

Meta-analytic approaches for multi-stressor dose-response function development: strengths, limitations, and case studies

Jonathan Levy, Sc.D.

Professor of Environmental Health

Boston University School of Public Health

Methods for Research Synthesis: A Cross-Disciplinary Approach

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Context

- Cumulative risk assessment: An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors (EPA, 2003)
 - Stressors = Chemicals, biological agents, physical agents, psychosocial factors, socioeconomic status, etc., etc., etc.
 - Epidemiological emphasis

Challenges in combining evidence

- Conventional meta-analyses may not be adequate for multi-stressor characterization
 - Single stressor epidemiological emphasis
 - Methodological variability
 - Disconnect between what risk assessors need and what epidemiologists report

3 case studies/3 approaches

- Differential toxicity of particle constituents
 - What can we learn from meta-analysis vs. new multi-city epidemiology?
- Effects-based CRA of blood pressure
 - What can we learn from meta-analysis vs. new structural equation modeling?
- Discrete event simulation of asthma exacerbation
 - How can we incorporate literature into a synthesis model that provides new insight?

Case #1

- Different particle constituents may have differing toxicity
- Does the available epidemiological literature provide a basis for incorporating differential values into risk assessments?
- If not, what is lacking, and can differential values be determined through new epidemiological approaches?

Literature review

- 1338 abstracts identified in Oct 2010
 - ➔ 65 primary epi studies including at least one of sulfate, nitrate, EC, OC
 - ➔ 42 studies with CRFs for at least one constituent, including uncertainty
 - ➔ 8 studies with quantitative estimates for all four constituents, largely from single-constituent models
 - ➔ 0 studies with probabilistic comparisons of toxicity across constituents

New epidemiology

- 119 counties with Medicare data from 2000-2008
- Bayesian hierarchical model of joint posterior distribution of health effects of four constituents
 - Posterior probability that each constituent is more toxic than another
 - Posterior correlation between each pair of health effects

Table 1. Pairwise Posterior Probability that a Particular Constituent of PM_{2.5} Had Greater Toxicity than Other Constituents, Expressed as Beta Coefficient per Unit Change in Concentration, United States, 2000–2008^a

	Cardiovascular Hospital Admissions				Respiratory Hospital Admissions			
	Nitrate	Sulfate	Organic Carbon Matter	PM _{2.5}	Nitrate	Sulfate	Organic Carbon Matter	PM _{2.5}
All 119 US counties								
Elemental carbon	0.999	1.000	1.000	1.000	0.710	0.719	0.576	0.669
Nitrate		0.890	0.977	0.940		0.447	0.055	0.194
Sulfate			0.802	0.427			0.125	0.253
Organic carbon matter				0.094				0.924
Eastern counties (<i>n</i> = 98)								
Elemental carbon	0.996	0.999	0.999	0.999	0.740	0.742	0.641	0.712
Nitrate		0.827	0.924	0.870		0.496	0.124	0.280
Sulfate			0.750	0.435			0.096	0.203
Organic carbon matter				0.131				0.869
Western counties (<i>n</i> = 21)								
Elemental carbon	0.850	0.874	0.852	0.868	0.613	0.658	0.558	0.593
Nitrate		0.692	0.740	0.718		0.602	0.342	0.411
Sulfate			0.436	0.345			0.286	0.330
Organic carbon matter				0.324				0.675

Abbreviation: PM_{2.5}, particulate matter less than 2.5 μm in diameter.
^a Each value represents the probability that the row constituent is more toxic than the column constituent.

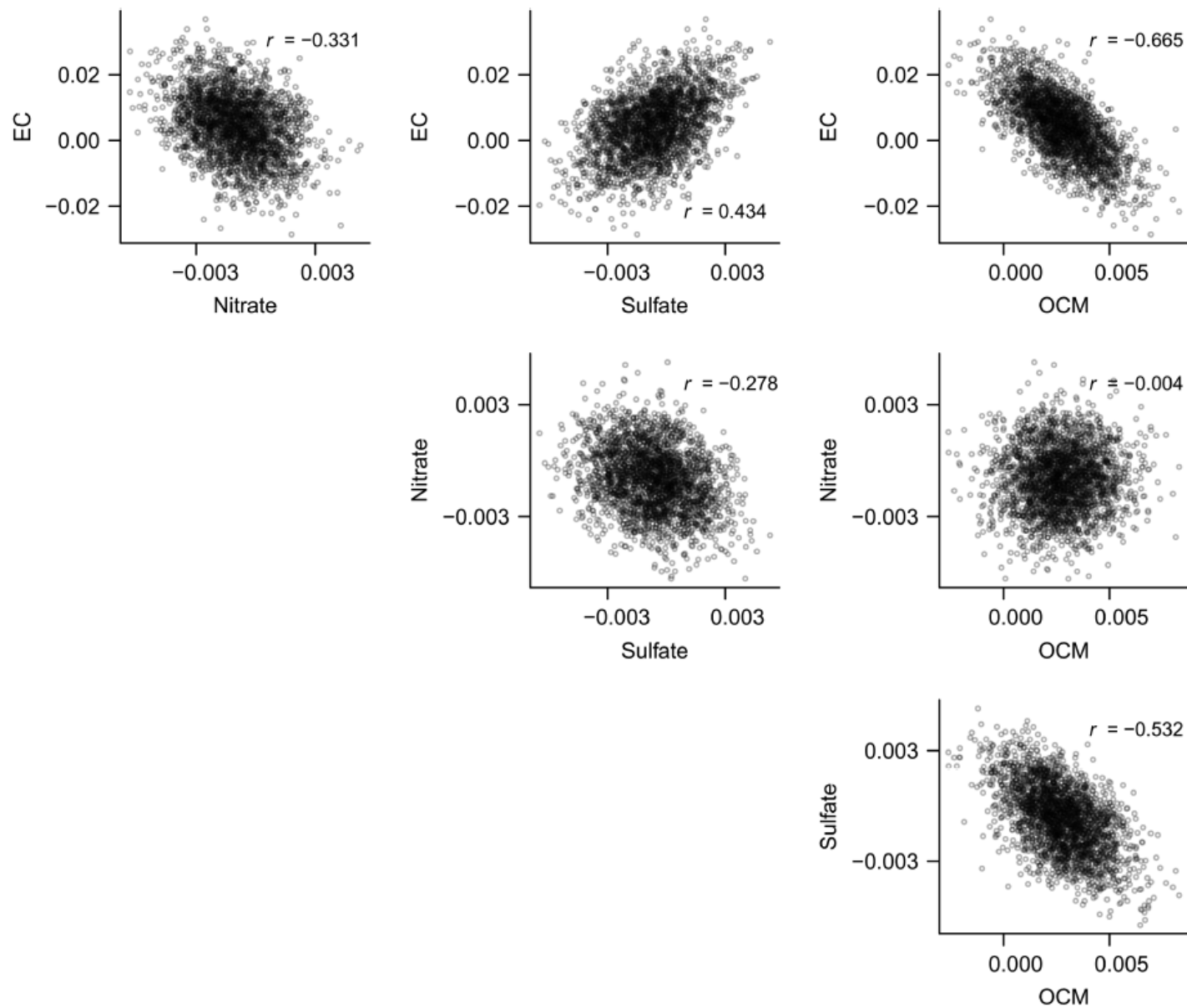


Figure 3. Scatterplots and correlations of posterior samples of beta coefficients per unit change in concentrations of fine particulate matter constituents for respiratory hospital admissions across the United States, 2000–2008. (EC, elemental carbon; OCM, organic carbon matter).

Approach	Most likely application	Strengths	Weaknesses
Literature meta-analysis	<ul style="list-style-type: none"> • RAs of limited number of related chemicals, where causality has been well established 	<ul style="list-style-type: none"> • Analytically less complex • Integrates current state of knowledge 	<ul style="list-style-type: none"> • Non-uniform methods • General lack of insight regarding multi-stressor associations
Multi-site epidemiology with Bayesian methods to pool evidence	<ul style="list-style-type: none"> • RA of mixtures of correlated pollutants (e.g., air pollution) • RA of chemical exposures monitored regularly, where associations may vary spatially 	<ul style="list-style-type: none"> • Standardized methods across locations • Ability to “borrow strength” across site-specific analyses 	<ul style="list-style-type: none"> • Statistically complex • Only applicable to limited number of exposures that can be characterized over many locations

Case #2

- Numerous chemical and non-chemical risk factors can influence blood pressure/hypertension
- Challenges in discerning associations from published literature given complex pathways
 - Benefits of fish consumption vs. adverse effects of mercury

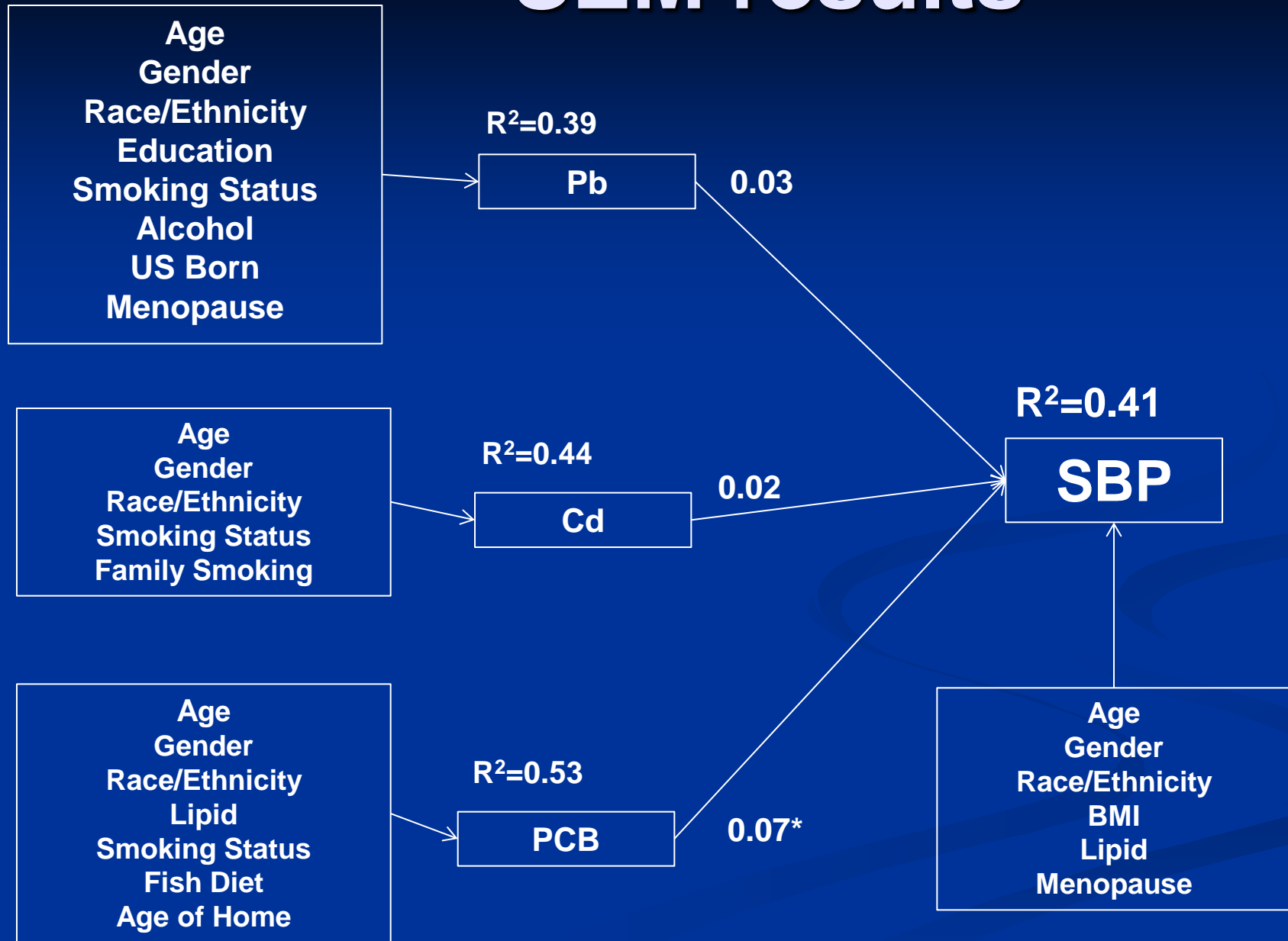
Literature review

Chemical Stressors	Synopsis of Epidemiological Evidence
Arsenic	Systematic review found association with prevalent hypertension. Study (Jones et al. 2011) in NHANES data found no association with SBP or DBP.
Bisphenol A	Two recent studies found association with hypertension, one using NHANES data.
Cadmium	Results with blood levels vary by gender, race and smoking status. Result with urinary levels inconsistent but suggests inverse relationship.
Lead	Systemic review suggested sufficient evidence to infer causal relationship with hypertension.
Mercury	Inconsistent findings with hypertension.
PCBs	Studies consistently report association with hypertension including in NHANES.

Structural equation modeling

- Ideal approach to evaluate simultaneous effects of multiple stressors that can operate through multiple pathways
- Requires clearly defined theoretical relationships among variables (not meant for data mining)

SEM results

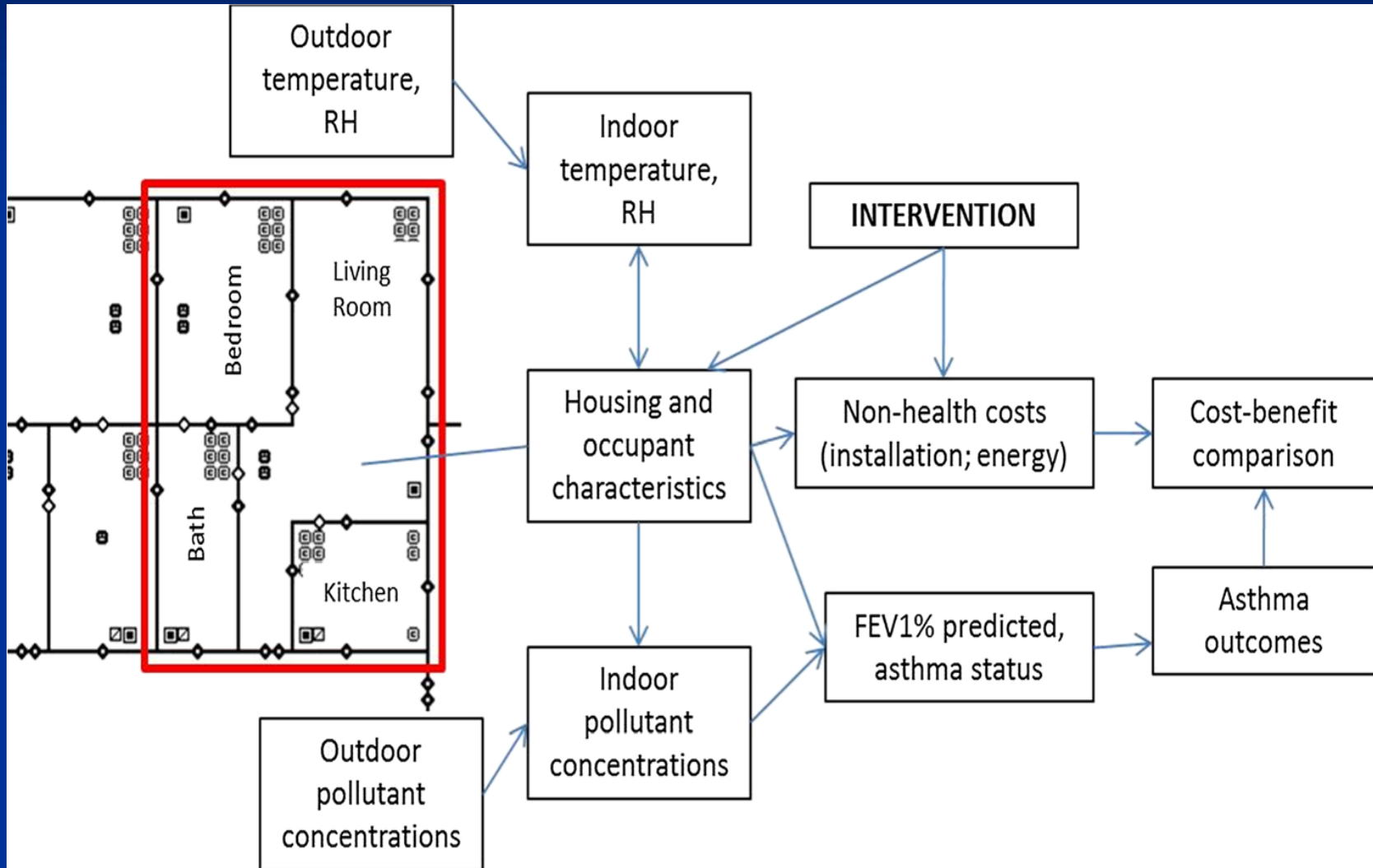


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Literature meta-analysis	<ul style="list-style-type: none"> • RAs of limited number of related chemicals, where causality has been well established 	<ul style="list-style-type: none"> • Analytically less complex • Integrates current state of knowledge 	<ul style="list-style-type: none"> • Non-uniform methods • General lack of insight regarding multi-stressor associations
Structural equation modeling	<ul style="list-style-type: none"> • Cumulative RA of chemical and non-chemical stressors • RAs in which non-chemical stressors could influence exposures and outcomes 	<ul style="list-style-type: none"> • Clarifies pathways among multi-level stressors • Flexible modeling approach 	<ul style="list-style-type: none"> • Statistically complex • Works best with continuous and normally-distributed covariates

Case #3

- Multiple indoor environmental stressors can exacerbate asthma, and interventions will change combinations of stressors in complex ways
- Standard literature synthesis cannot capture these complexities, especially for infrequent outcomes
 - Can we link literature synthesis with a modeling approach to develop new insights?

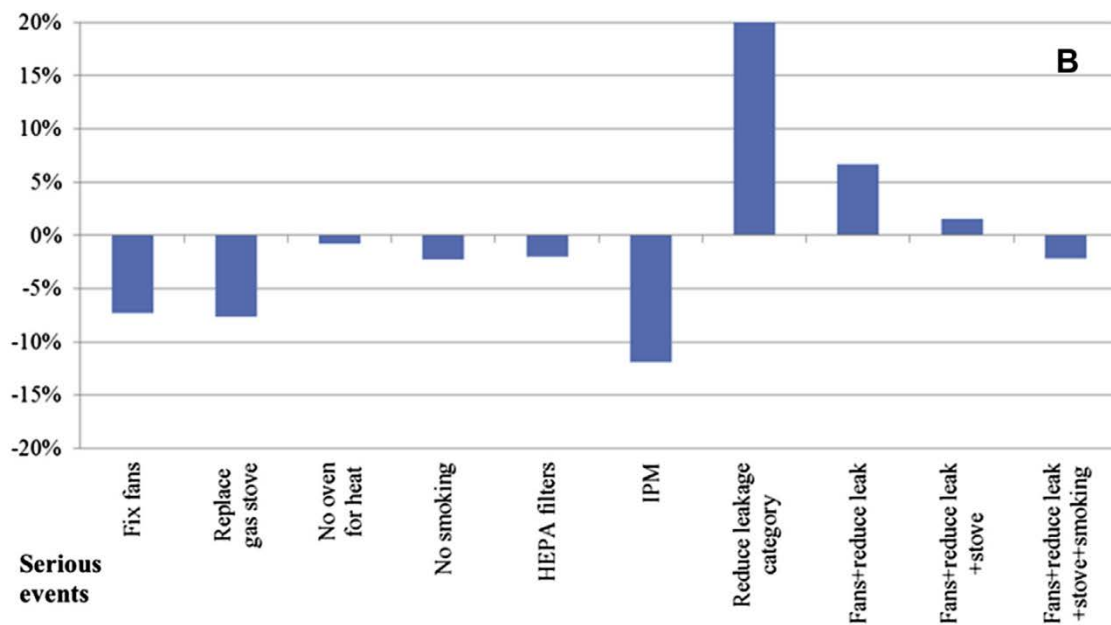
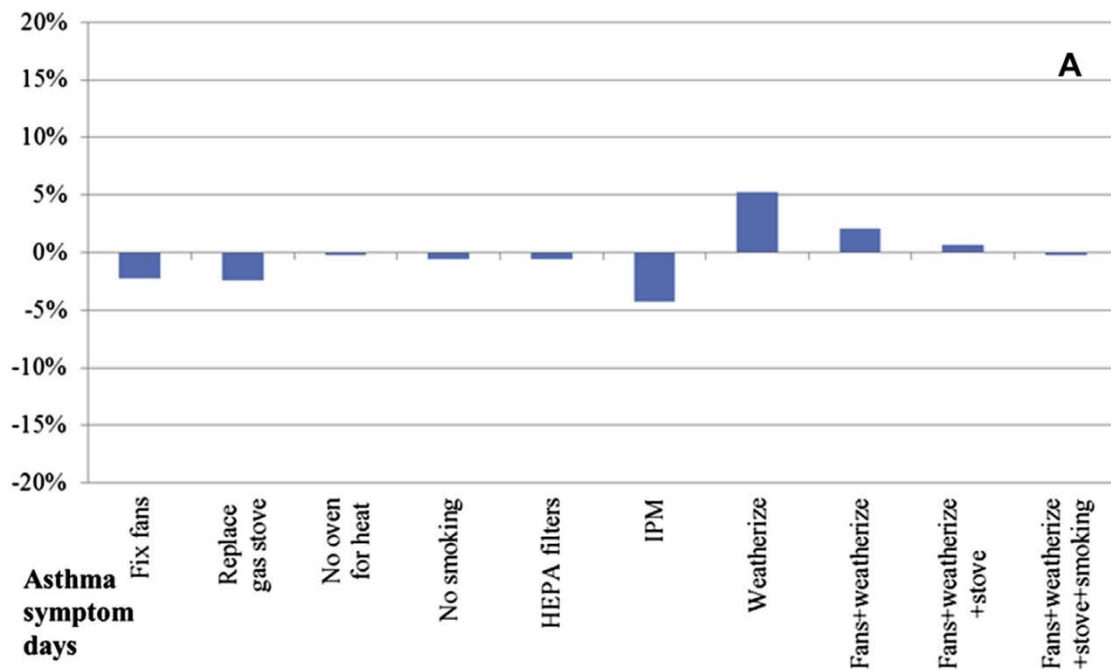
Discrete event simulation model



Example of literature synthesis (Fabian et al. 2012)

- Joint literature review of PM_{2.5} and NO₂ vs. FEV1%
 - 413 abstracts identified
 - ➔ 17 primary epi studies meriting closer scrutiny
 - ➔ 5 studies with relevant outcome measures and appropriate quantification
 - ➔ 1 study with multi-pollutant estimates that could be connected with our indoor air model

Percent change in health outcomes compared to baseline (event/year)



Interventions

Approach	Most likely application	Strengths	Weaknesses
Literature meta-analysis	<ul style="list-style-type: none"> • RAs of limited number of related chemicals, where causality has been well established 	<ul style="list-style-type: none"> • Analytically less complex • Integrates current state of knowledge 	<ul style="list-style-type: none"> • Non-uniform methods • General lack of insight regarding multi-stressor associations
Discrete event simulation modeling	<ul style="list-style-type: none"> • RA applications with time-varying associations and feedback loops • RAs in which multiple policy options are under consideration • RA of rare outcomes which would be logistically challenging to study with only epidemiology 	<ul style="list-style-type: none"> • Integrates multiple types of data to answer complex health outcome questions • Allows for evaluation of intervention scenarios modifying individual or clusters of factors • Generates evidence for policy analysis • Allows for inclusion of rare events and dynamic systems 	<ul style="list-style-type: none"> • Statistically complex and computationally demanding • Model parameterization limited by published literature

Important research needs

- Application of multiple approaches to the same question (meta-analysis vs. multi-city epidemiology)
- More formal consideration of optimal epidemiological methods for mixtures/multiple stressors
- More collaborative research between epidemiologists and risk assessors

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- Co-authors: Patricia Fabian, Junenette Peters
- Collaborators: David Diez, Yiping Dou, Christopher Barr, Francesca Dominici, Natasha Stout, Gary Adamkiewicz, Amelia Geggel, Cizao Ren, and Megan Sandel

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- Fabian MP, Stout NK, Adamkiewicz G, Geggel A, Ren C, Sandel M, Levy JI. The effects of indoor environmental exposures on pediatric asthma: a discrete event simulation model. *Environ Health*, 2012;11:66.