Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

"Modeling historic environmental pollutant exposures and non-Hodgkin lymphoma risk"

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October 24 - 25, 2023
Identifying Potential Health Impacts Session

Framework

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Exposome in risk assessment: "every exposure to which an individual is subjected from conception to death" (Wild 2012)

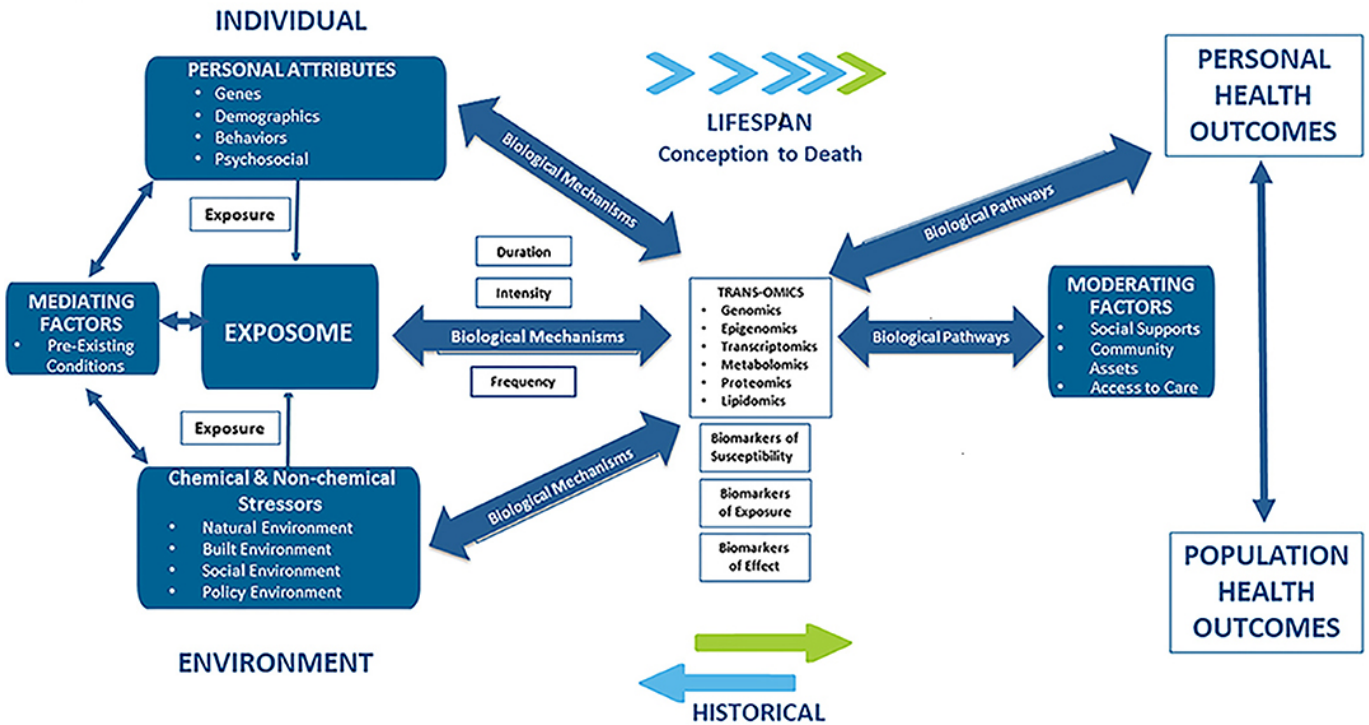


Figure: (Juarez et al. 2020)

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Background: NHL

- Expected to be the 7^{th} and 6^{th} highest incidence cancer for men and women, respectively, in the US in 2023, and account for the 9^{th} most cancer deaths (Siegel et al. 2023)
- Non-modifiable risk factors (Thandra et al. 2021) :
  - Age > 65, male sex, non-Hispanic White race, family history, immunosuppression
- Modifiable risk factors (IARC 2023) :
  - Sufficient evidence: Hepatitis C virus, HIV, Azathioprine, Cyclosporine, Lindane, Pentachlorophenol
  - Limited evidence: Benzene, Chlorophenoxy herbicides, DDT, Diazinon, Dichloromethane, Ethylene oxide, Glyphosate, Hepatitis B virus, Malathion, PCBs, Polychlorophenols, TCE, $X-$ and $\gamma-$ radiation

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

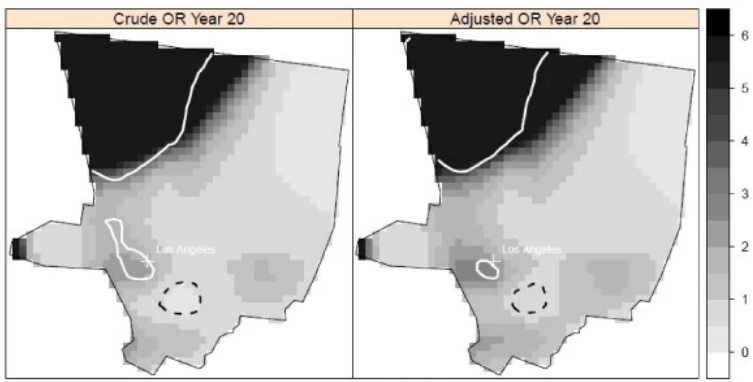
NCI-SEER NHL Study

Study:

- Case-control study of NHL
- Multi-center: Detroit, Iowa, Los Angeles County, Seattle
- 1321 cases, 1057 controls matched on age, sex, race, center

Previous analyses of data from this study (Boyle et al. 2022, Wheeler et al. 2011, 2012, Wheeler and Calder, 2016) identified:

- Significant associations between a mixture of pesticides (e.g., $\alpha-$ and $\gamma-$ chlordane, propoxur) and NHL
- Significantly elevated unexplained risk for NHL at areas in 3 study centers



Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Objectives

Research Objective: Estimate associations of historic environmental exposures with NHL risk while adjusting for chemical exposures inside the home, covariates, and cumulative spatial risk.

Operationalize historic environmental exposures as:

- Model 1: Carcinogenic RSEI scores at year $t \in \{0, 1, \ldots, T\}$
- Model 2: Cumulative mixture of carcinogenic RSEI scores taken over all years $t \in \{0, 1, \ldots, T\}$
- Model 3: Cumulative mixture of chemical-specific RSEI scores

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Exposures: TRI/RSEI

Models 1 and 2:

- Spatially intersected annual residential location with RSEI grid
- Assigned carcinogenic RSEI scores, either:
  - For grid cell containing residential location
  - Averaging scores for grid cell and its first-order neighbors

Model 3:

- Assigned annual exposures of chemical-specific RSEI scores using inverse distance weighting between location of the participant and locations of facilities releasing chemicals in the state containing the location (and the adjacent states)

For all models, used $\log(\text{RSEI scores})$ due to considerable skew

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Exposures: Vacuum Dust

Vacuum cleaner dust was sampled from homes of consenting participants, and the following chemicals in 4 mixtures were measured using gas chromatography/mass spectrometry:

- *Polychlorinated biphenyls (PCBs):* congeners 105, 138, 153, 170, 180
- *Polycyclic aromatic hydrocarbons (PAHs):* Benz(a)anthracene, Benzo(a)pyrene, Benzo(b)fluoranthene, Benzo(k)fluoranthene, Chrysene, Dibenz(ah)anthracene, Indenopyrene
- *Pesticides I:* α-chlordane, γ-chlordane, Carbaryl, DDE, DDT, *o*-phenylphenol, Pentachlorophenol, Propoxur
- *Pesticides II:* Chlorpyrifos, *cis*-permethrin, *trans*-permethrin, $2,4$-D, Diazinon, Dicamba, Methoxychlor

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Models

Model:

$$Y_i \sim Bernoulli(p_i), \quad \text{where} \quad \log\left(\frac{p_i}{1-p_i}\right) =$$

$$\beta_0 + \underbrace{\sum_{j=1}^{4} \beta_j \sum_{k=1}^{C_j} \omega_{jk} q_{ijk}}_{\text{in-home chemical exposures}} + \underbrace{\beta_5 * EE_i}_{\text{environmental exposures}} + \underbrace{\sum_{b=1}^{B} \theta_b x_{ib}}_{\text{covariates}} +$$

$$\underbrace{\sum_{r \in A_{(i)}} w_{ir} \sum_{m=1}^{n_K} \psi_m C\left[\|s_{ir} - \kappa_m\|/\rho\right]}_{\text{cumulative spatial risk}}$$

In separate models, environmental exposure (EE_i) is:

$$\left[\underbrace{rsei_{it}}_{\text{Class 1}}, \underbrace{\sum_{t=0}^{11} \omega_{t5} rsei_{it}}_{\text{Class 2}}, \underbrace{\sum_{t=0}^{11} \gamma_t \sum_{j=1}^{C_5} \omega_{jt} q_{ijt}}_{\text{Class 3}} \right]$$

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Results

Center	Detroit	Iowa	Los Angeles	Seattle
Sample Size	201	335	292	342
Status				
Case	127 (63)	188 (56)	168 (58)	182 (53)
Control	74 (37)	147 (44)	124 (42)	160 (47)
Age (years)	58 (11)	61 (11)	59 (11)	59 (11)
Sex				
Male	114 (57)	177 (53)	165 (57)	171 (50)
Female	87 (43)	158 (47)	127 (43)	171 (50)
Race				
White	164 (81)	331 (99)	215 (74)	316 (92)
Non-White	37 (19)	4 (1)	77 (26)	26 (8)
Education				
$<$12 years	23 (11)	32 (10)	31 (11)	19 (6)
12-15 years	124 (62)	241 (72)	171 (59)	201 (59)
16+ years	54 (27)	62 (19)	90 (31)	122 (35)

Table: Characteristics of NCI-SEER NHL study population.

Results: Model 1

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

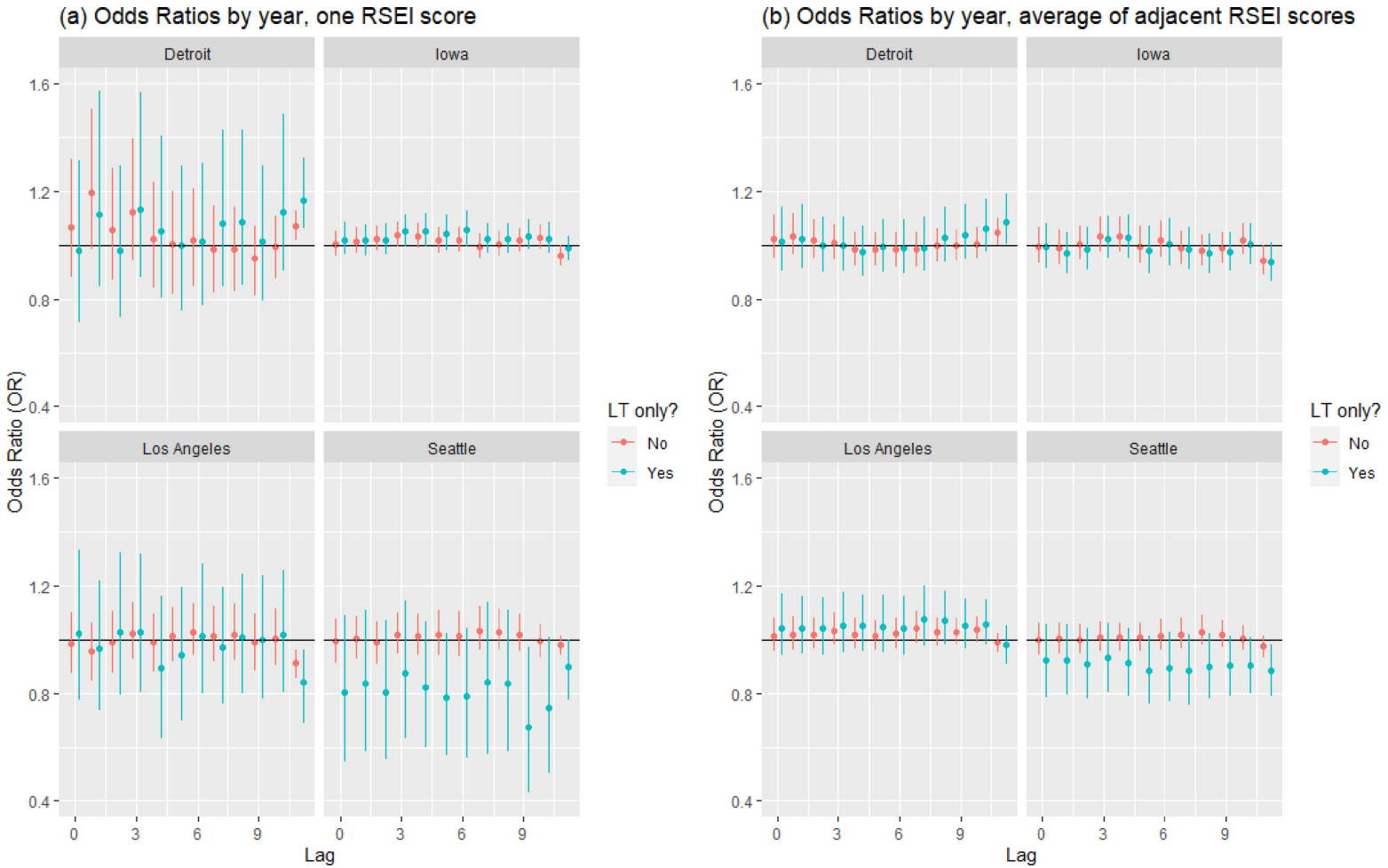


Figure: Summary of carcinogenic RSEI score associations with risk of NHL from Model 1. Several significant associations at lag 11 years.

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Results: Model 2

Center	Grid Cells	Residents	RSEI OR (CI)	Largest Wt.
DET	One	All	1.12 (0.92, 1.42)	11 (27%)
		LT	**1.29 (1.00, 1.82)**	11 (48%)
	Avg	All	1.18 (0.98, 1.54)	11 (29%)
		LT	**1.30 (1.02, 1.84)**	11 (47%)
IA	One	All	1.01 (0.95, 1.07)	11 (13%)
		LT	1.04 (0.97, 1.11)	4 (12%)
	Avg	All	1.01 (0.95, 1.08)	11 (13%)
		LT	1.03 (0.97, 1.11)	6 (11%)
LA	One	All	0.91 (0.82, 1.03)	11 (69%)
		LT	0.88 (0.67, 1.17)	11 (40%)
	Avg	All	0.91 (0.82, 1.03)	11 (63%)
		LT	0.86 (0.64, 1.13)	11 (36%)
SEA	One	All	1.01 (0.93, 1.10)	8 (9%)
		LT	0.75 (0.49, 1.03)	9 (15%)
	Avg	All	1.01 (0.93, 1.10)	8 (9%)
		LT	0.79 (0.53, 1.07)	9 (14%)

Table: Cumulative RSEI score mixture associations with NHL, Model 2. Entries in Largest Wt. column denote year lag with largest estimated importance weight and the corresponding weight in parentheses.

Results: Model 3

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

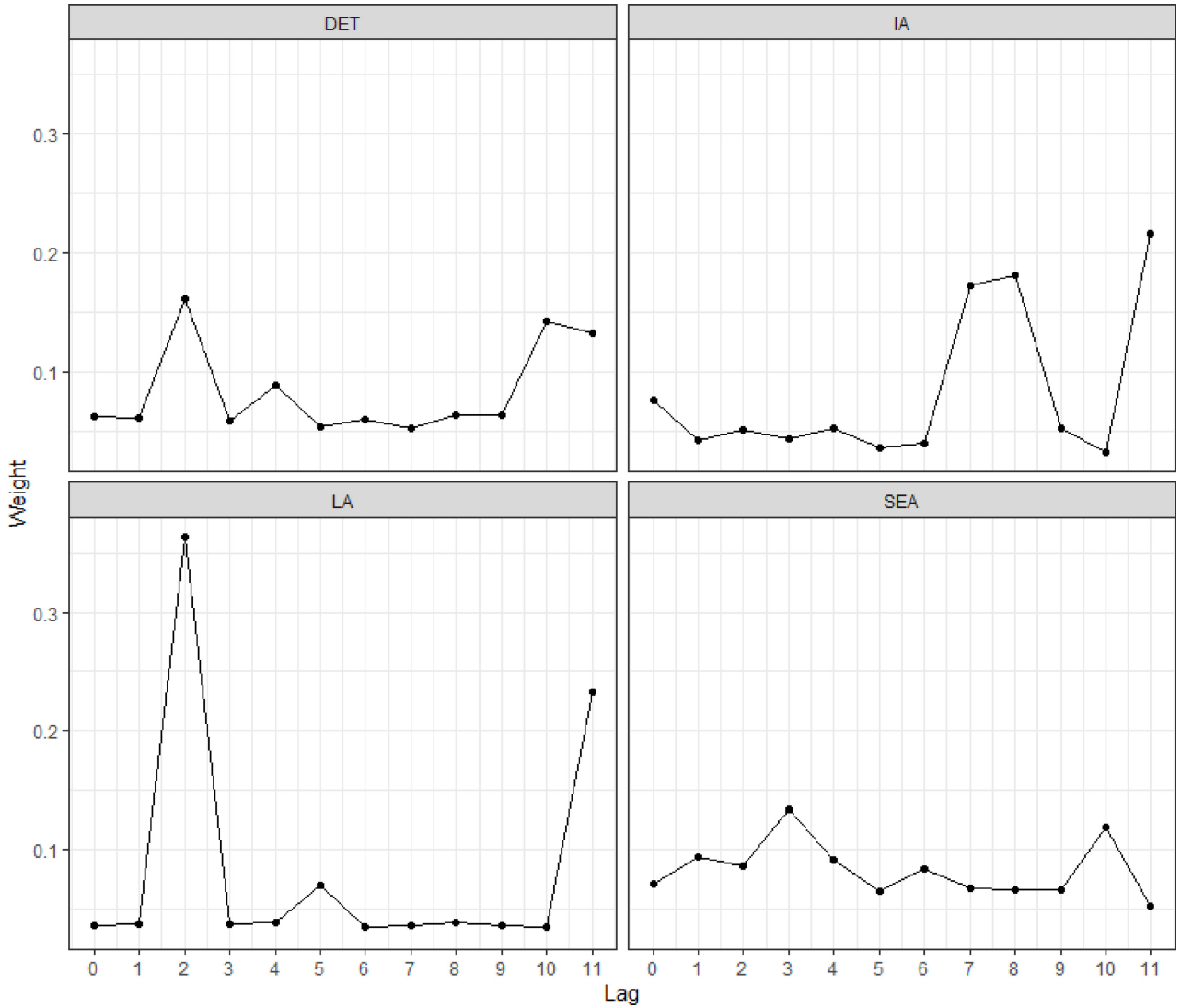


Figure: Summary of estimated yearly importance weights in cumulative chemical-specific RSEI mixture in Model 3.

Results: Model 3

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

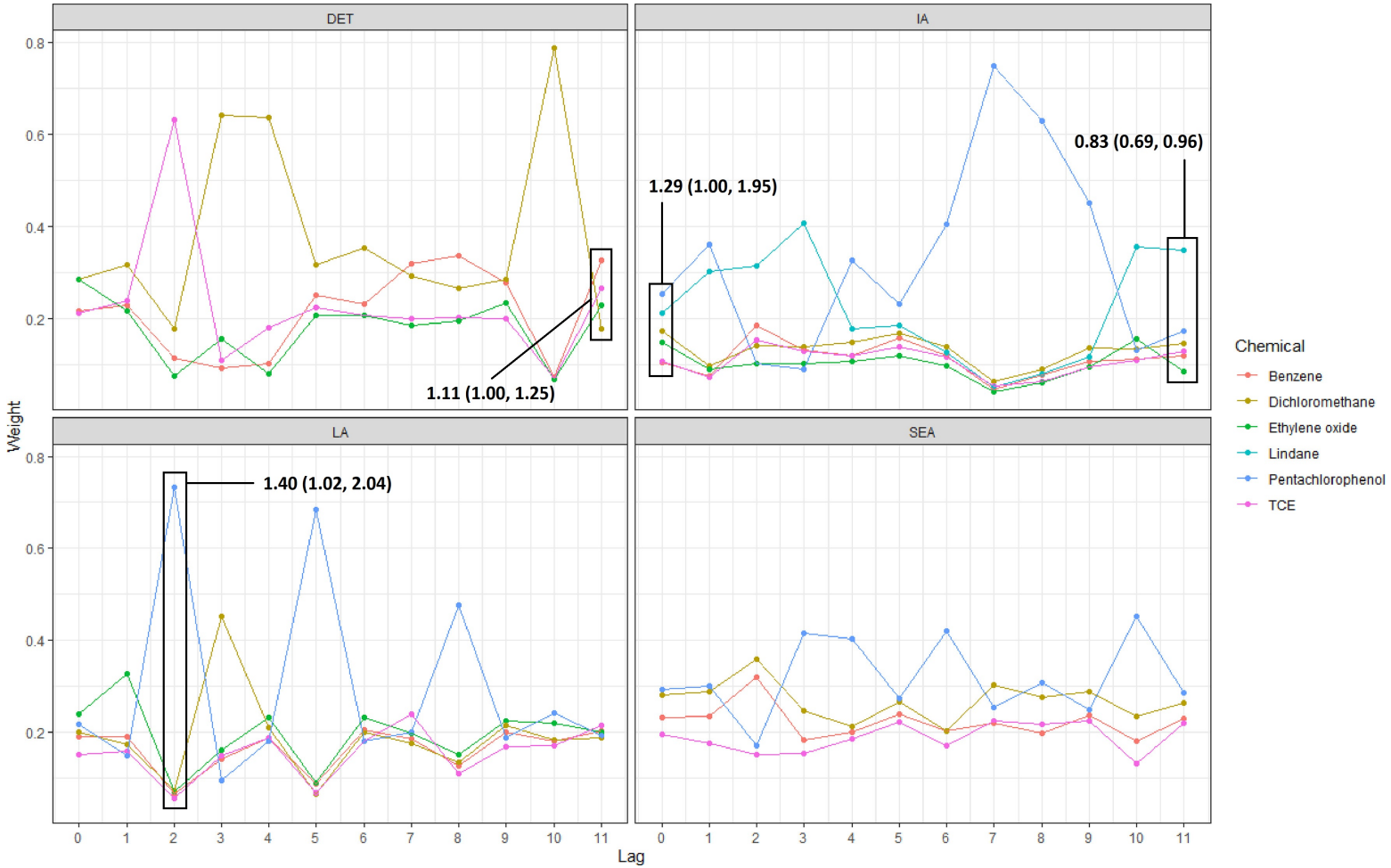


Figure: Summary of estimated chemical importance weights in Model 3 with odds ratio and credible interval for significant associations in text.

Results: Model 3

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Center	Odds Ratio	95% CI
Detroit	1.35	(0.89, 2.61)
Iowa	1.17	(0.56, 2.86)
Los Angeles	1.11	(0.61, 2.12)
Seattle	1.16	(0.74, 2.03)

Table: Odds ratios for cumulative chemical-specific carcinogenic RSEI mixture among long-term residents.

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Discussion

Findings with significant and positive association with NHL:

- RSEI scores 11 years before study entry in Detroit
- Cumulative RSEI mixture over the exposure period for long-term residents in Detroit
  - Exposures 11 years before entry had largest importance weight
- Mixture of specific RSEI carcinogens in Detroit at 11 years
  - Benzene, TCE received largest weights
- Further, positive associations with a mixture of chemical RSEI scores among long-term residents at each center
  - Pentachlorophenol, dichloromethane received largest weights

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Discussion

Strengths:

- Exposome approach to consider several dimensions of risk
- Bayesian index model to estimate mixture effects, chemical component importance weights, cumulative spatial risk
- Large public database with fine spatial precision (TRI, RSEI)
- Residential histories to proxy historic environmental exposures

Limitations:

- Reporting to TRI may undercount or miss certain releases
- Dates of enrollment for NCI-SEER study enabled us to estimate exposures for only up to 11 years before study entry
- Model 3 only included IARC-identified carcinogens for NHL
- Did not distinguish subtypes of NHL (Morton et al. 2008)

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Future Work

- Consider long or longer latency periods for environmental exposures
- Continue to analyze the role that benzene and TCE may play for NHL risk
- Harmonize TRI/RSEI with other data sources for more comprehensive environmental exposures

Introduction
Framework
NHL
Methods
Data
Objectives
Exposures
Models
Results
Model 1
Model 2
Model 3
Discussion
Acknowledgement

Acknowledgement

Disclaimer: Research reported in this presentation was supported by the National Cancer Institute of the National Institutes of Health under Award Number U01CA259376. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

NCI-SEER NHL collaborators: David C. Wheeler, Mary H. Ward, Nat Rothman, James R. Cerhan