Incorporating Non-chemical Stressors into Cumulative Risk Assessment (CRA)

SOT Risk Assessment Specialty Section (RASS)
& Mixtures Specialty Section (MSS)
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Motivation…

- Epidemiologic evidence suggests greater susceptibility to air pollution & other toxicant exposures among lower-SEP populations. (Jerrett et al 2004; Krewski et al 2000; Hicken et al 2013; Shmool et al 2015)
  - Have not identified "causal components" of SES (Matthews and Gallo 2011).
  - Epidemiologic and toxicologic evidence suggests chronic stress as one important contributor. (Clougherty et al., 2007, 2014; Chen et al 2008; Cory-Slechta et al 2013; Peters et al 2007; Virgolini et al 2005)
- Chronic stress confers broad physiologic changes, known as allostatic load. (McEwen 1998)
  - HPA-axis regulation
  - Glucocorticoid receptor alteration
  - Sympathetic-adrenal-medulary (SAM) regulation
  - Early life immune function (e.g., Th-1/ Th-2)

Motivation… (cont'd)

- Thus, there is now growing attention towards disentangling social and physical environmental risks & understanding potential synergies.
  - Towards identifying modifiable exposures,
  - protecting susceptible populations,
  - and improving population health. (U.S. EPA 2008)

Motivation… (cont'd)

- Thus, recent cumulative risk assessments (*CRAs) have begun to incorporate non-chemical stressors*, including psychosocial stressors.
  - A large number of review papers and frameworks have now been offered:
    - Alves et al 2012; August et al 2012; Hicken et al 2011; Harper et al 2013; Lewis et al, 2011; McEwen & Tucker 2011; Morello-Frosch et al 2011; Rider et al 2013; Schwartz et al 2011; Sexton & Linder, 2011; Wason et al 2012
  - Though operationalizing these frameworks remains challenging.

- Finally, many stressors (physical & psychosocial) may impact upon any given health outcome.
  - May be derived from *community or occupational environment*

    & exposures from one setting may modify impacts of exposures in the other.

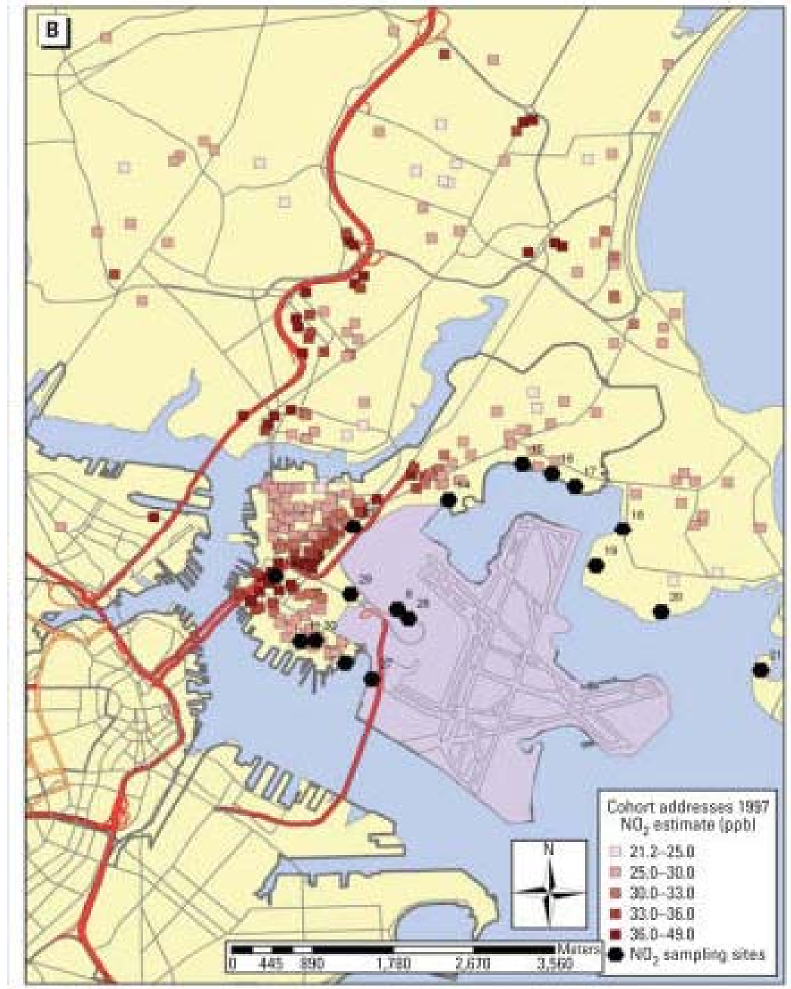
  => there is a growing need to incorporate *multiple exposures* derived from *multiple environments* into CRAs.

Epidemiologic evidence suggests heightened susceptibility to air pollution under chronic stress.

Table 4. Multivariate model for asthma diagnosis [OR (95% CI)].

	Full cohort
Maternal asthma (ever diagnosed)	1.31 (0.58–2.96)
In utero tobacco smoke exposure	1.07 (0.44–2.58)
Maternal smoking since birth	1.10 (0.70–1.72)
Less than high school education	1.14 (0.71–1.81)
Child's sex (female)	0.85 (0.54–1.34)
Child's age (≥ 7 years)	1.44 (0.90–2.33)
High ETV	0.89 (0.56–1.43)
NO_2 year of diagnosis: low ETV	0.99 (0.73–1.34)
NO_2 year of diagnosis: high ETV	1.63 (1.14–2.33)

ORs for NO_2 are associated with a 1-SD (4.3 ppb) increase.



Clougherty JE, et al *Environ Health Perspect*. 2007 Aug;115(8):1140-6.

Toxicological results suggest stress-differing respiratory response to PM.

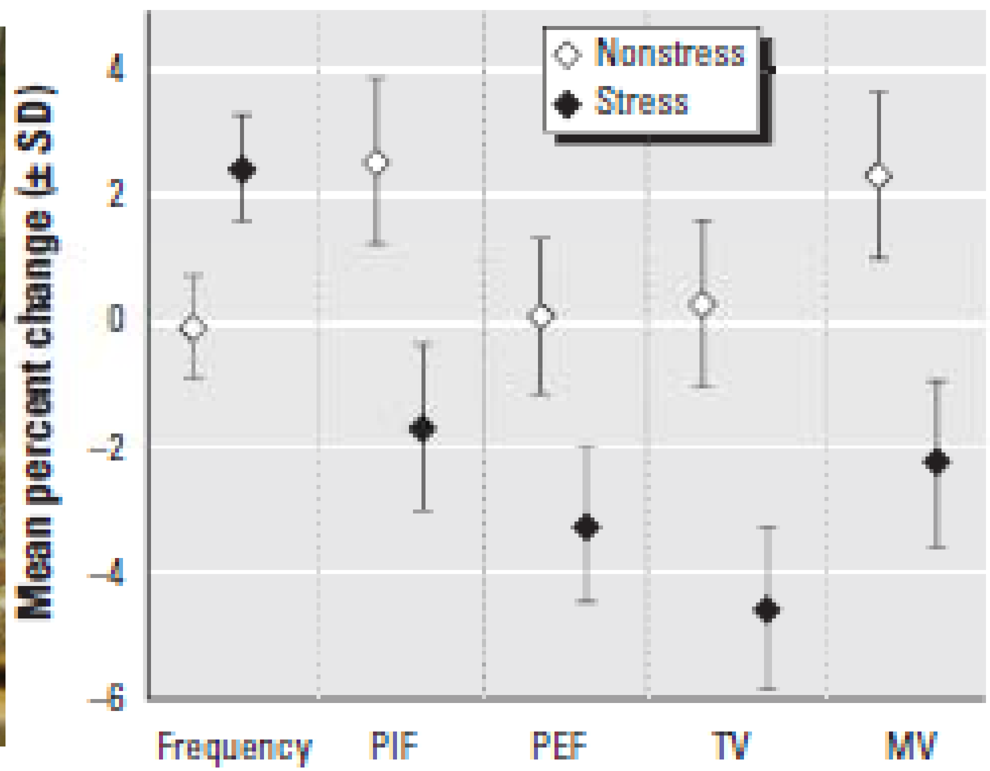


Figure 1. Estimated change in respiratory measures with a 1-SD (164.5 μg/m^3) change in PM mass concentration, by stress group.

Clougherty et al., *EHP*, 2010

Case Example: Integrating one non-chemical stressor into a cumulative risk framework

Case Example: Exposure to violence and air pollution in childhood asthma

- Environmental and occupational risk assessors typically focused on chemical/ physical exposures.
  => Consider non-chemical stressors as modifier/ contextual factors

- Following steps in *Science and Decisions* and Menzie et al (2007) frameworks

- Detail drawn from:
  - Clougherty JE, Kubzansky LK. A framework for examining social stress and susceptibility to air pollution in respiratory health. *EHP* 2009.
  - Clougherty JE, Levy JI. "Chapter 17: Psychosocial and chemical stressors" in *Mixtures Toxicology and Risk Assessment.* Rider C & Simmons JE, eds. Springer *(forthcoming).*
  - "Community Stressors and Susceptibility to Air Pollution in Urban Childhood Asthma" (RD-83457601-0)
    - Mechanism: EPA-G2009-STAR-E2 (Understanding the Role of Nonchemical Stressors and Developing Analytic Methods for Cumulative Risk Assessments)

Violence as a Chronic Stressor…

- One of the few stressors rarely positively appraised.

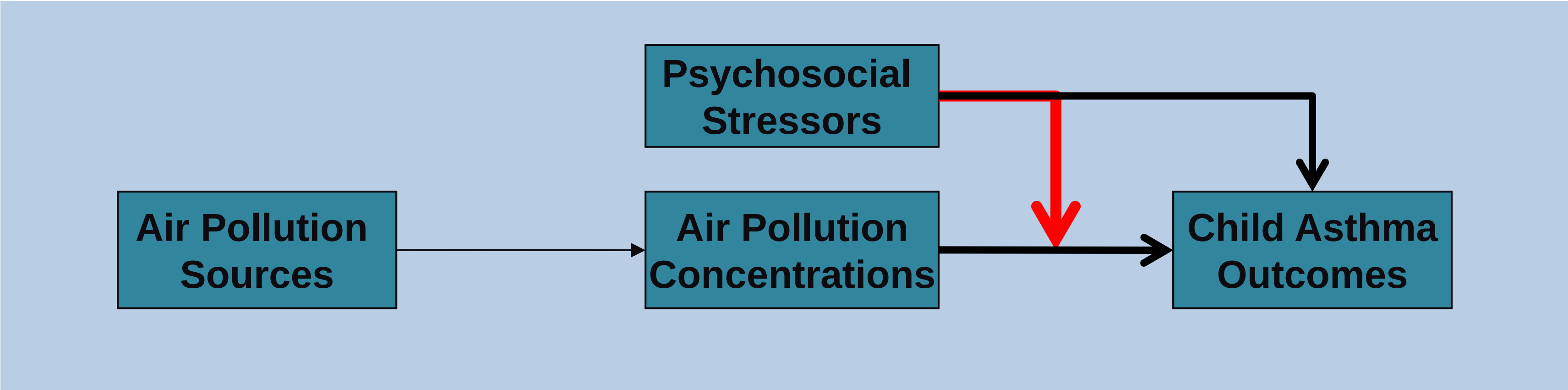
- Substantial ETV impact through fear, hyper-vigilance, other stress-related pathways.
  - Unlike other urban stressors (e.g., housing quality, noise), less confounded by inherent (or co-linear) physical exposure.
  - => Health impacts of ETV might be disentangled from other SEP effects.

- Crime data (albeit imperfect) is collected systematically by every police department nationwide.

Step 1: Conceptual Model

- Develop a clear, simple depiction of hypothesized relationship(s) among key exposures
  - attention to modes of action (MOA)/ pathways
  - common adverse outcomes.

COMMUNITY STRESSORS AND SUSCEPTIBILITY TO AIR POLLUTION IN URBAN CHILDHOOD ASTHMA



Here, we capture 2 key constructs:

- Stressors and pollution exposures may separately influence childhood asthma etiology or exacerbation.

- A chronic stressor may, through allostatic load pathways, alter individual susceptibility to pollution exposures

US EPA STAR grant #RD-83457601-01 (PI: JE Clougherty)

Review Conceptual Model

- Review model and incorporated stressors, receptors and endpoints of interest:
  - with diverse stakeholders (e.g., community, policy makers…)
  - identify overlooked exposures, modifiers & health outcomes of interest to community.
  - to emphasize most important exposures.

  - Review:
    - Evidence base for each hypothesized association
    - Rationale for how exposure indicators were derived
    - Processes by which exposures were included/ excluded.

Step 2: Screen Stressors to Focus on a Manageable Number

- Possibly not relevant for stressor-based CRA
- Evaluate effects of individual stressors
  - One predominant stressor may drive effect(s).

- Here, consider epidemiological and toxicological evidence for independent effects of ETV, air pollution (or other stressors) on outcomes.
  - Attention to relative effect size for each exposure, from peer-reviewed literature.

2a) Identify Data Resources/ Needs

- Identify and catalogue data available to capture construct(s) of interest
  - e.g., census demographics, police crime data, school quality indicators …
  - *Validate* administrative (aggregate) indicators against individual-level data, as possible.
  - Determine what *additional data* needs be collected.

Cataloguing Stressor Indicators

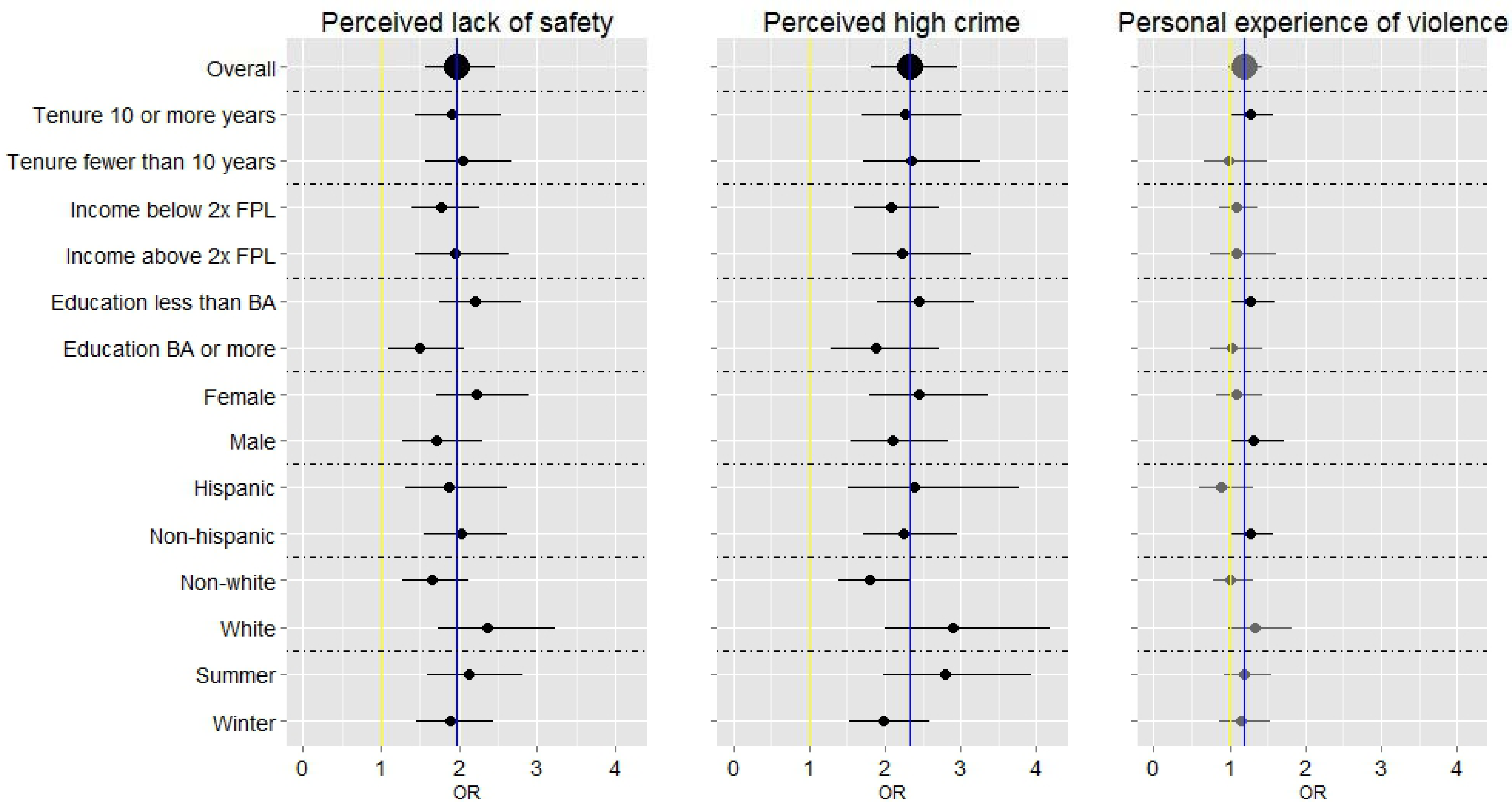
Crime & Violence	Murder and non-negligent manslaughter per 10,000 (PP) Felonious Assault per 10,000 (PP) Robbery per 10,000 (PP) Burglary per 10,000 (PP) Felony Larceny thefts per 10,000 (PP) % Perceptions of Neighborhood Safety (self-report) (UHF)	NYPD (FY 2009) NYPD (FY 2009) NYPD (FY 2009) NYPD (FY 2009) NYPD (FY 2011) DOHMH CHS (2010)
Mental and General Health Status	% Depression diagnosis ever (self-report) (UHF) % Mental health treatment in past year (self-report) (UHF) % Fair or Poor general health (self-report) (UHF)	DOHMH CHS (2009) DOHMH CHS (2009) DOHMH CHS (2009)
Physical/Built Environment	% Small parks not acceptably clean (CD) % Sidewalks not acceptably clean (CD) Serious housing violations per 1,000 Rental Units (CD) Air Quality complaints per 10,000 residents (CD) % Residential Crowding (>1 occupant/room) (USCBG)	NYC Parks (FY 2009) MOoO (FY 2009) HPD (2009) DEP (FY2009) US Census ACS (2005-09)
Access to Healthcare	% With no type of insurance coverage (self-report) (UHF) % Went without needed medical care (self-report) (UHF) % Without a personal care provider (self-report) (UHF) Public Health Insurance enrollment per 10,000 (CD)	DOHMH CHS (2009) DOHMH CHS (2009) DOHMH CHS (2009) MOO (FY 2009)
Noise disruption	% Frequent noise disruption (3+ times/wk over 3 months) (self-report) (UHF) % Noise disruption, by noise sources (i.e. neighbors, traffic) (self-report) (UHF)	DOHMH CHS (2009) DOHMH CHS (2009)
Childhood-specific stressors	% Students in schools exceeding capacity (SD) % School buildings in good to fair condition (SD) % Average daily student attendance (SD) Substantiated cases of Child Abuse/Neglect per 10,000 (CD)	NYC DOE (SY 2006-07) NYC DOE (SY 2006-07) NYC DOE (SY 2008-09) NYC ACS (2008)
Socioeconomic Position (SEP)	% Living below 200% federal poverty line (USCBG) % Delayed rent or mortgage payment in past year (self-report) (UHF) Food Stamp program enrollment per 10,000 (CD) % Less than high school education (self-report) (UHF) % Unemployed for less than 1 year (USCT)	US Census ACS (2005-09) DOHMH CHS (2009) MOO (FY 2009) DOHMH CHS (2009) US Census ACS (2005-09)

Carr Shmool, *Environ Health* 2014

Validating Community Stressors

- Focus Groups (n = 25)
  – To identify most important stressors experienced in communities across NYC, by residents
  – e.g., *Which stressors most affect people in your community?*
- Systematic Spatial Survey (n = 1,000)
  – To validate relationship between area-level stressors (e.g., poverty rate) and individual stress.
  – e.g., *Where do you live, and are <u>you</u> stressed?*

Odds of reporting higher perceived exposures, per IQR increase in area **Assault Rate**



Models adjusted for age, sex, residential tenure, season, sampling frame, and nesting of participants within administrative areas (random intercept); except for models stratified by sex, tenure and season.

Identify Data Gaps

Community-identified Stressors	# of grou
Safety (violence, crime)	14
Drugs (dealers, use)	9
Sanitation (trash, rats, pests)	9
Police presence (Stop-and-Frisk)	9
Public transportation	7
Lack of involvement from city officials	6
Gang activity	6
Gentrification	6
Lack of community pride, unity, involvement	6
Poor housing conditions, inadequate housing	6
Disrespect, harassment among community members	5
Diminishing services, funding cuts	5
Traffic	4
Noise, raised voices, loud music	4
High cost of living	4
Lack of emergency services, hospitals	3
Sexual assaults	3
Schools	3
Prostitution	2
Construction	2
Guns	2
Pollution	2
Lack of grocery stores	2

Stressor Construct	Indicator and Administrative Scale
Crime & Violence	Felony Larceny Crimes per 10,000 (PP) Murder and non-negligent manslaughter per 10,000 (PP) Felonious Assault per 10,000 (PP) Robbery per 10,000 (PP) Burglary per 10,000 (PP) % Perceptions of Neighborhood Safety (self-report) (UHF)
Mental Health	% Depression diagnosis ever (self-report) (UHF) % Mental health treatment in past year (self-report) (UHF)
Physical/Built Environment	% Small parks not acceptably clean (CD) % Sidewalks not acceptably clean (CD) Serious housing violations per 1,000 Rental Units (CD) Air Quality complaints per 10,000 residents (CD) % Crowding (>1 occupant/room) (USCT)
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Socioeconomic Position (SEP)	% Living below 200% federal poverty line (USCBG) % Delayed rent or mortgage payment in past year (self-report) (UHF) Food Stamp program enrollment per 10,000 (CD) % Less than high school education (self-report) (UHF) % Unemployed for less than 1 year (USCT)

Carr Shmool, *Am J Comm Psych* 2015

2b) Explore Exposure Distributions

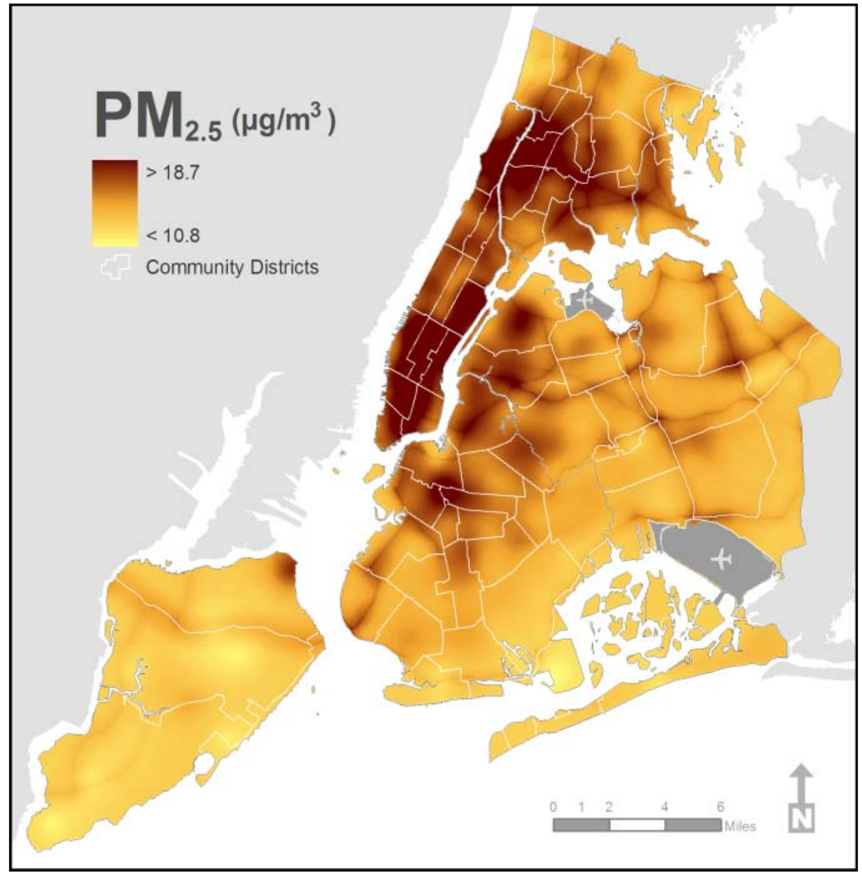
- Explore spatial & temporal distributions:
  - Environmental exposures of interest (e.g., air pollution)
  - Susceptibility indicators (i.e., community stressors - e.g., crime rates)
- Evaluate spatial distributions *within* and *between* both exposure types.
- Here, we examine:

  (a) Spatial variability *within* ETV and pollution.

  (b) Common spatial variance *between* exposures.

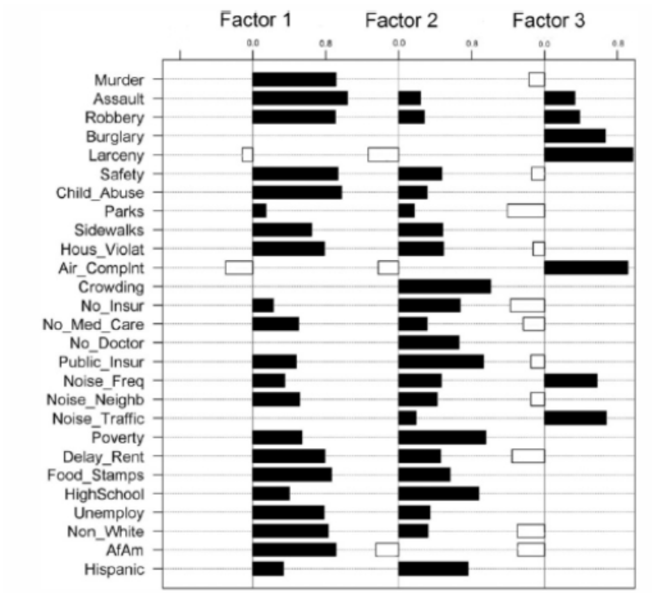
(a) Examine Spatial Relationships *within* Exposures

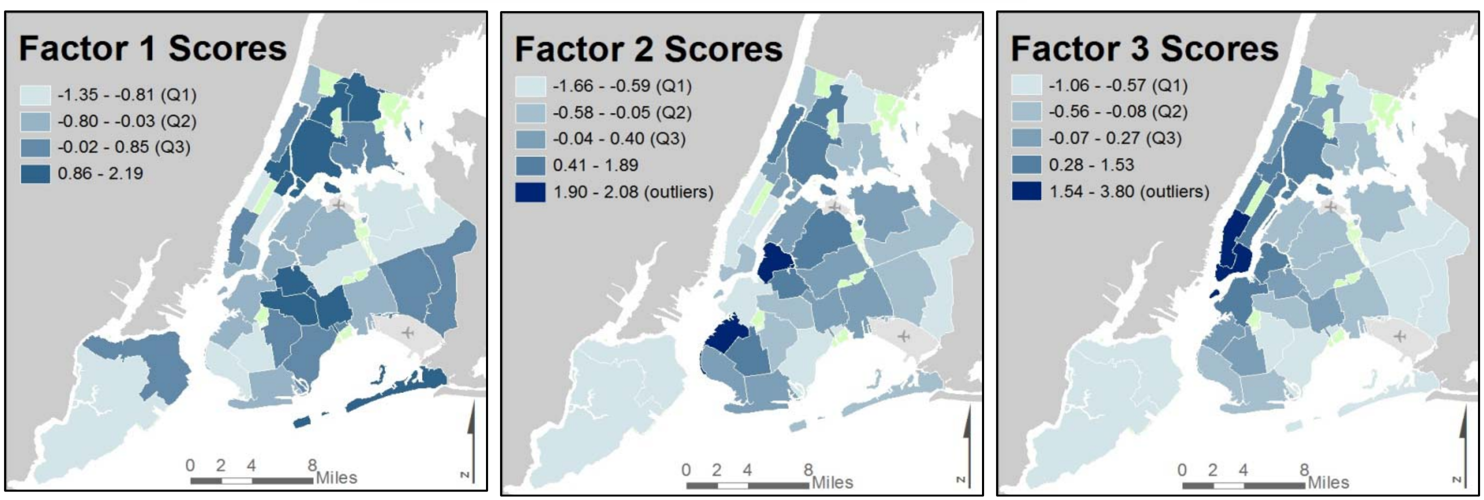
- Examine spatial variability *within* AP and ETV indicators (e.g., across neighborhoods)
- How each exposure varies across region of interest.
- Quantify spatial autocorrelation ("clustering") e.g., geographically-weighted regression (GWR)
  - Local Indicators of Spatial Association (LISA)



Clougherty et al, *JESEE* 2013
Map credit: Grant Pezeshki, NYC DOHMH

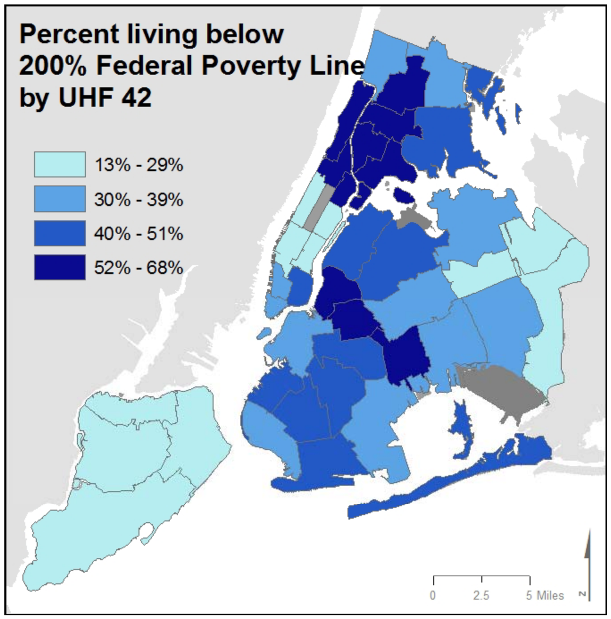
Spatial patterns *among multiple* social stressors

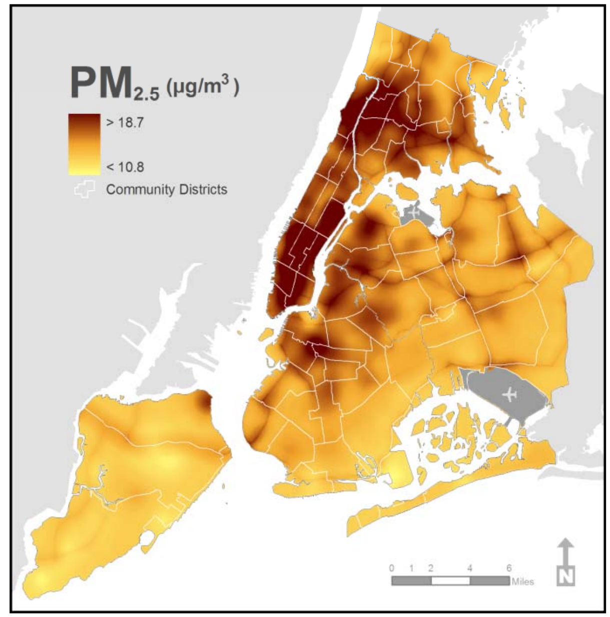




Carr Shmool, *Environ Health* 2014

(b) Examine spatial relationships *between* social & environmental exposures





	BC	NO_2	$PM_{2.5}$	SO_2	O_3
Factor 1 (violent crime and physical disorder)	−0.02	−0.01	−0.07	0.08	−0.01
Factor 2 (crowding and poor access to resources)	0.12	0.04	0.06	0.11	0.08
Factor 3 (noise complaints and property crime)	0.80**	0.83**	0.83**	0.44*	−0.74**

*indicates statistical significance at $p < 0.01$, **$p < 0.0001$.

Carr Shmool, *Environ Health* 2014

Step 3: Examine *Separate* Effects of Exposures on Health

- Underlying epidemiological models :
  - Asthma outcomes = [best metric(s) of ETV] + confounders
  - Asthma outcomes = [best metric(s) of AP] + confounders

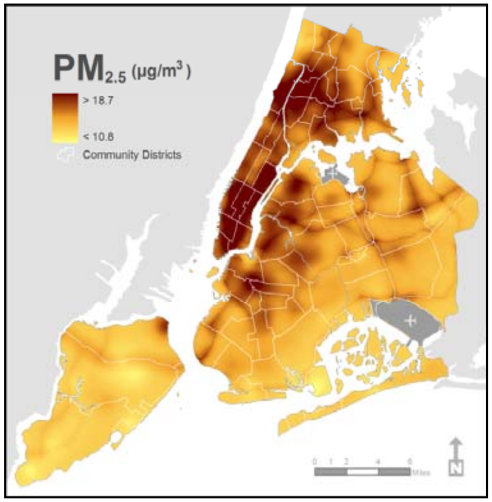
- Confounders may include the other stressor
  - Effect modification (interactions) ***not*** considered at this stage.

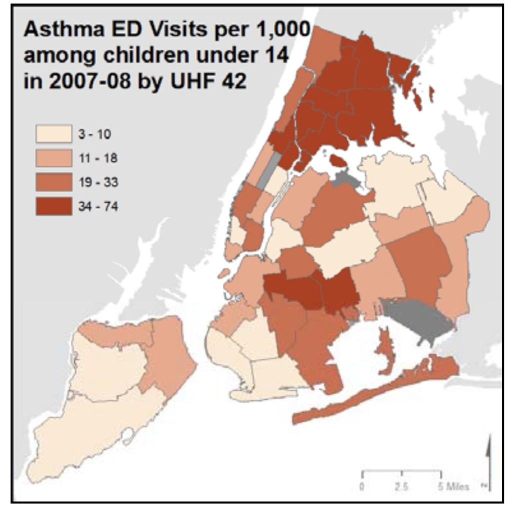
- *Best available metric for each exposure may differ in sensitivity and specificity.
  - Need consider differential exposure misclassification
    - in comparing separate models for each exposure
    - and when combining both exposures in the same model.

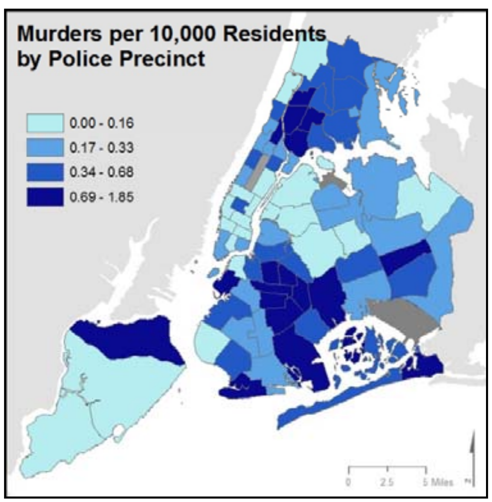
Examine *separate* health effects, cont'd

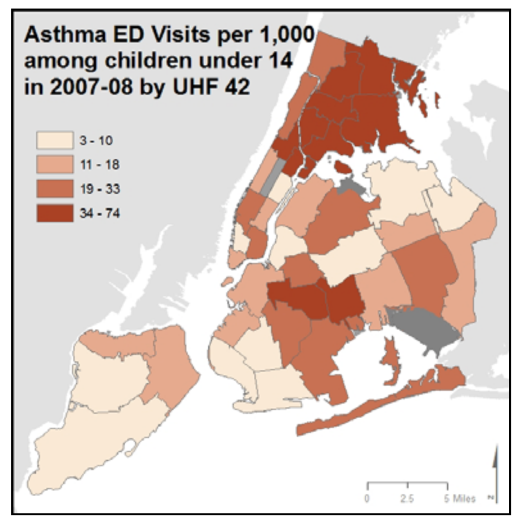
- Use GIS to visualize, assess spatial relationships *between* each exposure and health endpoint.
  - e.g.: Correlation between ETV and asthma;
    Correlation between AP and asthma
- May compare maps of each stressor vs. outcome (e.g., asthma hospitalizations), quantify relationship using SAR.
- If two+ exposures correlated (confounded), may need mutually adjust.

Examine *Separate* Health Effects









Step 4: Evaluate *combined* health effects, *without* interactions

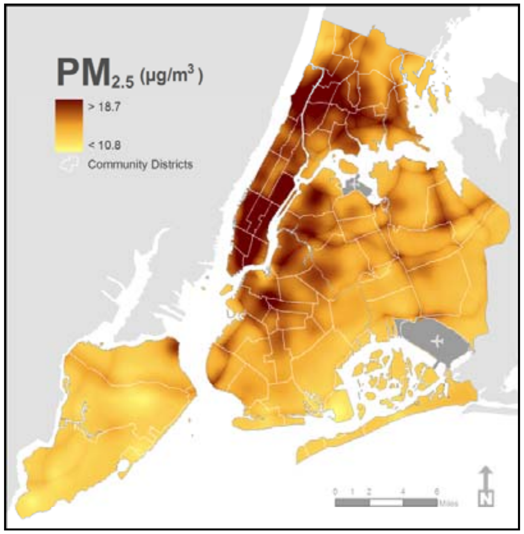
- Epidemiologic model (additive):
  Asthma = [best metric of ETV] + [best metric of AP] + confounders

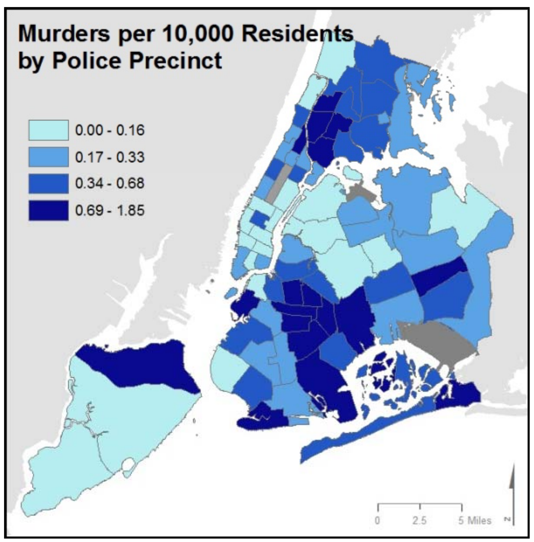
- Tests whether each exposure has independent association with outcome (regardless of co-exposures, modifiers).

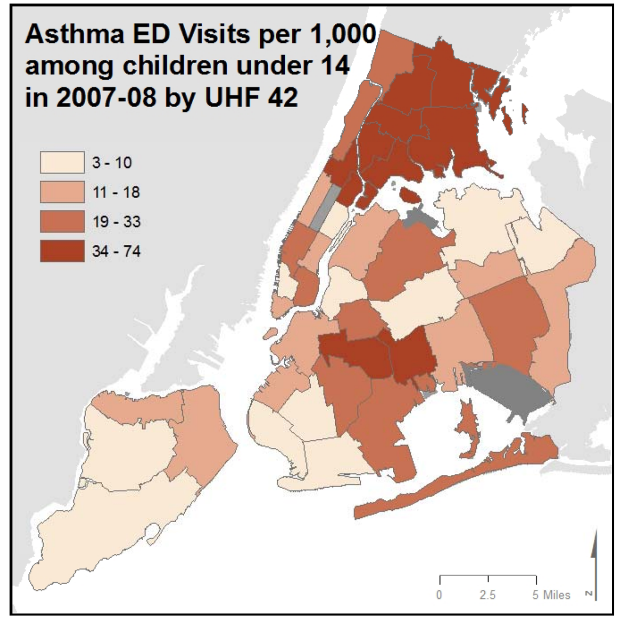
- Under strong effect modification, some exposures may be non-significant, if high prevalence of low-susceptibility individuals.
  - But, effects may be observed within high-risk groups.
  - e.g., have observed significant associations between NO_2 and asthma solely among children with elevated ETV (Clougherty et al 2007)

- Can alleviate this concern through sensitivity-testing
  - considering potential modifiers and exposures iteratively.

Evaluate *combined* Health Effects, *without* Interaction







Step 5: Evaluate combined health effects, *with interactions*.

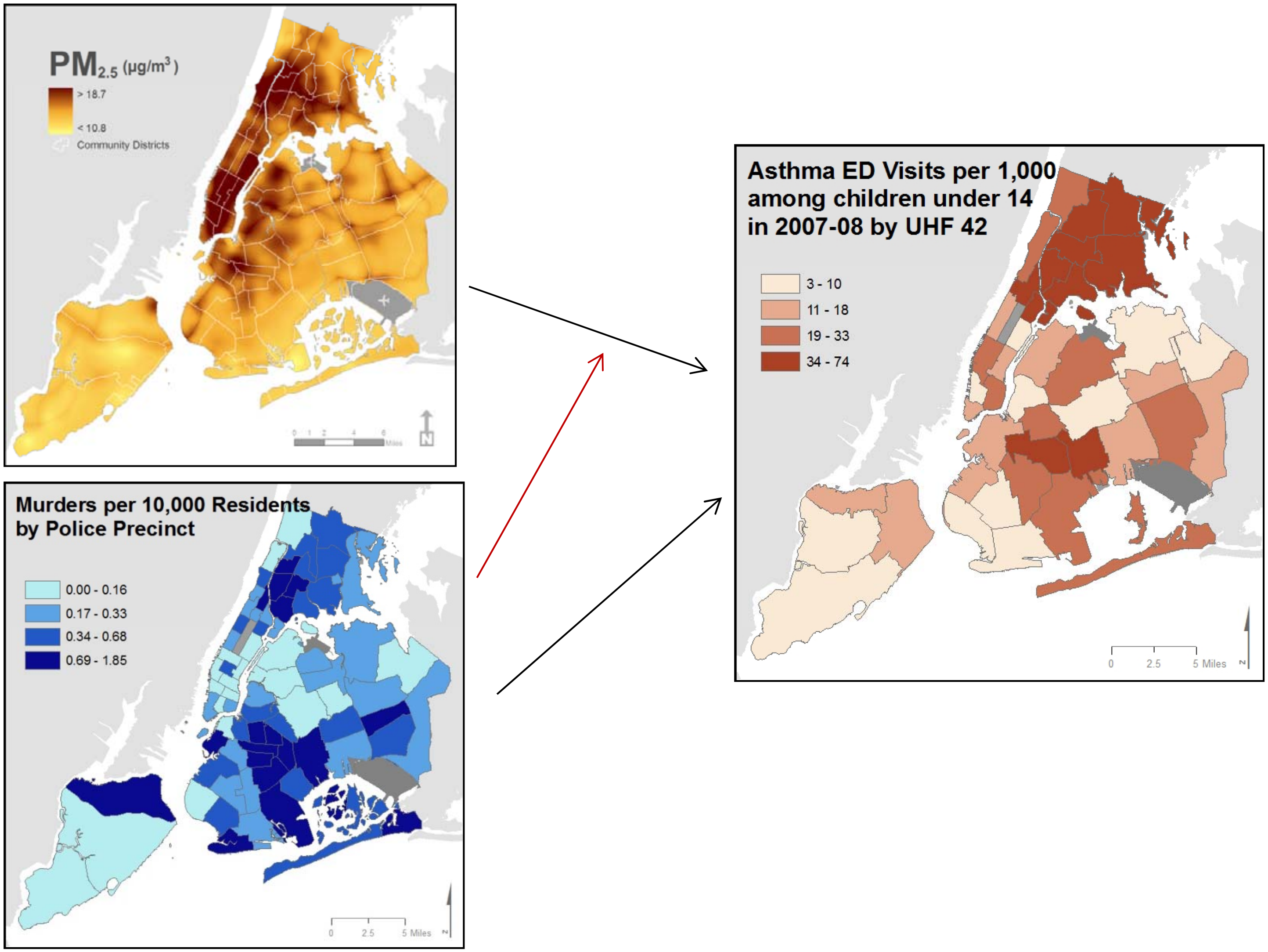
- Conceptual model provides grounding (and limits on) interactions considered at this stage.

- Too many interactions, or those without a plausible mechanistic pathway, can:
  - Complicate the analysis
  - Reduce statistical power
  - Produce uninterpretable results (esp. as # of stressors increases)

- Epidemiological model:

  Asthma = [best metric(s) of ETV]
  + [best metric(s) of air pollution]
  + [best metric(s) of ETV] x [best metric(s) of AP]
  + confounders

Evaluate combined Health Effects *with Interaction*



Additional topics re: integrating non-chemical stressors into CRA

- Risk management options
- Uncertainty analysis
- Sensitivity-testing on covariate selection
- Validating indicators of non-chemical stressors

Risk Management Options

- *Science and Decisions* emphasizes evaluating the benefits of various risk-management options.
  - Here, no specific risk management option to evaluate.
    - = generalized stressor-based CRA.

- Most interventions options available to environmental & occupational risk assessors will be on chemical exposures
  - Thus, may be most useful to consider non-chemical stressors as modifiers of impacts of chemical/ physical exposures.

  - Main effect of non-chemical stressor helps understand background disease rates, identify/ characterize high-risk populations.

Uncertainty analysis

- Key component of cumulative risk assessment.
- In the epidemiology, includes confidence intervals and sensitivity analyses on predictors.
  - Recommend extracting information on the epidemiology – to assess sensitivity of risk estimates to key assumptions.
  - Researchers conducting epi studies for cumulative risk assessment should report this information.
    - Available exposure data may be incomplete, biased, capture only a subset of true exposures, or mis-classify exposures.

Sensitivity-testing
the covariate selection

- In some cases, key predictors may be omitted (in error) before testing interactions.
  - i.e., significant effects only among high-risk subgroup

- Sensitivity-testing may include:
  - Swapping order of terms/ interactions tested.
  - Identifying key predictors and modifiers of interest
    - carry these throughout the analysis, regardless of significance.
  - Automated variable selection (e.g., regression trees)
    - To identify under-recognized exposure(s) associated with outcome
    - Avoid assumptions of linearity or model structures (e.g., decision trees, random forest).
  - Tests of co-linearity, confounding.

Validating Exposure Metrics

- Involve communities of concern & other stakeholders from early stages
  - Such that selected indicators capture key stressor(s) of interest to community.

- For community-level stressor indicators (e.g. crime rates), implement surveys, focus groups, etc., to determine:
  (1) whether indicators accurately capture community-level variation in individual exposures, and
  (2) to select the community-level indicators which best capture individual variation in stressor exposures.

Future Directions

- Integrate workplace non-chemical stressors (i.e., job grade) into occupational cumulative risk assessment (Clougherty et al., 2007; 2009).

- Integrate stressors from multiple setting (i.e., home, community, workplace) into CRA.

- Upcoming symposium with colleagues at NIOSH:
  - *'Current Cumulative Risk Assessment Research Directions'* at Society for Risk Analysis (SRA) Annual Meeting, San Diego, December 2016

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