				
<5 µg/L	166	345	1.00	1.00
5-10 µg/L	22	41	1.12 (0.64, 1.93)	1.13 (0.64, 2.02)
>10 µg/L	31	44	1.46 (0.89, 2.40)	1.13 (0.67, 1.92)
			p^b=0.14	p^b=0.55
Age 40-49				
<5 µg/L	151	335	1.00	1.00
5-10 µg/L	29	41	1.57 (0.94, 2.62)	1.62 (0.94, 2.77)
>10 µg/L	34	40	**1.89 (1.15, 3.10)**	1.55 (0.92, 2.63)
			p^b=0.005	**p^b=0.04**
Age 50-59				
<5 µg/L	141	304	1.00	1.00
5-10 µg/L	21	33	1.37 (0.77, 2.46)	1.25 (0.68, 2.32)
>10 µg/L	22	35	1.36 (0.77, 2.40)	1.24 (0.67, 2.28)
			p^b=0.19	p^b=0.39
Age 60-69				
<5 µg/L	100	200	1.00	1.00
5-10 µg/L	15	21	1.43 (0.71, 2.89)	1.20 (0.56, 2.57)
>10 µg/L	9	12	1.50 (0.61, 3.68)	1.78 (0.67, 4.75)
			p^b=0.22	p^b=0.24

*Adjusted for smoking (ever/never), race (Black/white/other), gender, age, education.
[b] = p value for test of trend.

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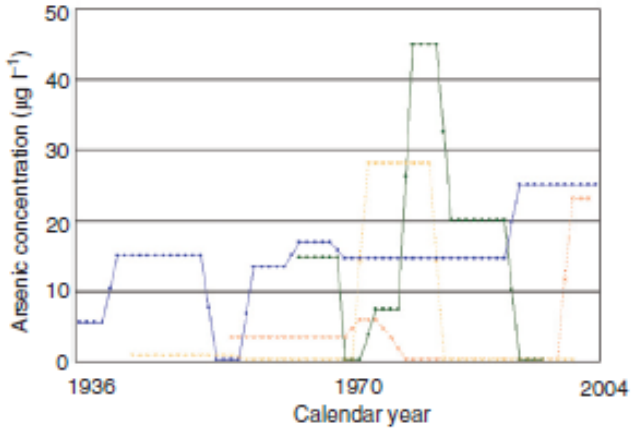
TEMPORAL TERMINOLOGY

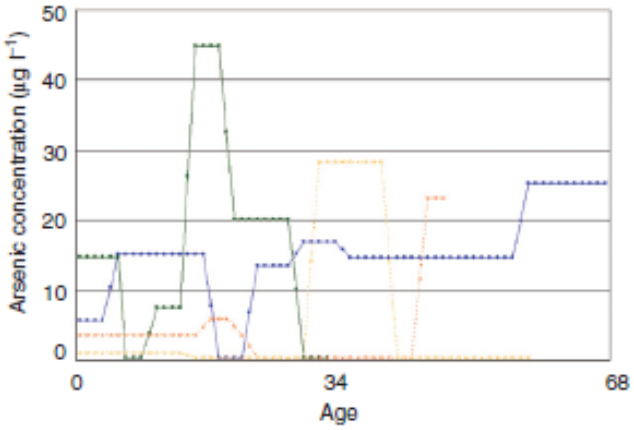
- Duration
- Frequency
- Magnitude (typically expressed in units of concentration multiplied by time (e.g., (mg/m^3)* h))

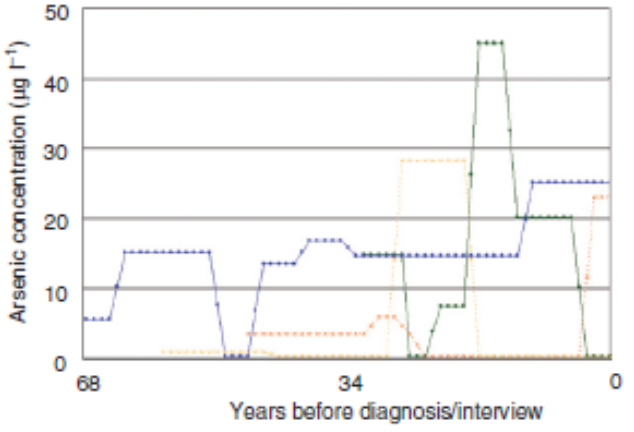
- Cumulative exposure (e.g., (mg/m^3) * years)
- Time-weighted average (TWA) exposure ((mg/m^3) per year)
- Peak exposure

- Time-specific exposures
  - Time windows
  - Temporally continuous
  - Which measure of time: age, calendar year, years prior to diagnosis, or others (years since menarche/or since beginning an occupation)

EXAMPLE: TIME-SPECIFIC EXPOSURES







Lifetime exposure to arsenic in drinking water for two cases (dark lines) and two controls (orange lines)

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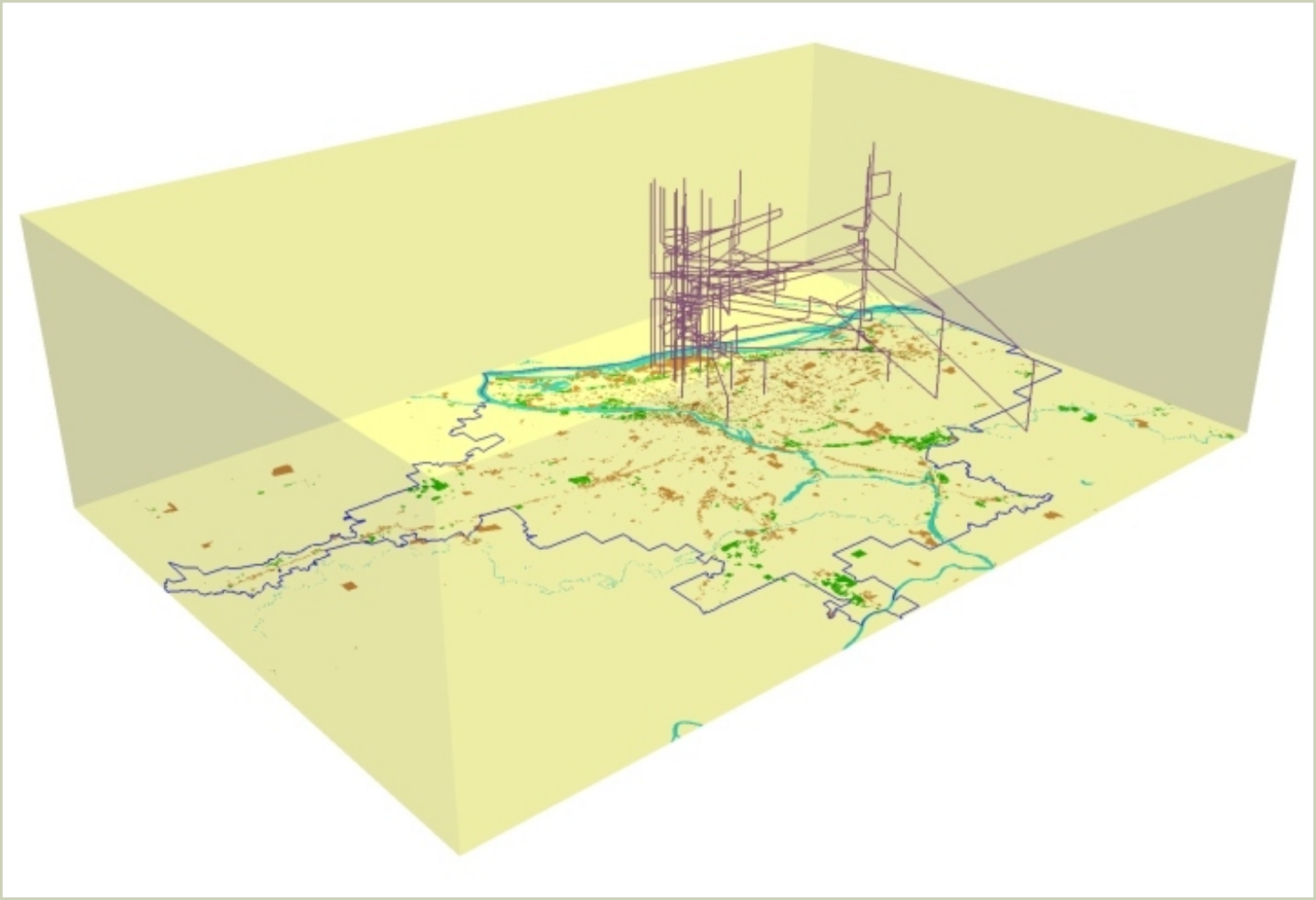
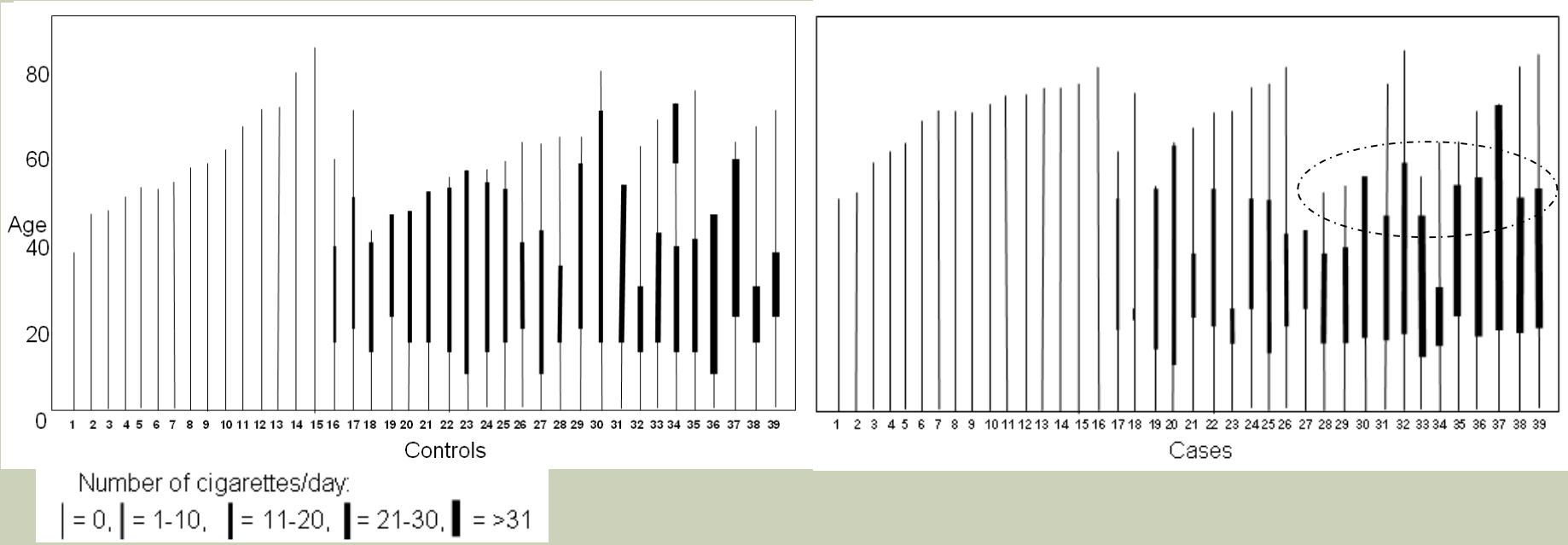
GEOSPATIAL LIFELINES



From
Mei Po Kwan

EXPOSURE LIFE-LINES FOR CIGARETTE SMOKING

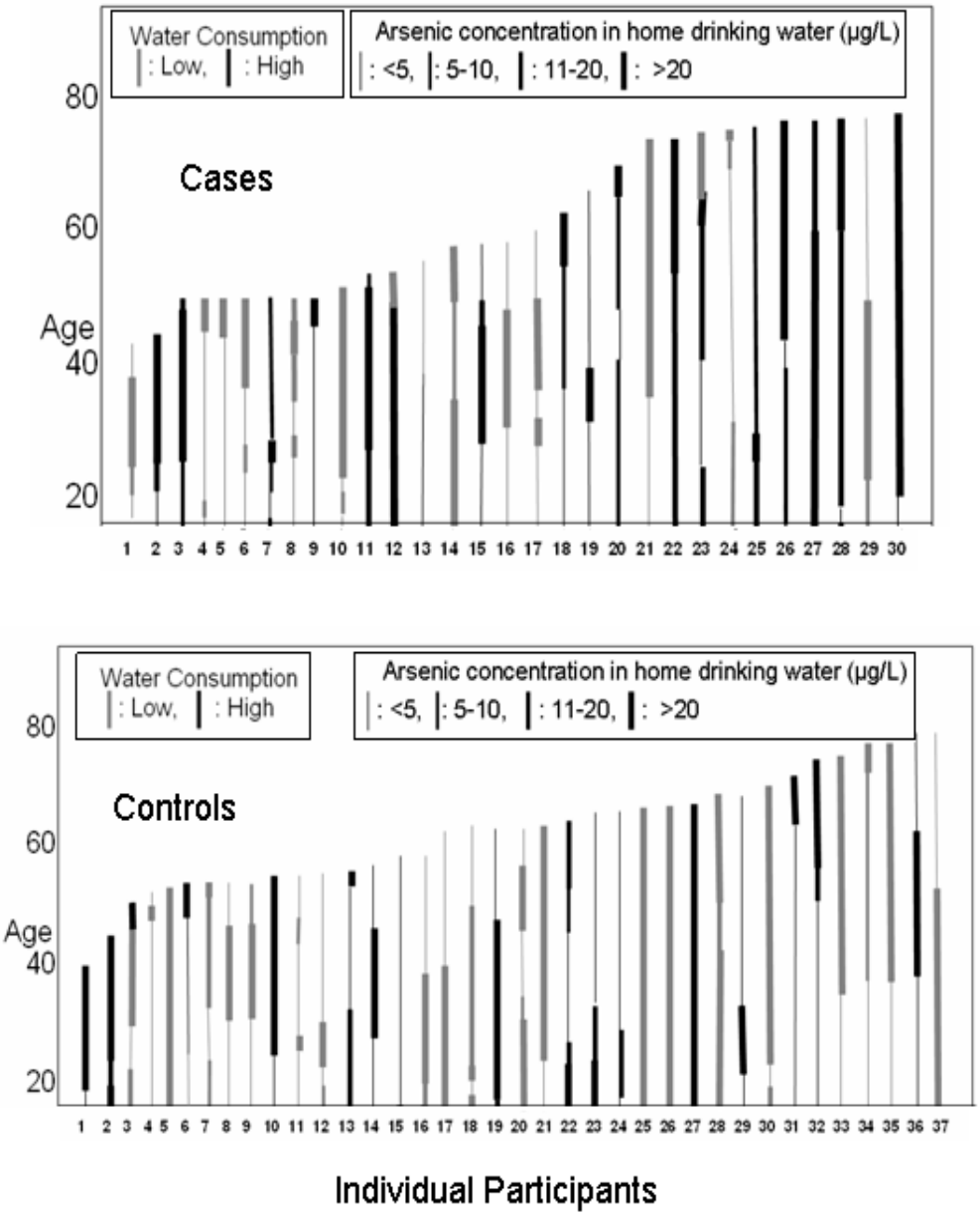


- Thickness of life-line increases with higher frequency of cigarettes smoked.

- There appear to be more heavy smokers around 40-50 years old among cases, compared with controls.

Meliker et al., 2005, J. Geographic Systems 7: 49-66.

Exposure Life-Lines for Cases and Controls Exposed to > 20 µg/L in Home Drinking Water at Some Point in Their Lives, and Their Water Consumption History.



EXPOSURE LIFELINES: COMMENTS

- Useful for visualization of timing of exposure and disease patterns
- Able to stratify or show results across 2 sets of categories

- Difficult to visualize large amounts of data
- Unable to control for important covariates (age, race, sex)

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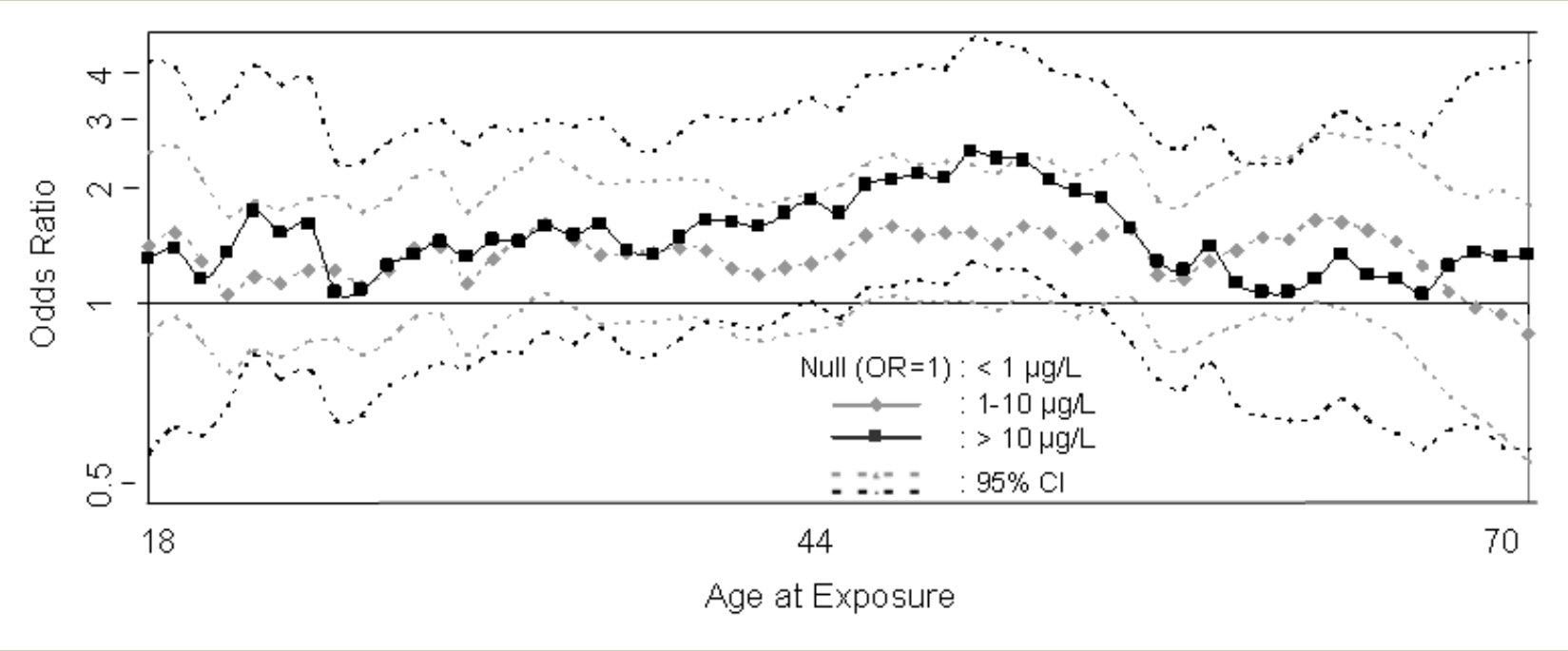
RESULTS USING YEARLY EXPOSURES

- Considered age, calendar year, years prior to diagnosis
  - Moving 5-year averages over each year of a participant's life



Only observe significant effects using age as temporal measure.
Among those who consume >1 L/day of water from home.
Not associated with age at diagnosis.

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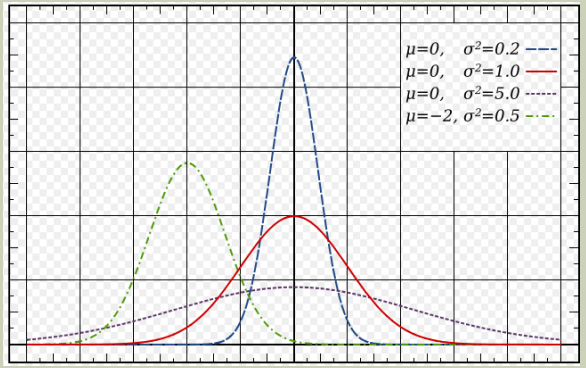
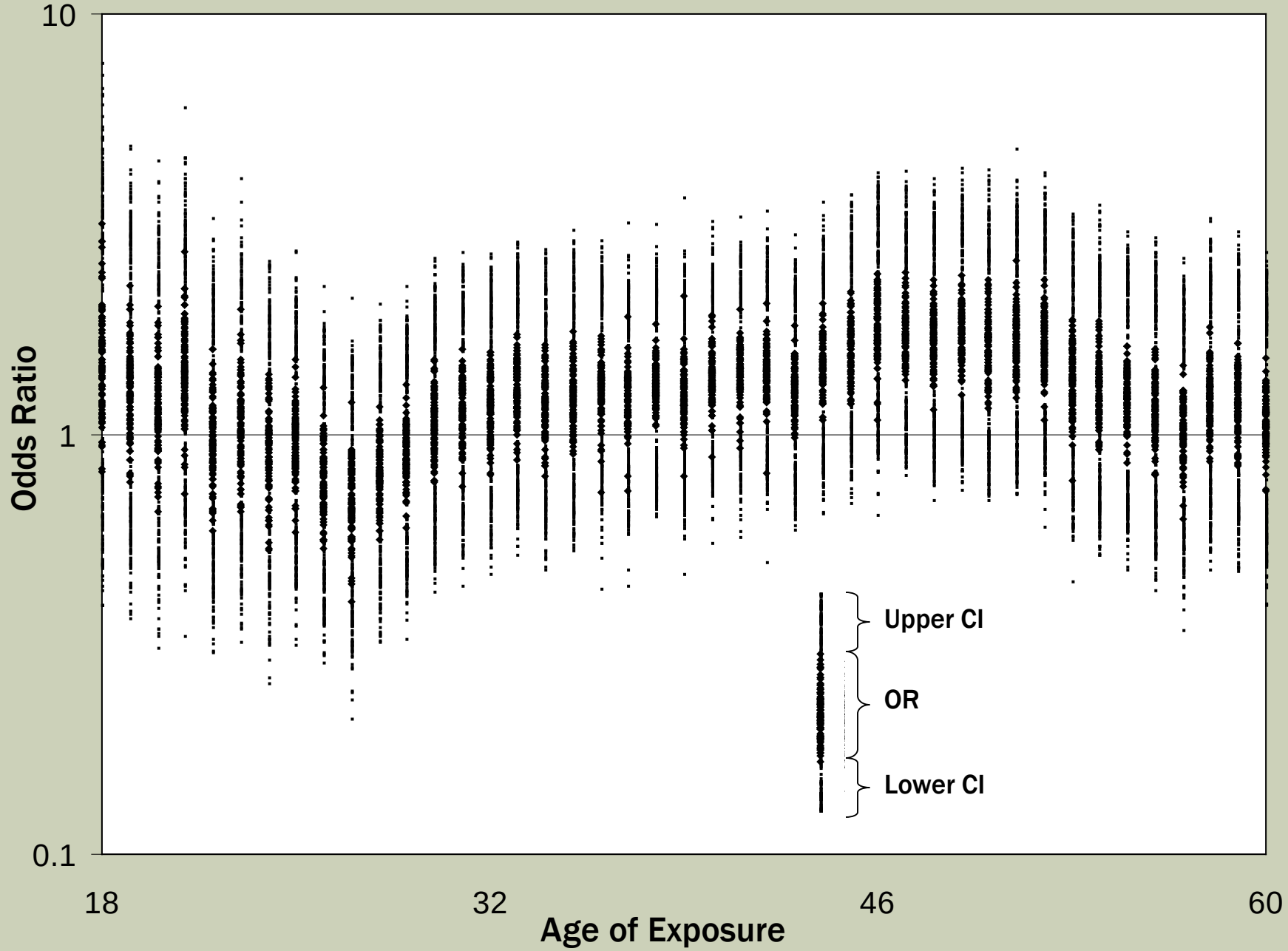
INCORPORATING DISTRIBUTIONS OF ERROR IN EXPOSURE: APPROACH

- Instead of only using point estimates of exposure, incorporate distributions of error in the estimate of exposure
  - Estimates of error terms in exposure from different databases
  - Draw exposure estimates from a probability distribution (e.g., normal)
  - Distribution is individual-level, and can be time-varying
- Evaluate exposure-disease relationship
  - Repeat 99 times (or more)
  - Generate a range of possible risk estimates
- Propagate error in the exposure estimate through the epidemiologic analysis



Meliker et al., 2010, Annals of Epi 20: 750-758.


10
1
0.1
Odds Ratio
18
32
46
60
Age of Exposure
Upper CI
OR
Lower CI

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STUDY POWER

- Most studies do not have adequate power to include a multiple testing adjustment (Bonferroni; false discovery rate, etc.)
  - These adjustments would require substantially more sample size.
  - False positives are a distinct possibility

CONCLUSIONS FOR THE EPI STUDY

- Overall, little evidence of association using summary exposure metric (TWA)
  - Possible association when stratified by high water consumption and low consumption of other liquids
- Some evidence of elevated risk when individuals are exposed to arsenic in drinking water in their 40s.
  - Evidence remains to some extent when propagating exposure error though the model.
- Difficult to explain why risk might increase when individuals are exposed in their 40s.
- No significant associations using calendar year or years prior to diagnosis as the temporal measures.
- Observed temporally-specific association may be a false positive

CONCLUSIONS FOR TEMPORAL EXPOSURES

- Temporal resolution (years, days, hours, minutes)
- Temporal measure (since birth; prior to diagnosis; calendar year, etc.)
- Utility of visualizations?
- Errors in exposure over the life-course
- Multiple testing
- A strategy might be to treat results of temporally-specific analyses as exploratory; and if results are compelling then to design a follow-up study to confirm them.

ACKNOWLEDGMENTS

- Collaborators
  - University of Michigan: Jerome Nriagu, Al Franzblau, David Schottenfeld, Mark Wilson, Melissa Slotnick, Stacey Fedewa, Zorimar Rivera-Nuñez, Kathy Welch
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- Study Participants

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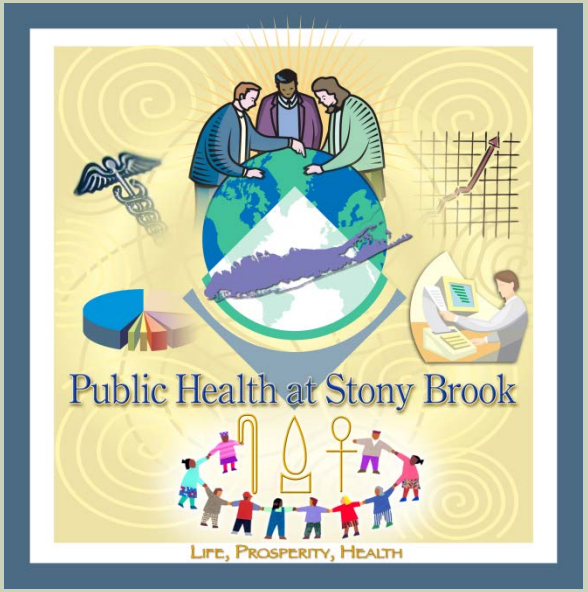

BioMedware
Software for the Environmental and Health Sciences

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Thank you!