Leveraging regulatory information for environmental exposure assessment in studies of cancer etiology: opportunities, strategies, and pitfalls

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TRI National Conference
TRI: Identifying Potential Health Impacts
October 25, 2023

Exposure data for cancer epidemiology studies

De novo exposure data collections

- Environmental samples
- Biologic media
- Surveys

Secondary data

- Measurements collected for regulatory monitoring
- Area-based surveillance/census data
- Satellite imagery

Common approaches and challenges in studies of environmental etiology of cancer

General framework

Case-control and cohort designs

Link geographically-referenced data to study participants:

- Census characteristics (e.g., neighborhood SES)
- Environmental exposures (e.g., drinking water contaminants, industrial emissions)

Individual-level information for potential confounders / effect modifiers

Key challenges

Low levels or low frequency of exposure in ambient environment

Opportunistic – use data collected for other purposes

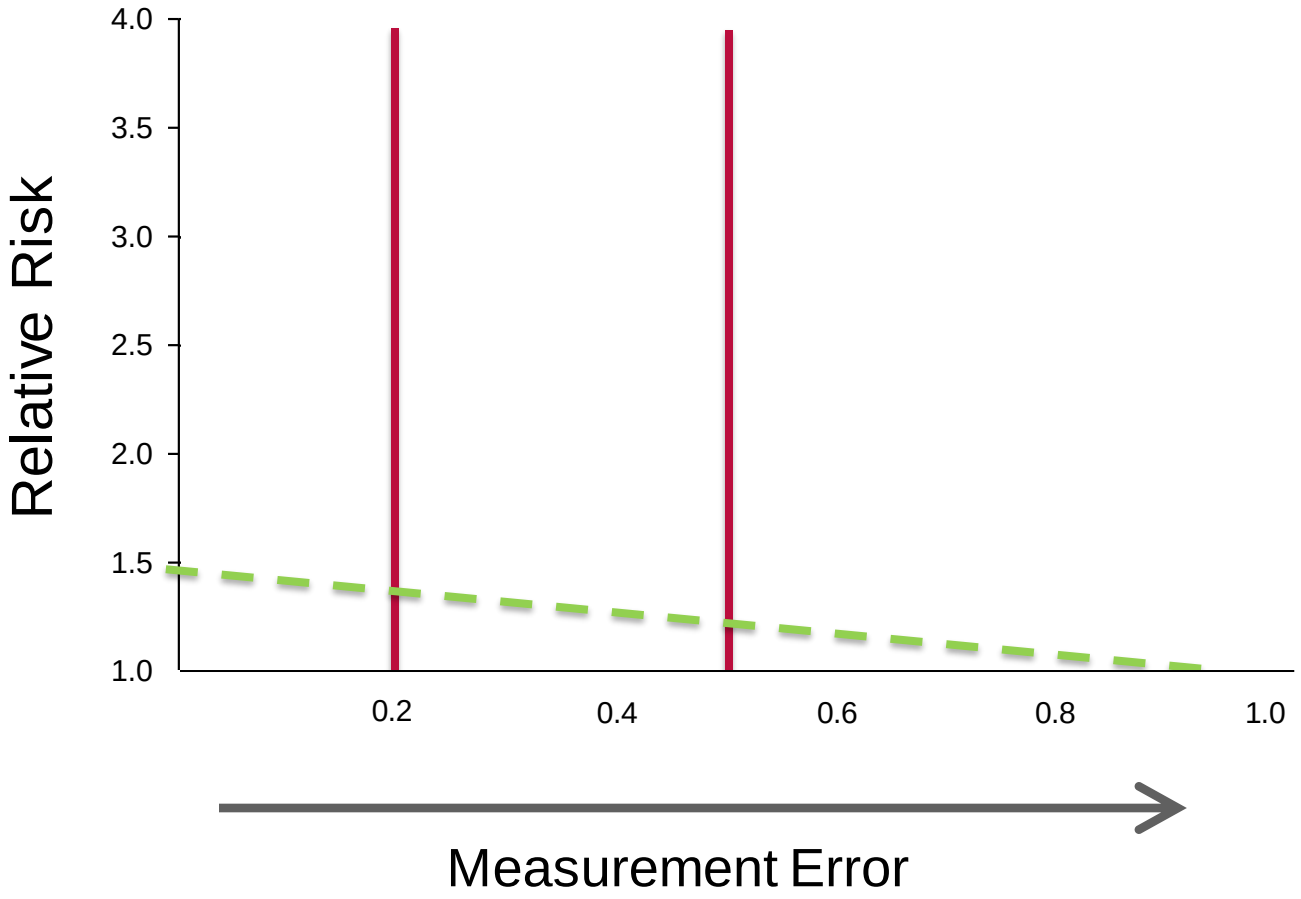
Relevant exposure windows not necessarily captured

Exposures most often assessed only at residence locations

Need to estimate long-term exposure

Exposure misclassification and attenuation of effect estimates

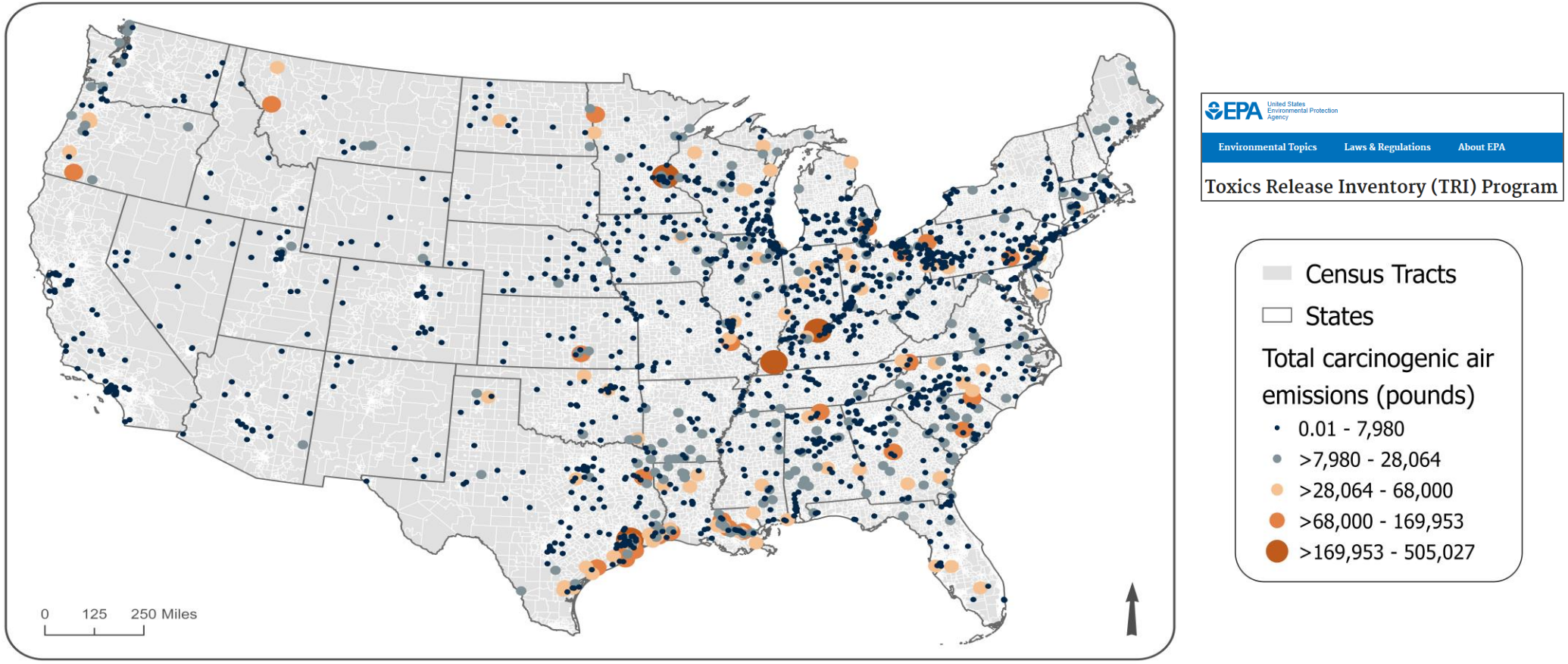
Impact of measurement error



Jones et al., 2014; 2018

Burden of carcinogenic industrial emissions in the U.S.

- 2,254 facilities reported 12 million pounds of IARC Group 1 emissions (2018)



Epidemiologic evidence for IARC classification comes predominantly from worker populations, studies of environmental exposure more limited

Most Highly Emitted Carcinogens in 2018, overall and by toxici

Overall (pounds):

Toxicity-Weighted (µg/m^3)

Inequities in exposure burdens as possible driver of cancer disparities

- People from historically underrepresented racial and ethnic groups, experiencing poverty, or with low educational attainment experience a disproportionate burden of exposure to environmental pollution
  - Unequal exposure burden among populations that live near industrial facilities
- Existing studies have not quantified air emissions of specific chemicals
  - Little is known about the amount of potential exposure to carcinogenic industrial air pollutants

Southern Community Law Center

Jose M. Osorio / Chicago Tribune

Analysis of carcinogenic exposure burdens in U.S.

Evaluated air emissions of known carcinogens across U.S. census tracts using GIS methods (21 Group 1 agents)

- 2018 TRI data and 2010 Census tracts
- Multinomial logistic regression of associations with race, ethnicity and SES
  - Compared tracts with high (Q5) emissions to those with no emissions
  - Adjusted for population density

Ethylene oxide

- Multi-site carcinogen; mutagenic & genotoxic
- Occupational studies demonstrate risk for lymphohematopoietic and breast cancers

Chicago Tribune

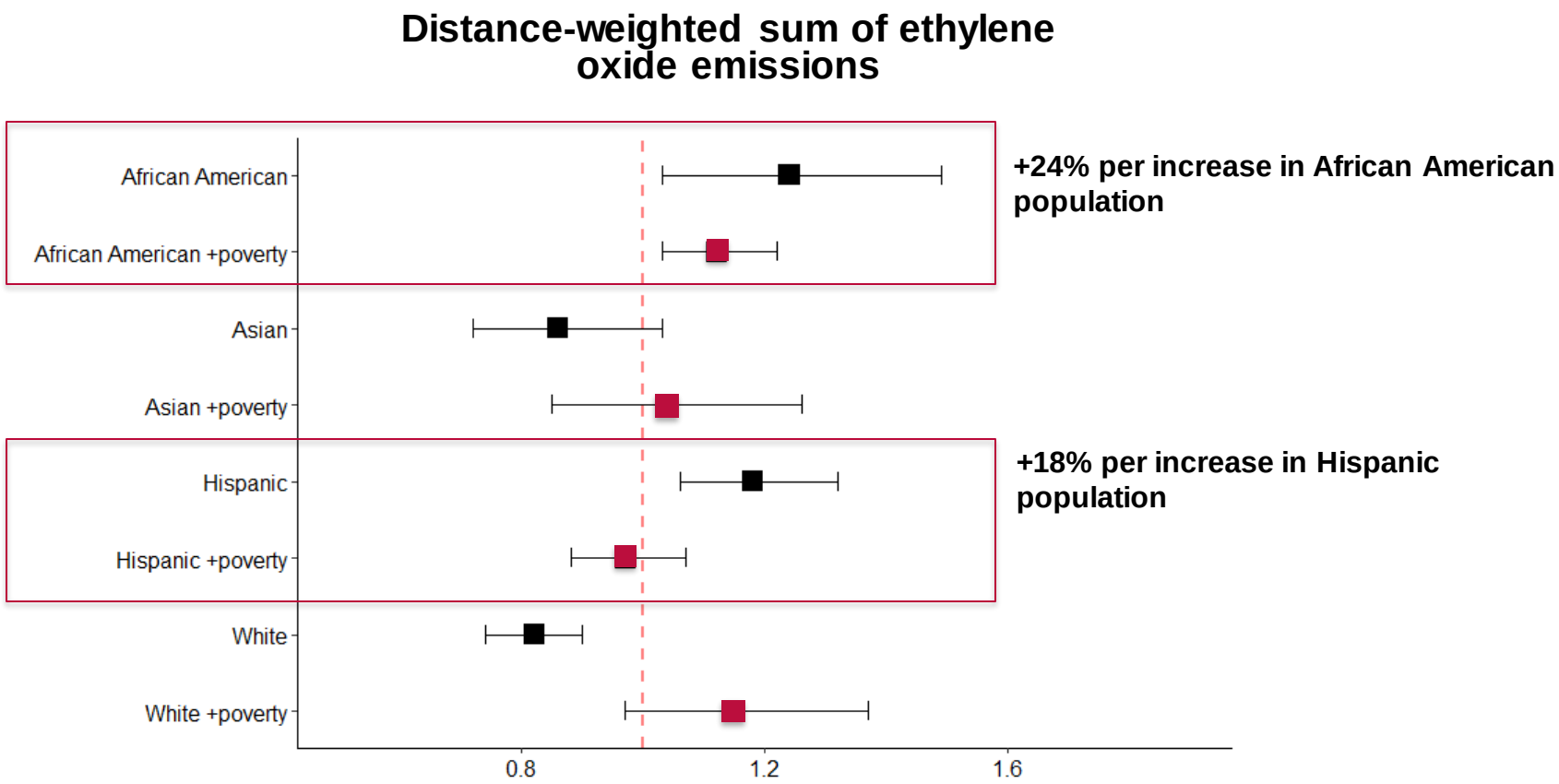
Sterigenics is leaving Willowbrook, eliminating key source of cancer-causing ethylene oxide in Chicago's western suburbs

By MICHAEL HAWTHORNE
CHICAGO TRIBUNE | SEP 30, 2019 AT 8:13 PM

Sterigenics settles hundreds of ethylene oxide lawsuits for $408 million

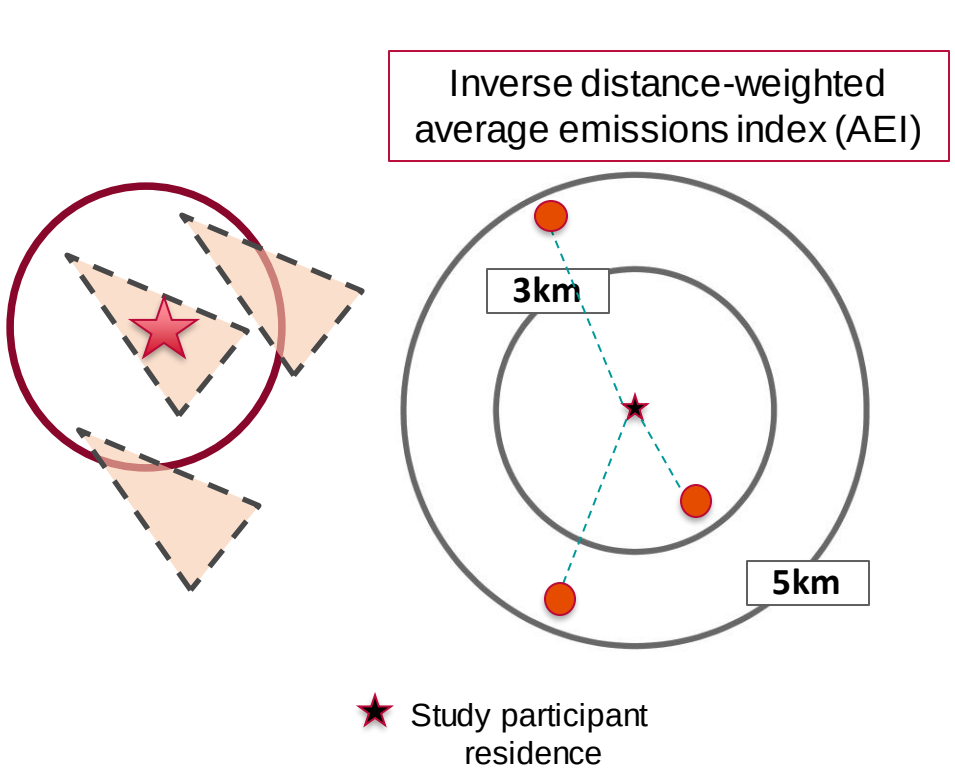
By Michael Hawthorne
Chicago Tribune • Last Updated: Jan 09, 2023

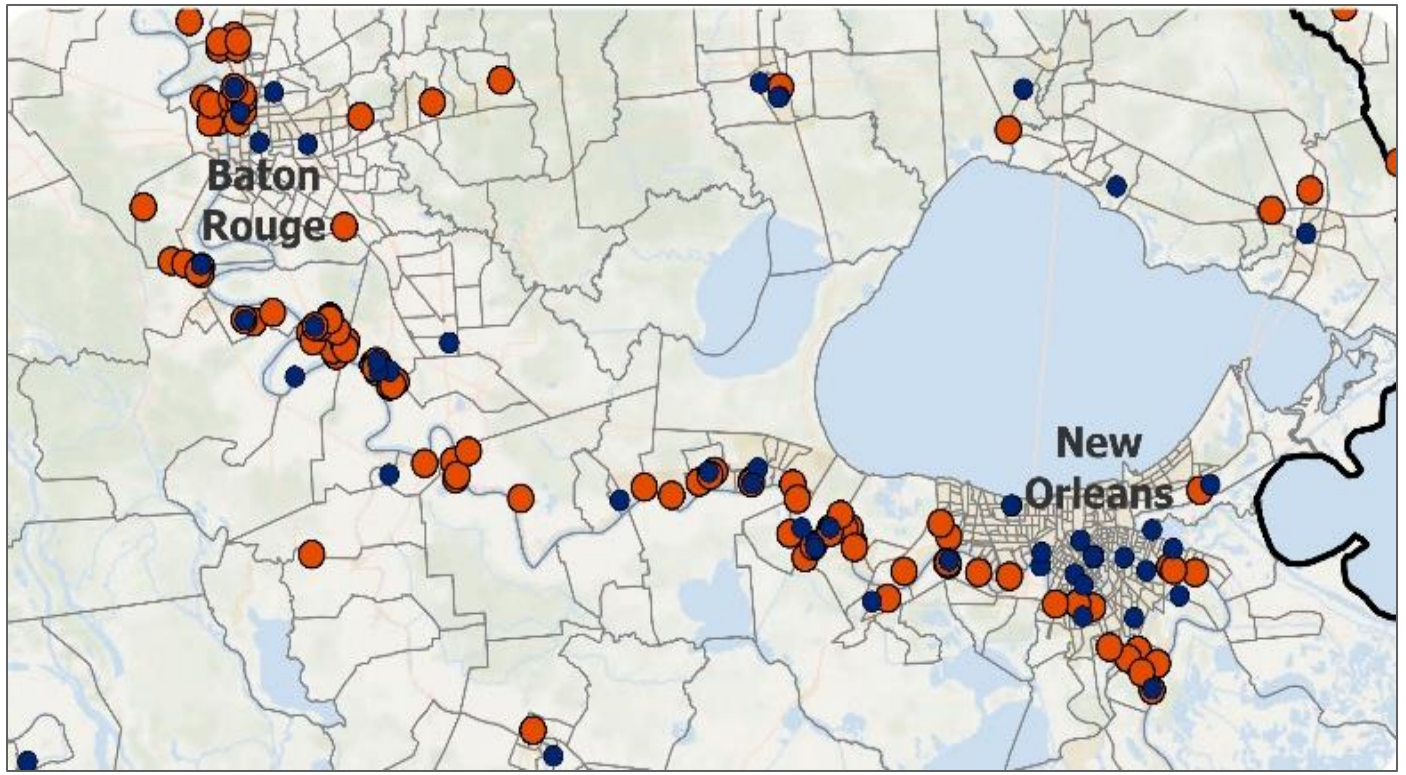
Associations of race and ethnicity and poverty with ethylene oxide exposure burden



Madrigal…Jones, *under review*

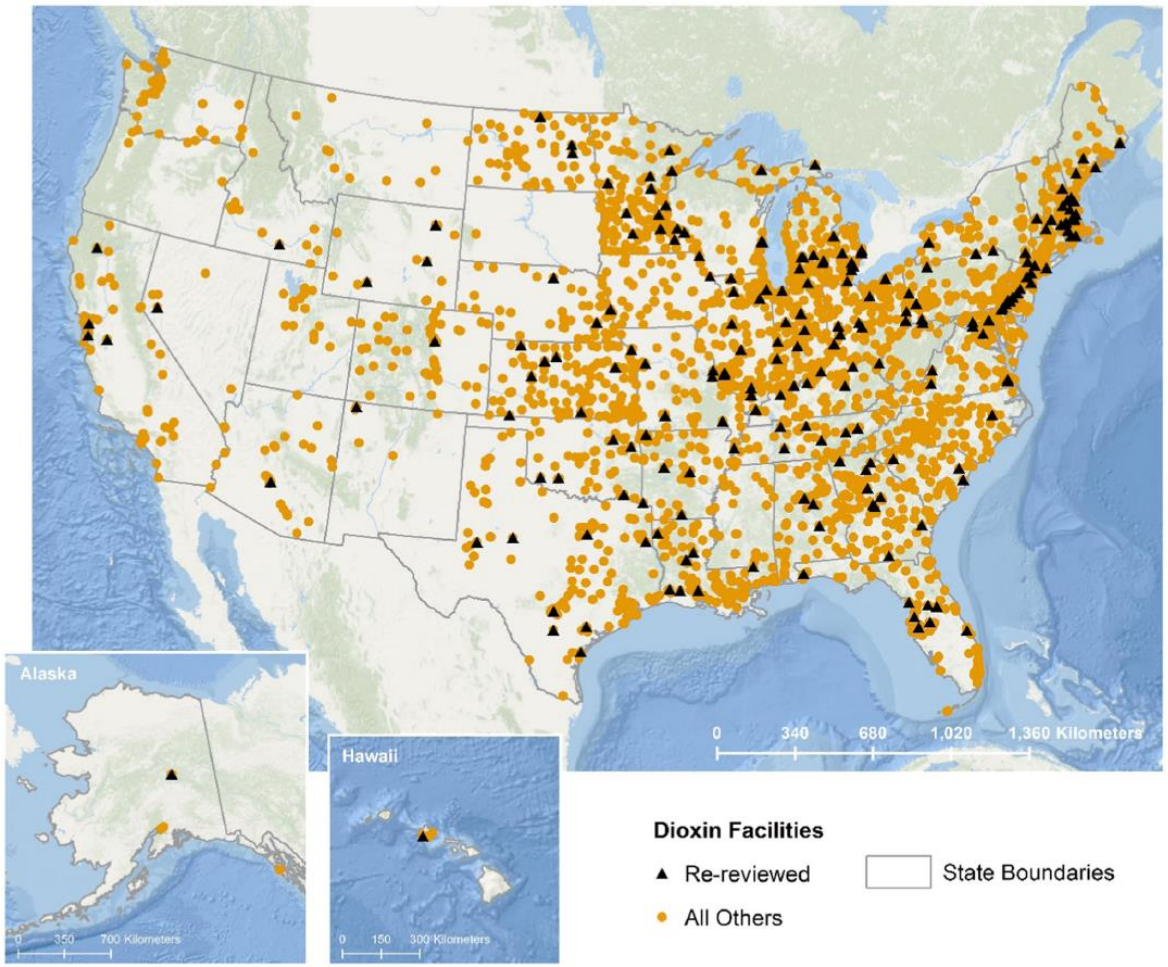
Translating point source regulatory data into an exposure estimate

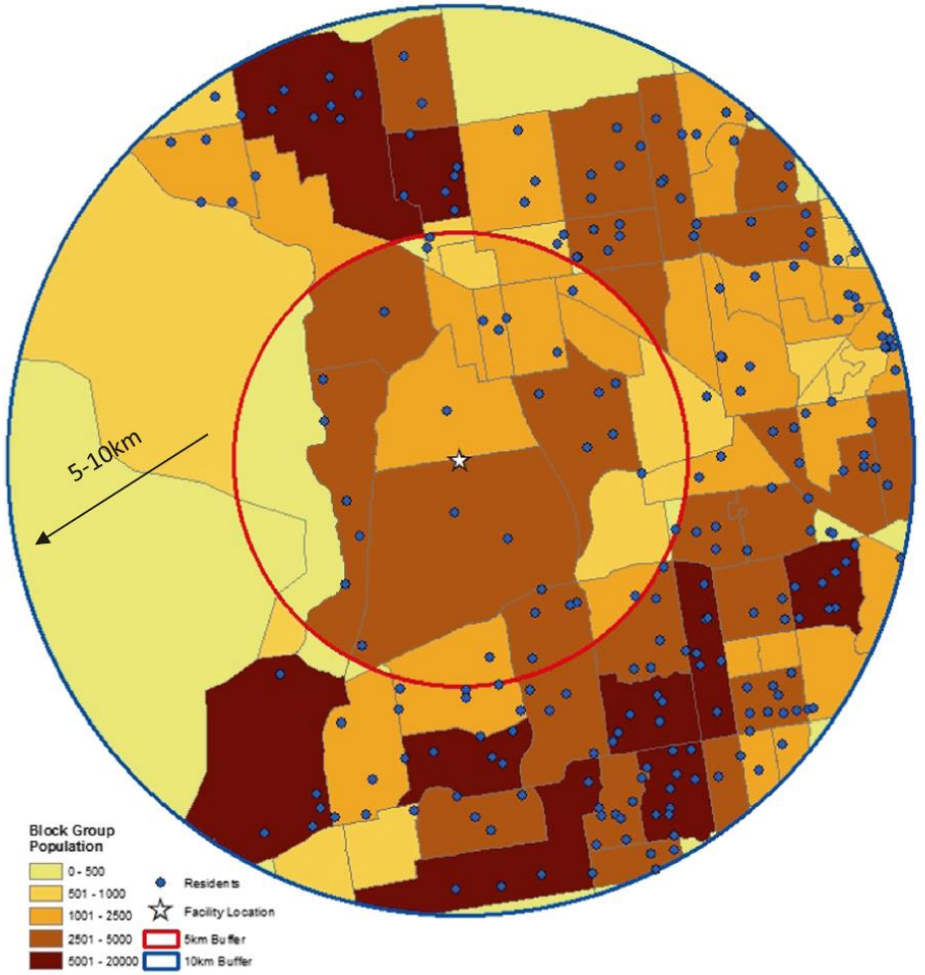




AEI= [(200 lbs EtO/4.7km)+ (10 lbs benzene/2.9km) + (300 lbs TCE/4.9km)]

Enhancing point source exposure estimation – verifying facility locations





Jones et al, *J Exp Sci Env Epi,* 2018

Enhancing point source exposure estimation – verifying facility locations

Facility type	Prevalence within 5 km (%)[a]	Sensitivity	Specificity	$OR_{observed}$[b]
All facilities	8.0	91.9	97.1	1.72
Cement kiln, hazardous + non-hazardous waste	2.0	69.0	95.8	1.24
Coal-fired power plant	7.0	95.5	98.3	1.80
Hazardous waste incinerator	1.0	95.2	97.9	1.31
Medical waste incinerator	28.0	95.0	97.2	1.89
Municipal solid waste incinerator	4.0	90.3	95.7	1.46
Sewage sludge incinerator	4.0	70.6	98.2	1.60

[a]Based on facilities verified in both the original review (2009 and 2016 combined) and re-review sample ($N = 192$); gold standard is the verified location from re-review

[b]$OR_{true} = 2.0$

Jones et al, *J Exp Sci Env Epi,* 2018

Enhancing point source exposure estimation – validate GIS-based exposure metrics using serum-based measures

nhanes National Health and Nutrition Examination Survey

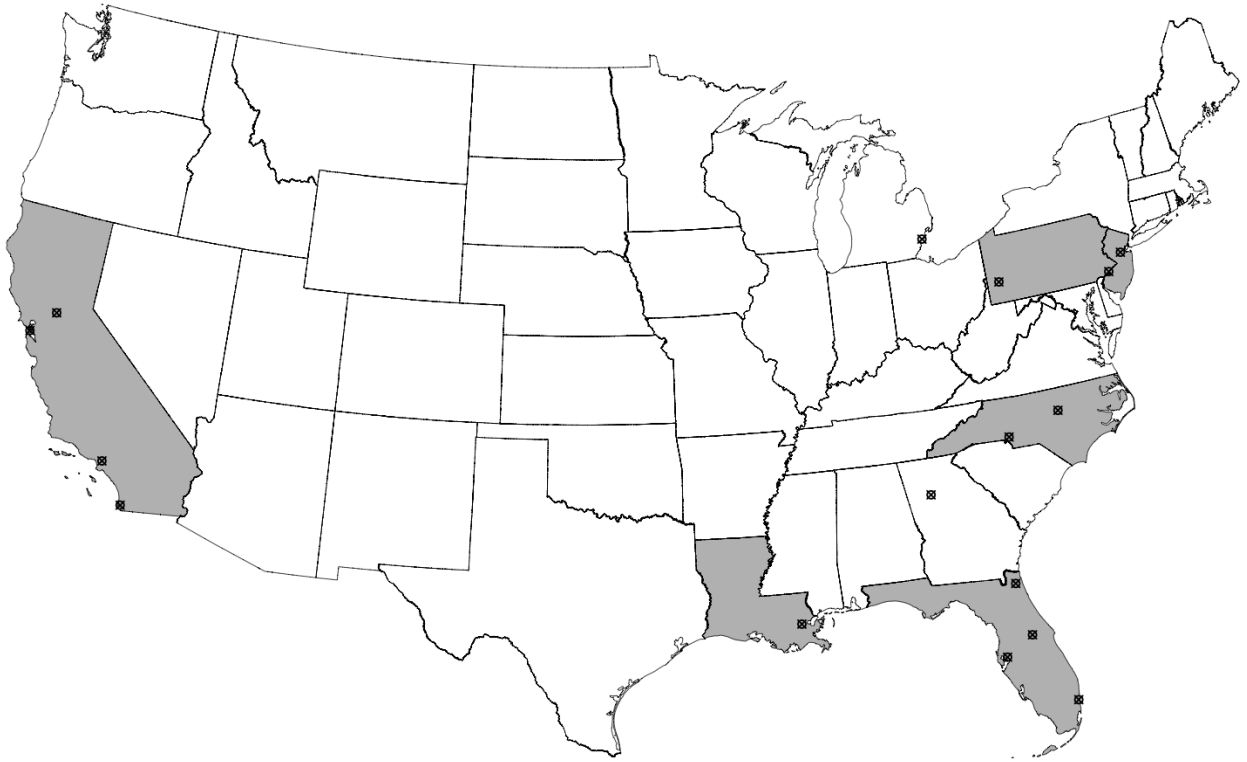
	PCDD		PCDF		PCB		TEQ	
Facility type	**Estimate**	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**
Medical	0.0049	0.0004	0.0025	0.0071	0.0049	0.0005	0.0048	<.0001
Electric utility	-0.0683	0.011	-0.0327	0.2462	0.0436	0.1104	0.0255	0.2725
Cement kiln	0.0544	<.0001	0.0285	<.0001	0.0607	<.0001	0.0265	0.0004
Municipal solid waste	-0.004	0.1326	-0.0012	0.1343	0.0023	0.0886	-0.0018	0.2214
Sewage sludge	5.1099	0.1432	0.1645	0.9274	3.0257	0.3948	0.84560	0.7056
Hazardous waste	-28.37	0.0001	-7.2425	0.5503	46.3843	0.4313	-0.8122	0.9526
Other	-0.0042	0.0001	-0.0019	0.0234	-0.0013	0.2372	-0.0033	0.0006

Facility-specific emissions indices calculated as the sum of distance-weighted emissions from all facilities of that type within 5km Σ(g TEQ/km^2).

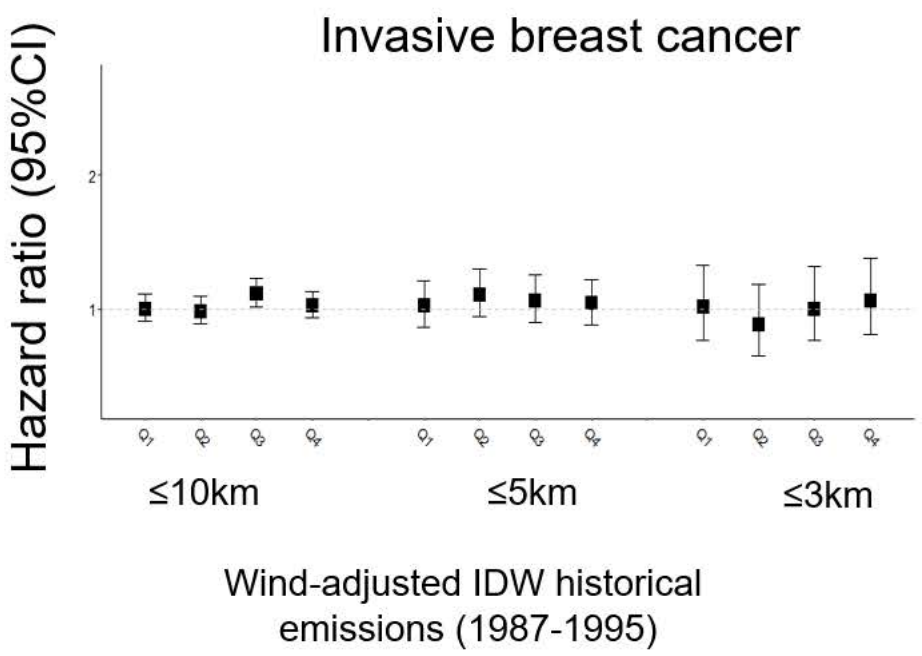
Fisher…Jones, *in prep*

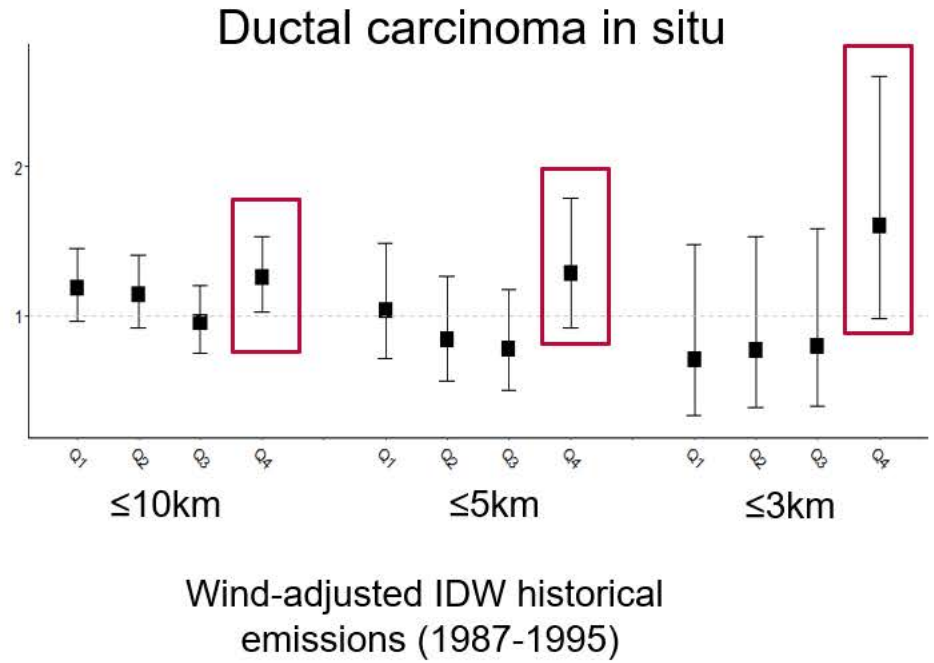
NIH-AARP Diet and Health Study

- Prospective cohort recruited from AARP membership, aged 50-71 years (N~500,000)
- Residing in 6 states and 2 cities in the U.S. at enrollment (1995-1996)
- Demographic, lifestyle, and dietary factors ascertained at enrollment
- N=6,747 incident NHL cases diagnosed through 2011



Association between ethylene oxide emissions near the home and risk of breast cancer in the NIH-AARP cohort





No clear pattern of association with NHL or its subtypes

Jones et al., *JNCI,* 2023

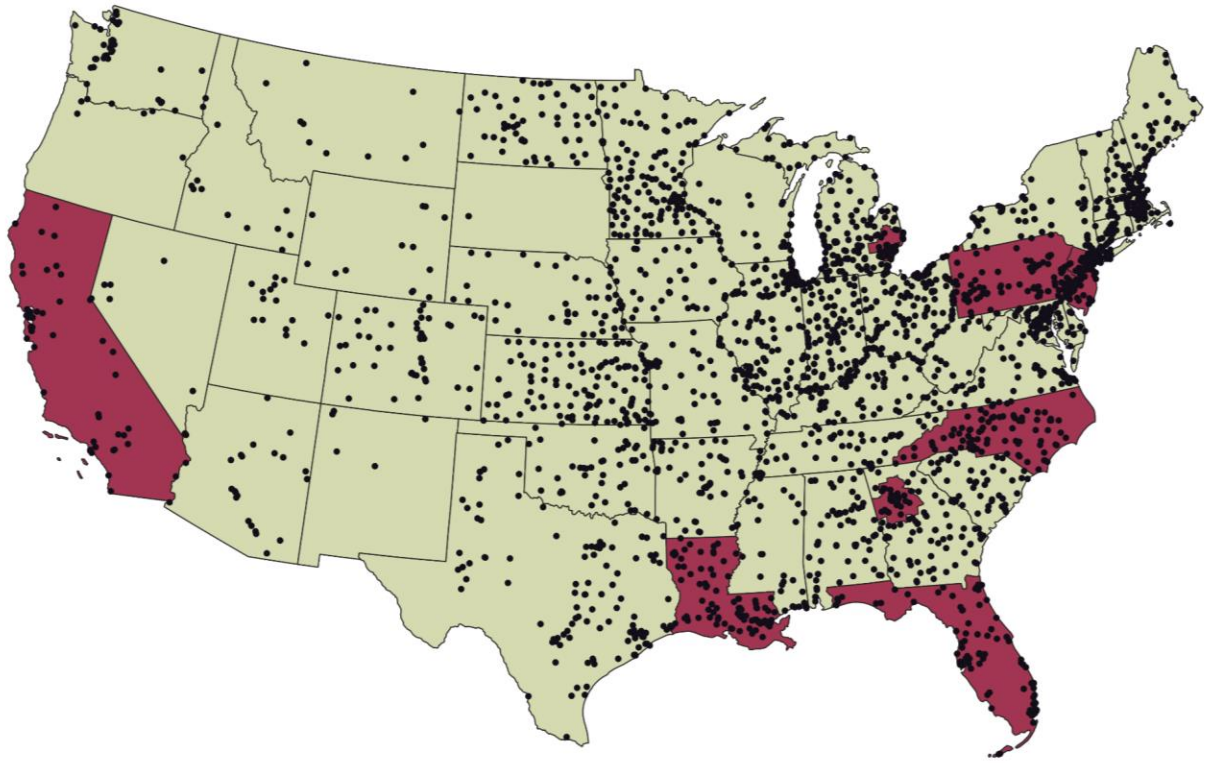
Association between historical dioxin emissions and NHL

1987, 1995, and 2000 dioxin emissions inventories

- Municipal solid waste incinerators
- Medical waste incinerators
- Cement kilns
- Coal-fired power plants
- Hazardous waste incinerators
- Sewage sludge incinerators

-Verified and updated locations with satellite imagery

-Interpolated emissions estimates between years

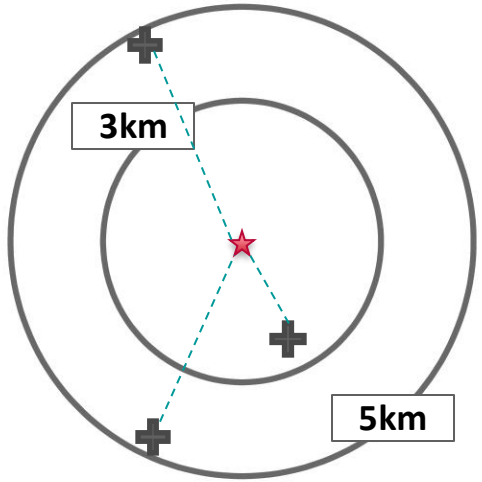


U.S. EPA, 2006

Exposure assessment

- Linked geocoded enrollment addresses to a U.S. EPA database of 4,478 historical PCDD/F sources
  - Facility type
  - Toxic equivalency quotient (TEQ) emission estimates in 1995 (toxicity relative to TCDD)
  - Imputed values back to 1980s using a linear interpolation approach [Pronk et al., 2013]

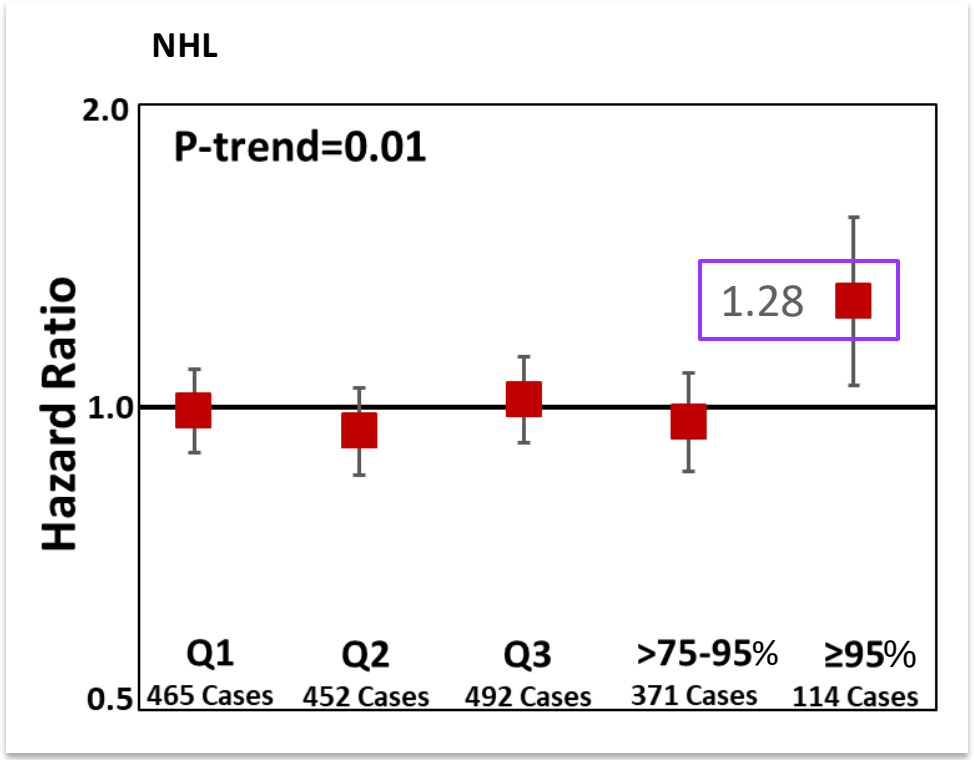
- Two exposure metrics
  - Proximity-based: **presence/absence** of dioxin facility within 3 and 5km
  - Emissions-based: distance-, wind- and toxicity-weighted average emissions index (**AEI; ng TEQ/km^2**) from all facilities within 3 and 5km
    - Facility-specific AEIs



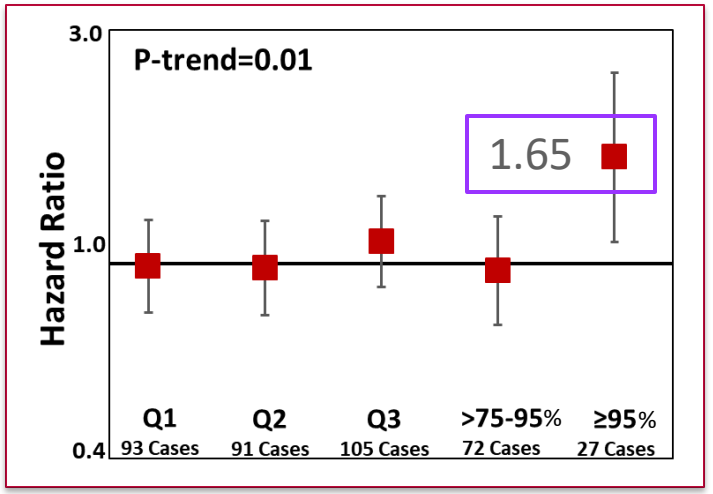
Demographics and Proximity to Dioxin-Emitting Facilities

	Overall	Distance to nearest facility ≤5 km	>5km
	N=455,744	N=132,755	N=322,989
Age (mean ± sd; yr)	62.0 ± 5.4	62.0 ± 5.4	62.1 ± 5.4
Gender (% Male)	59.7	58.0	60.4
Race/Ethnicity (%)			
Non-Hispanic White	90.9	88.1	92.1
Non-Hispanic Black	4.0	7.2	2.7
Hispanic	2.0	1.8	2.1
Other/Unknown	3.1	3.0	3.2
Schooling Achieved (%)			
Less than HS or HS	25.1	28.3	23.7
Post-HS Education	32.9	30.5	34.0
College Graduate	19.1	18.2	19.4
Post-Graduate	20.0	19.9	20.0
Unknown	3.0	3.1	2.9
Median Income (thousands)	54.9 ± 23.6	53.1 ± 24.3	55.6 ± 23.3

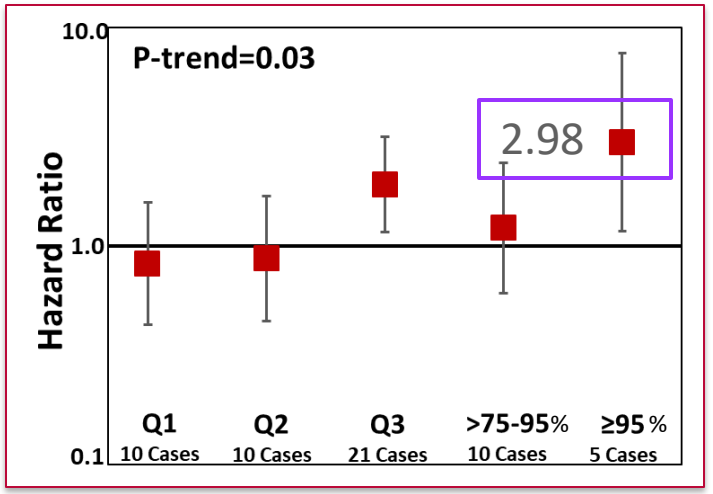
Association between dioxin AEI within 5km of participant homes and risk of NHL in the NIH-AARP cohort (1987-1995 average)



diffuse large B-cell lymphoma



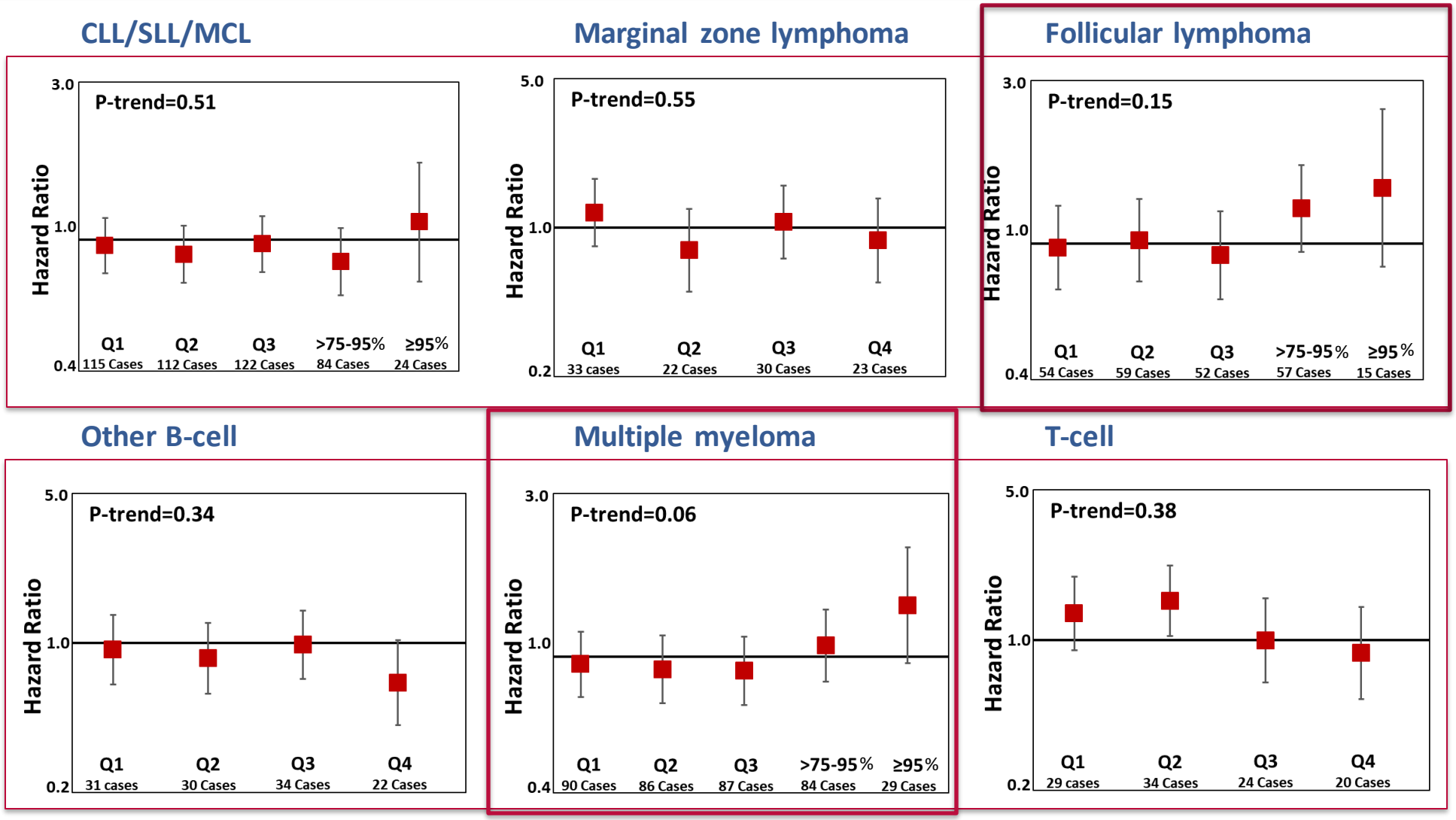
lymphoplasmacytic lymphoma



UNPUBLISHED DATA – DO NOT COPY

Fisher…Jones, in prep

Association between dioxin AEI within 5km of participant homes and risk of NHL in the NIH-AARP cohort (1987-1995 average)



Fisher…Jones, in prep

Exposure misclassification due to residential mobility over time

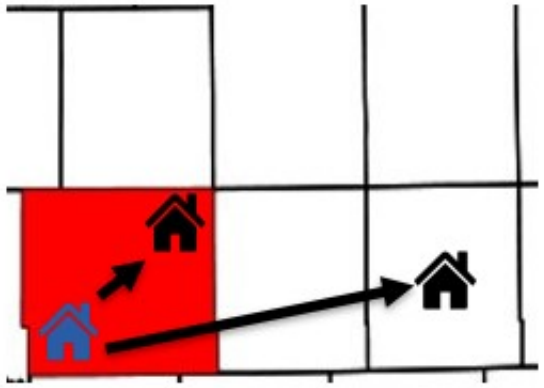
Many longitudinal studies use only the study enrollment address to assess exposure

- May be interested in past exposure and assume participant lived there previously

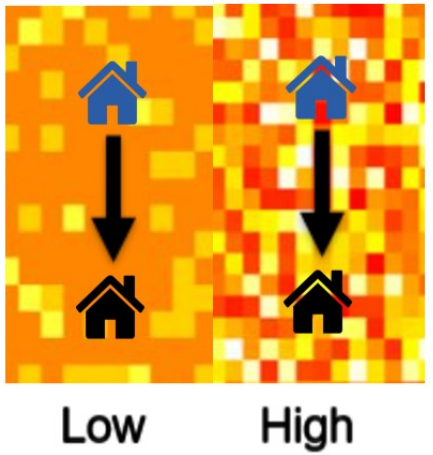
Misclassification can occur if participants moved during an exposure period of interest and this is not accounted for

The extent depends on:

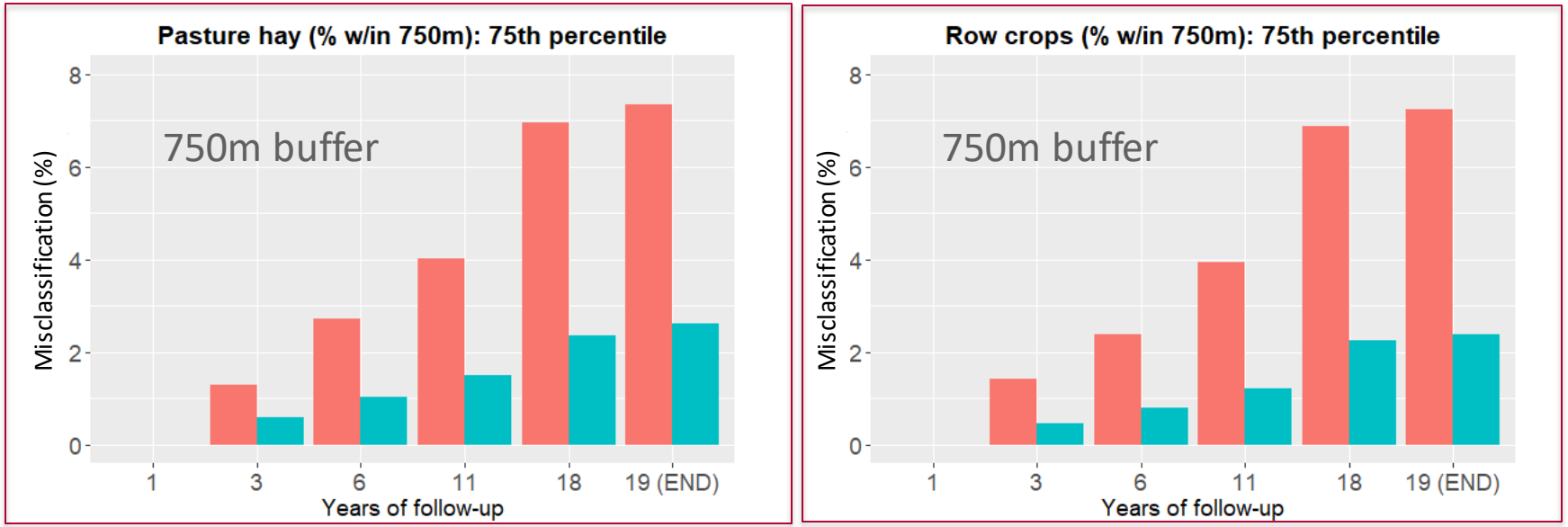
- Distance moved

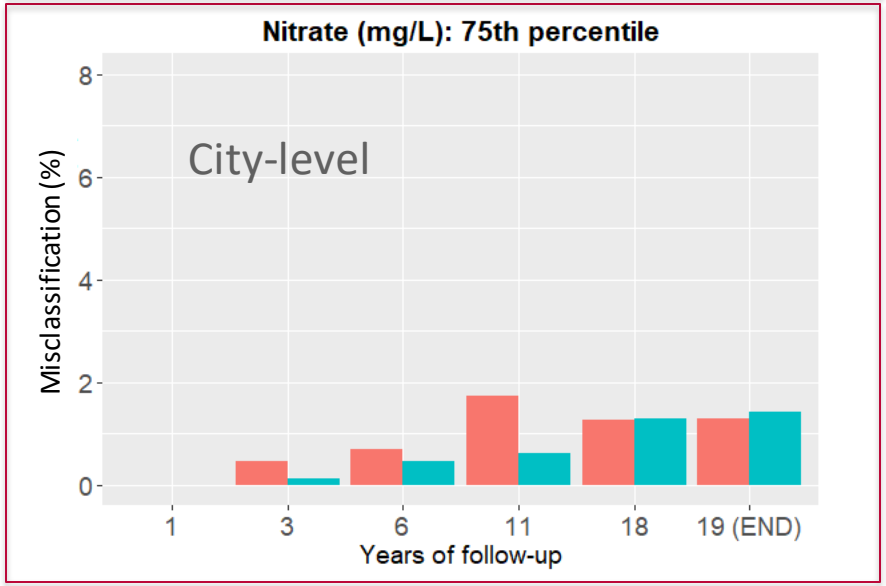


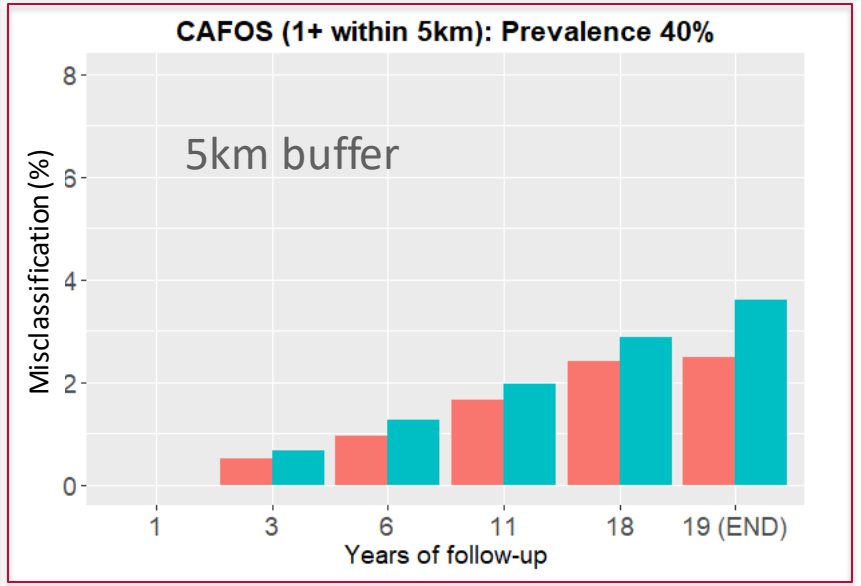
- Spatial variability of the exposure

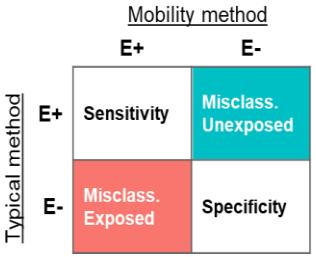


Influence of spatial scale on extent of misclassification

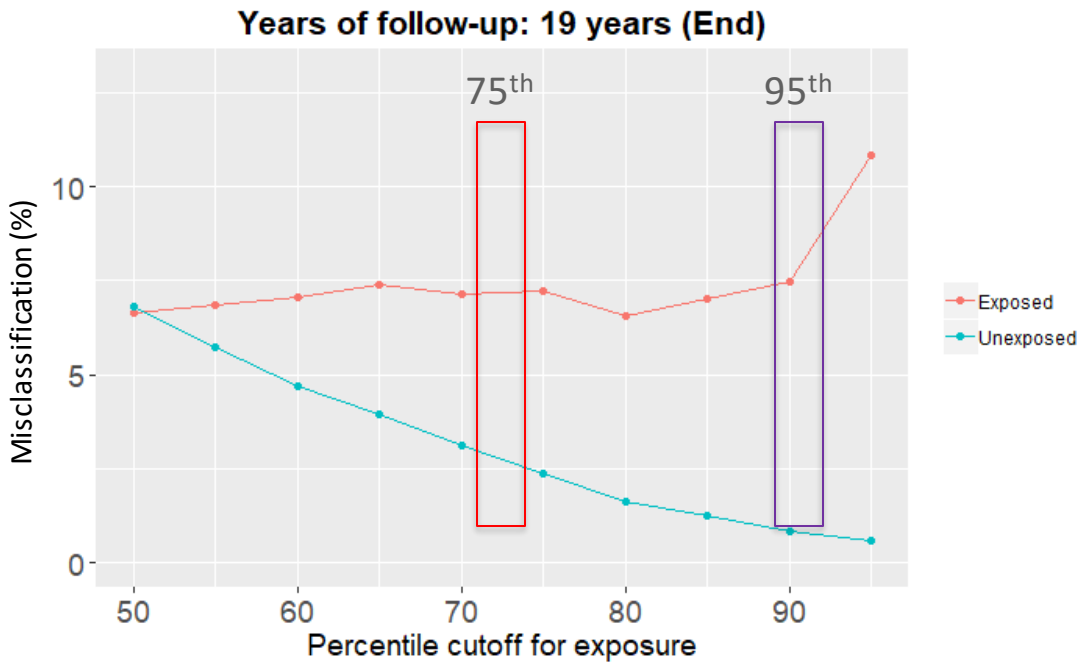


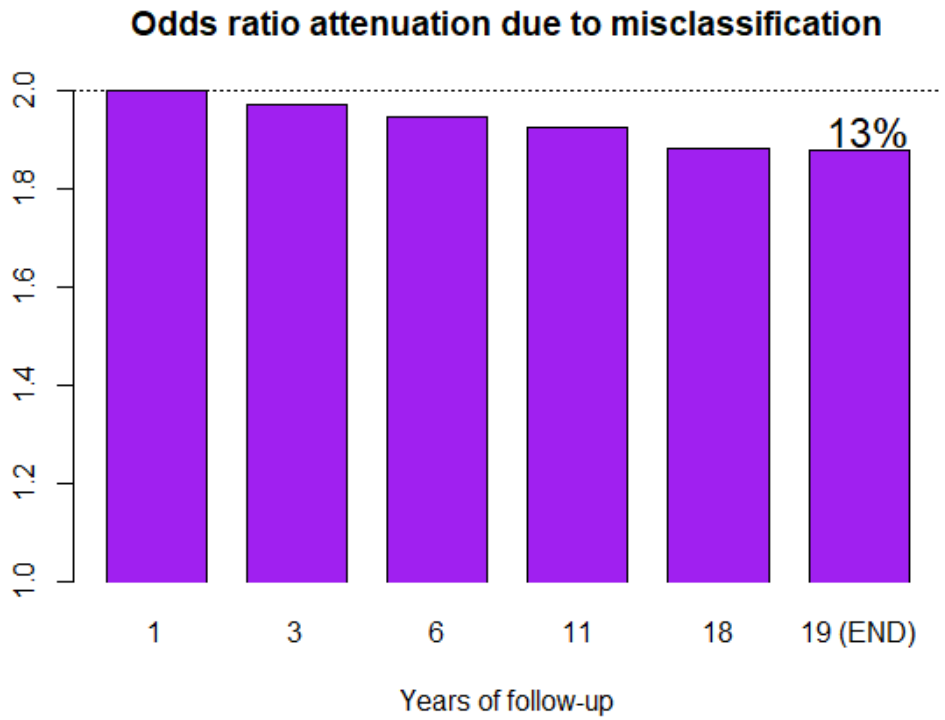




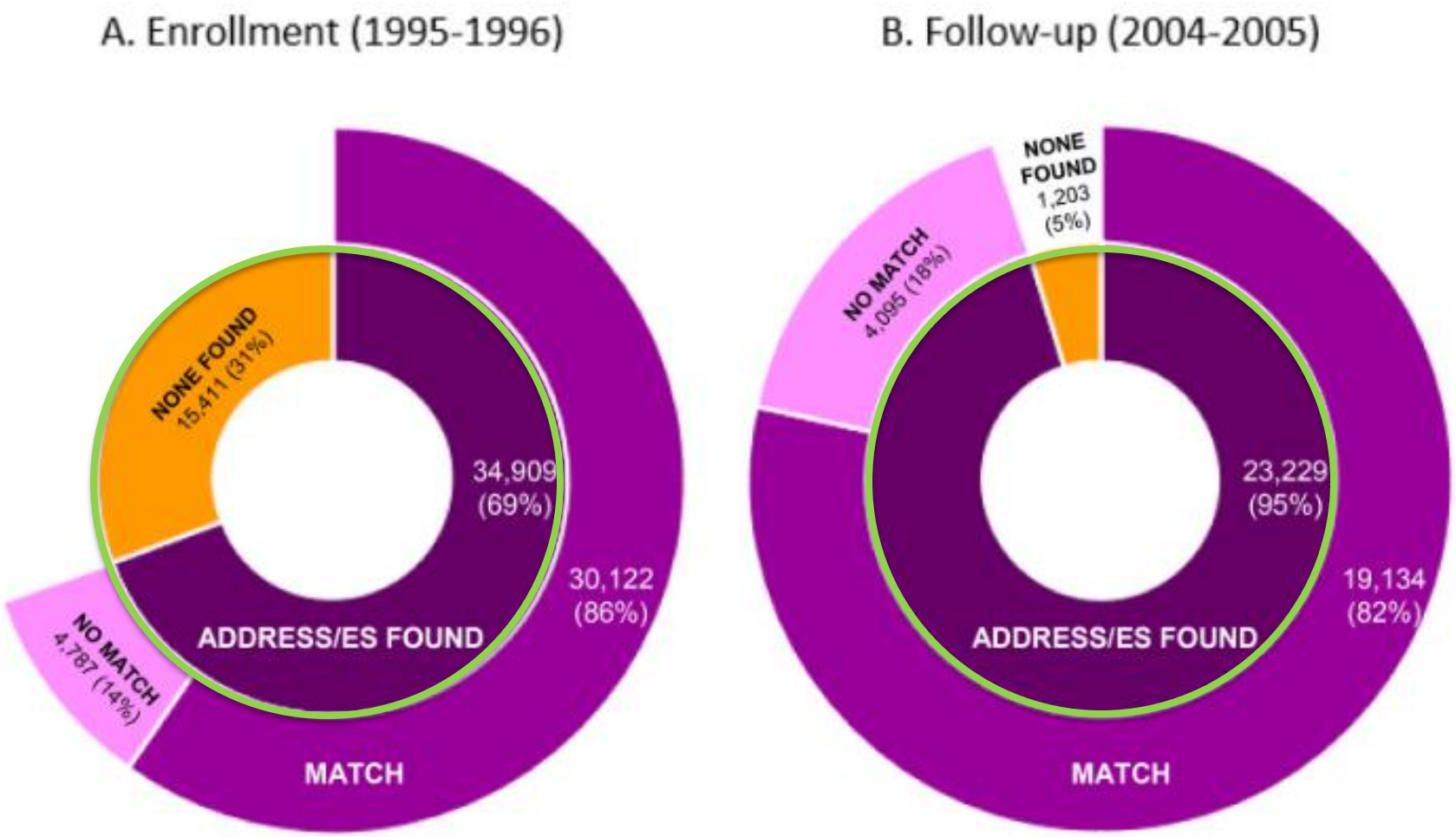


Resulting attenuation of relative measures of association





Fill residence history gaps using commercial data sources



Medgyesi…Jones, *Env Res*, 2021

Summary

Epidemiologic studies of long-term exposure to environmental contaminants and cancer are important given frequency of emissions and potential disparities in exposure burdens

Opportunities

- Combine GIS-based linkage/modeling, environmental monitoring, participant surveys, & other data to estimate exposure in key microenvironments
- Where historical data are available, ideally estimate exposure over the lifetime, during windows of susceptibility

Limitations are most commonly related to exposure assessment

- Challenges in using data collected for surveillance and regulatory purposes
- Modeled estimates can be difficult to validate

Acknowledgements

NCI
Jared Fisher
Melissa Friesen
Neal Freedman
Barry Graubard
Danielle Medgyesi
Jongeun Rhee
Josh Sampson
Elizabeth Sharp
Mary Ward

University of Minnesota
Anna Prizment

Colorado State University
John Nuckols

Westat GIS
Matt Airola
Abby Flory

Yale University
Nicole Deziel

TNO, Netherlands
Anjoeka Pronk

Harvard University
Francine Laden

NIEHS
Dale Sandler
Lexie White

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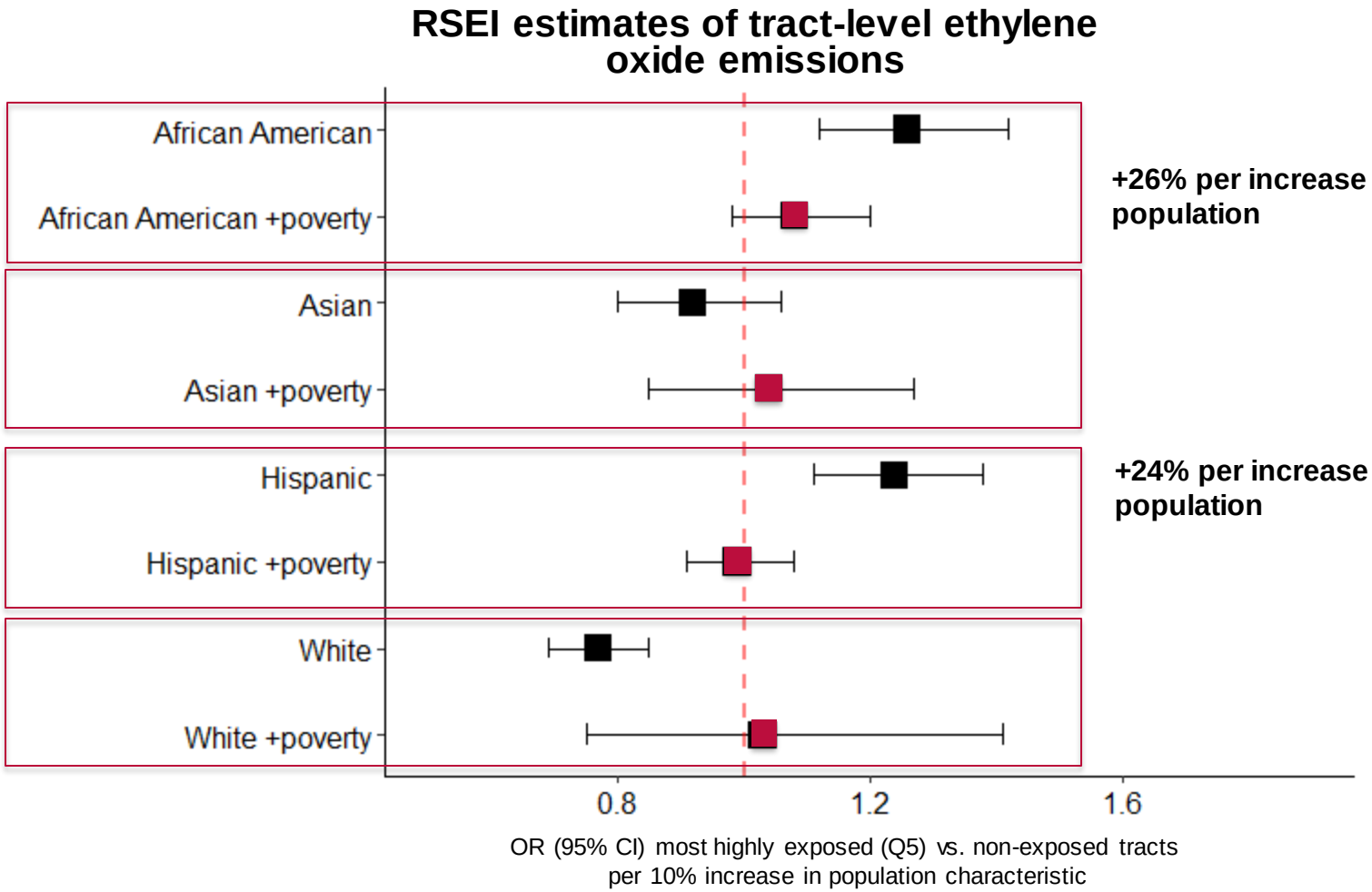
Associations of race and ethnicity and poverty with ethylene oxide exposure burden

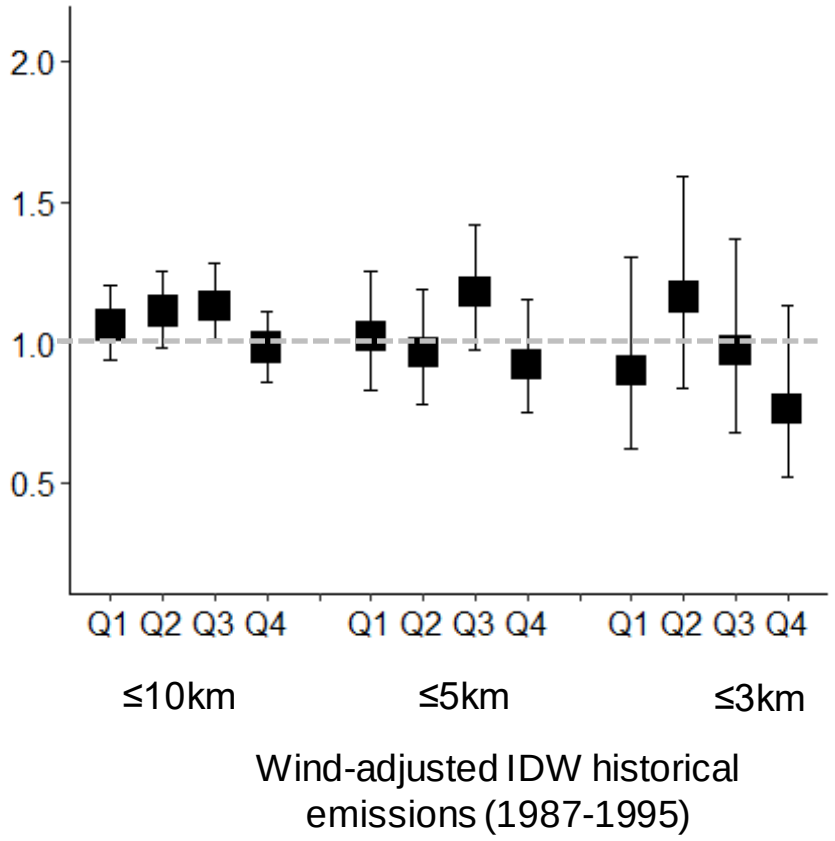


+26% per increase in African American population

+24% per increase in Hispanic population

Madrigal…Jones, *under review*

Association between ethylene oxide emissions near the home and risk of non-Hodgkin lymphoma (NHL)



By NHL histologic subtype:

-Suggestion of increased risks of follicular lymphoma and chronic lymphocytic leukemia

-Not in a dose-response fashion and analyses had sub-optimal power

Risk models adjusted for: state of residence, age, race and ethnicity, and smoking status.

Jones et al, *JNCI,* 2023