Lessons learned from the Navigation Guide:

Risk of bias tools for exposure metrics in epidemiology studies

Photo : Original illustration by Patrick Lynch, Yale University

Juleen Lam

December 16, 2015

EPA Advancing Systematic Review for Chemical Risk Assessment

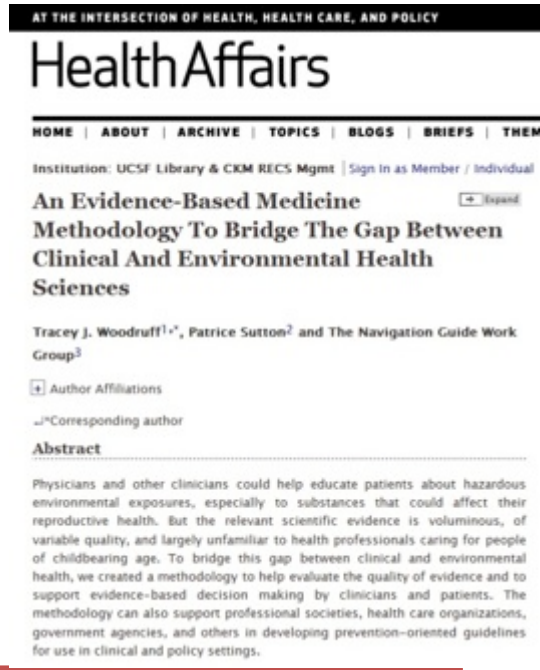
Crystal City, Arlington

The Navigation Guide (2011)

Developed in 2009 by UCSF's Program on Reproductive Health and the Environment in collaboration with

22 clinicians and scientists from:

- Federal and state government agencies
- Other academic institutions
- Non-governmental organizations



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An Evidence-Based Medicine Methodology To Bridge The Gap Between Clinical And Environmental Health Sciences

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Author Affiliations

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Abstract

Physicians and other clinicians could help educate patients about hazardous environmental exposures, especially to substances that could affect their reproductive health. But the relevant scientific evidence is voluminous, of variable quality, and largely unfamiliar to health professionals caring for people of childbearing age. To bridge this gap between clinical and environmental health, we created a methodology to help evaluate the quality of evidence and to support evidence-based decision making by clinicians and patients. The methodology can also support professional societies, health care organizations, government agencies, and others in developing prevention-oriented guidelines for use in clinical and policy settings.

GOAL: Establish a systematic and transparent method to evaluate the quality of evidence and to support evidence-based decision making, bridging the gap between clinical and environmental health

Clinical sciences have faced and addressed these same challenges

Evidence-Based Medicine (EBM)

EBM aims to apply the best available evidence gained from the scientific method to clinical decision making

- Developed to prevent harm from treatment decisions being made without strong basis in the evidence
- Transparent and systematic approach to evaluating evidence

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Models for Navigation Guide

GRADE

How can we better evaluate and synthesize environmental health science to inform decision-making by policy makers and clinicians?

Overview of the Methodology

- ✓ 6 Navigation Guide case studies to date
  - ✓ 3 completed case studies
  - ✓ 5 publications & 1 manuscript under review
  - ✓ 2 publications in draft
  - ✓ 1 case study initiated November 2015
- ✓ Recognition from the National Academy of Sciences (Nav Guide methodology noted in 2 recent reports)

Accelerating trajectory of uptake of systematic review methods in environmental health.

Case Study: Study Question

Does developmental exposure to air pollution affect diagnosis of Autism Spectrum Disorder?

Case study: Review team

- Review team → varied topic experts
  - Epidemiology
  - Air pollution/exposure assessment
  - Autism
  - Biostatistics
  - Systematic review methodology

- All review team members participated and contributed to case study

- EEARN → Topic expert advisors
  - Advice, input along the process

Case Study: PECO Statement

- **P**opulation: Humans
- **E**xposure: Any developmental exposure to air pollution that occurred prior to the ASD assessment
- **C**omparator: Humans exposed to lower levels of air pollution than the more highly exposure humans
- **O**utcome: Any clinical diagnosis or other continuous or dichotomous scale assessment of ASD

Systematic Approach for Each Evidence Stream

Human Data

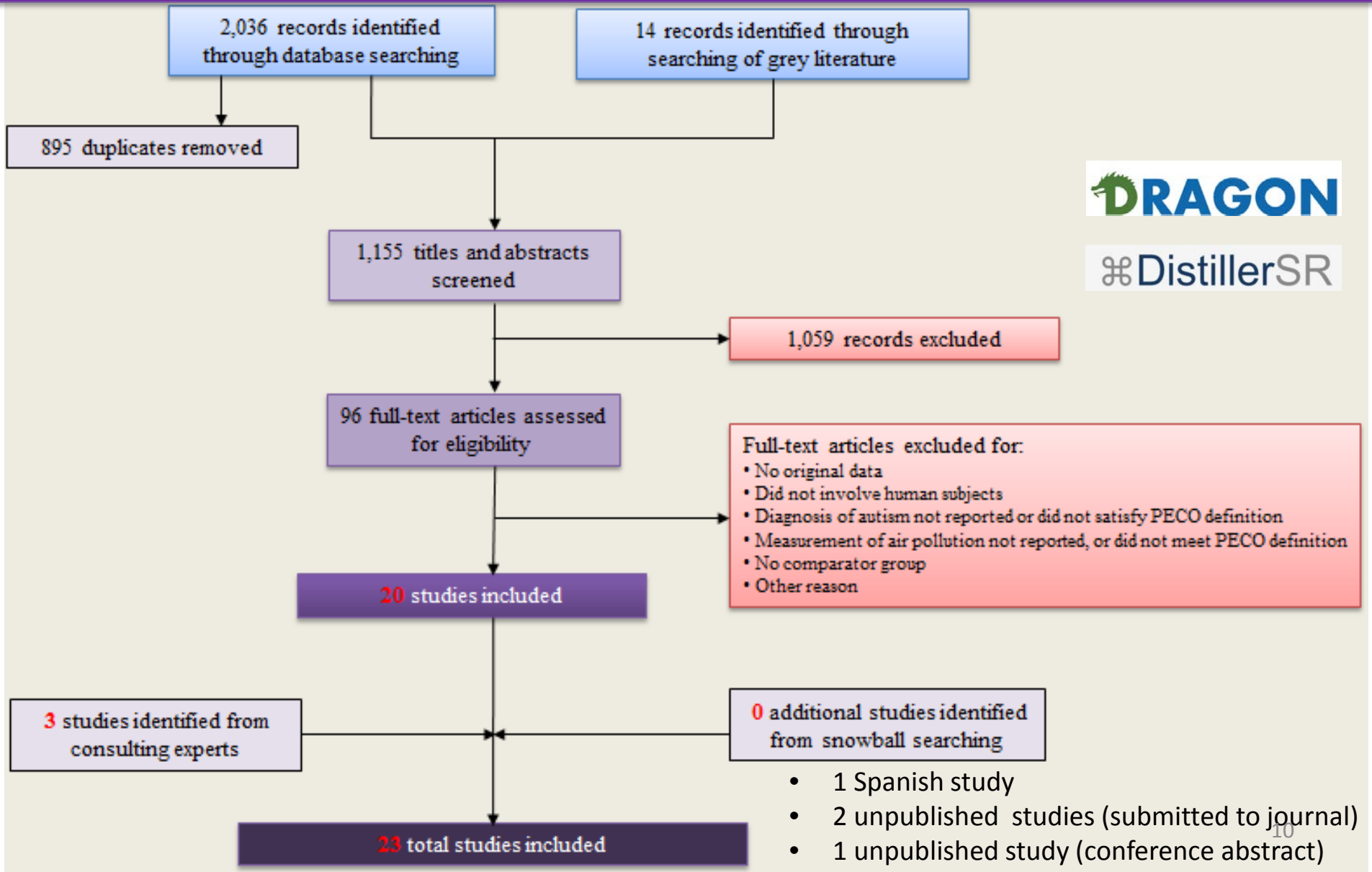
"PECO" Statement → Systematic search → Select Studies → Extract Data & Data Analysis → Rate Quality of Evidence → Rate the Strength of Evidence → Overall Conclusion

Applying the Navigation Guide Systematic Review Methodology
Case Study #4

Association between Developmental Exposures to Ambient Air Pollution and Autism

A Systematic Review of the Evidence
Protocol
March 2015

Autism: Selecting the Evidence



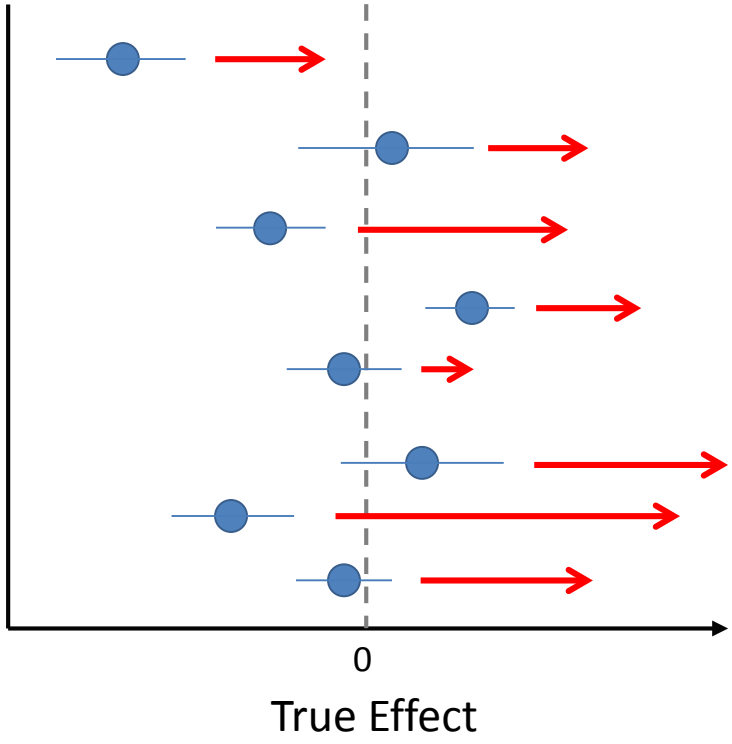
DRAGON

DistillerSR

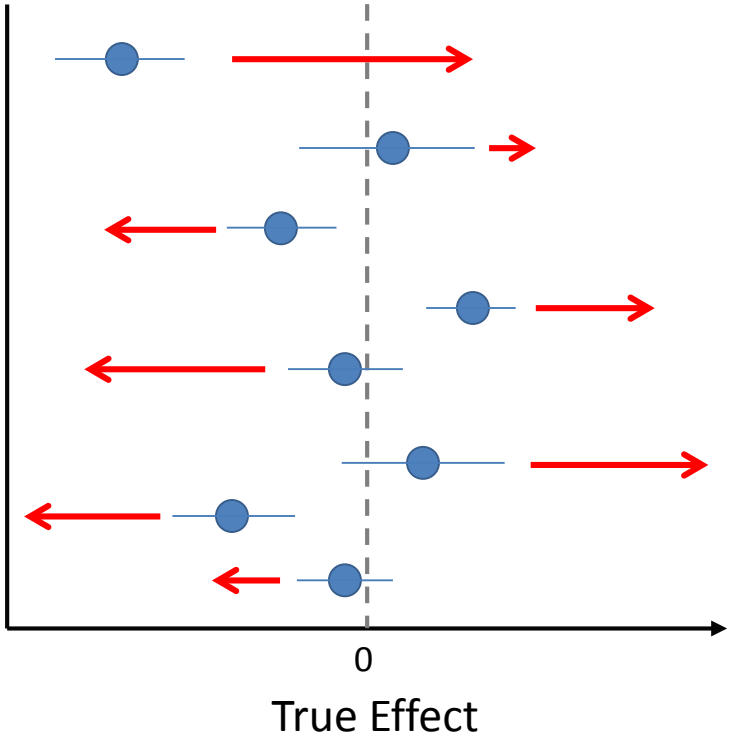
- 1 Spanish study
- 2 unpublished studies (submitted to journal)
- 1 unpublished study (conference abstract)

Risk of Bias (vs Random Error)

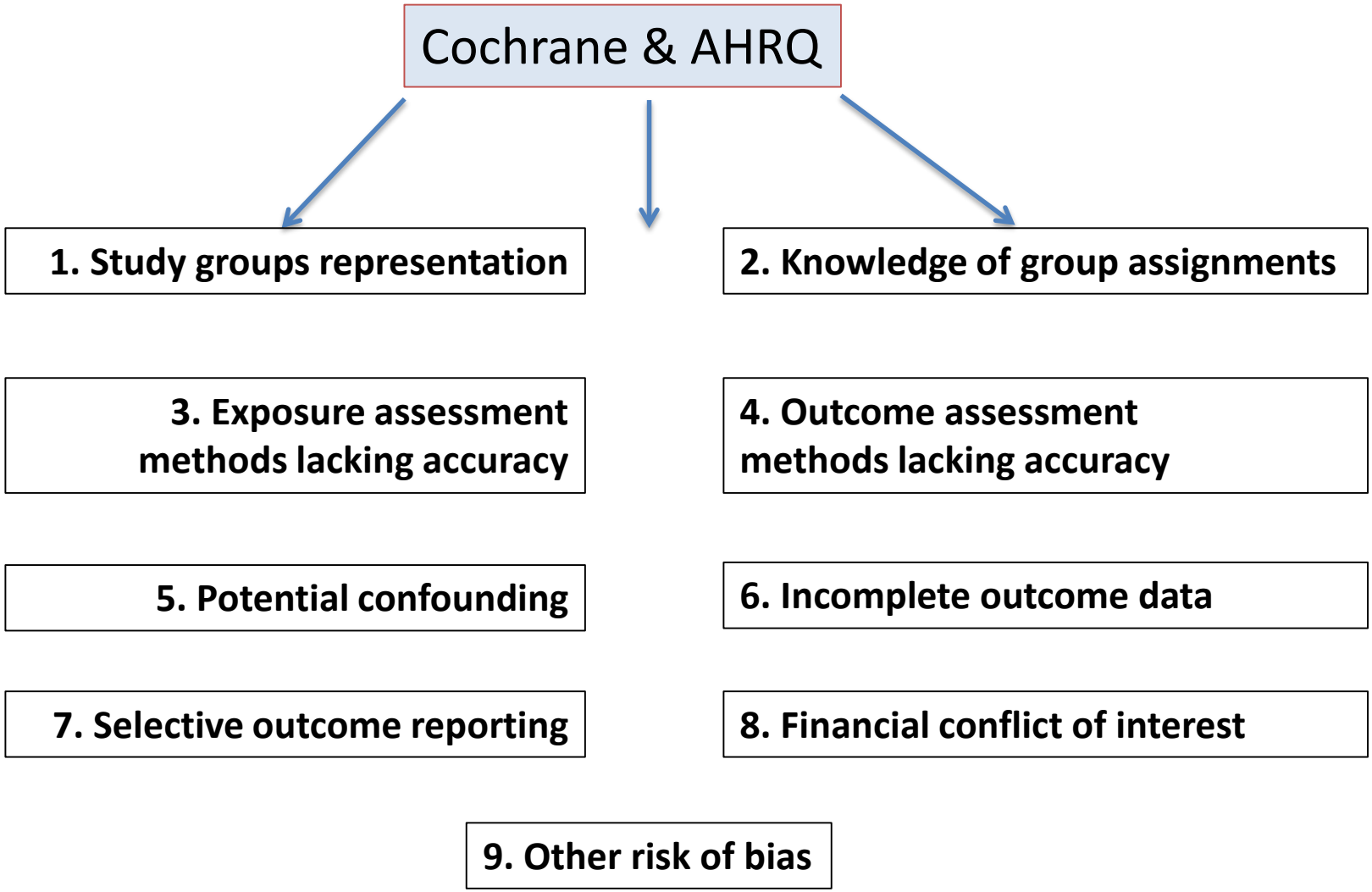
1. Bias



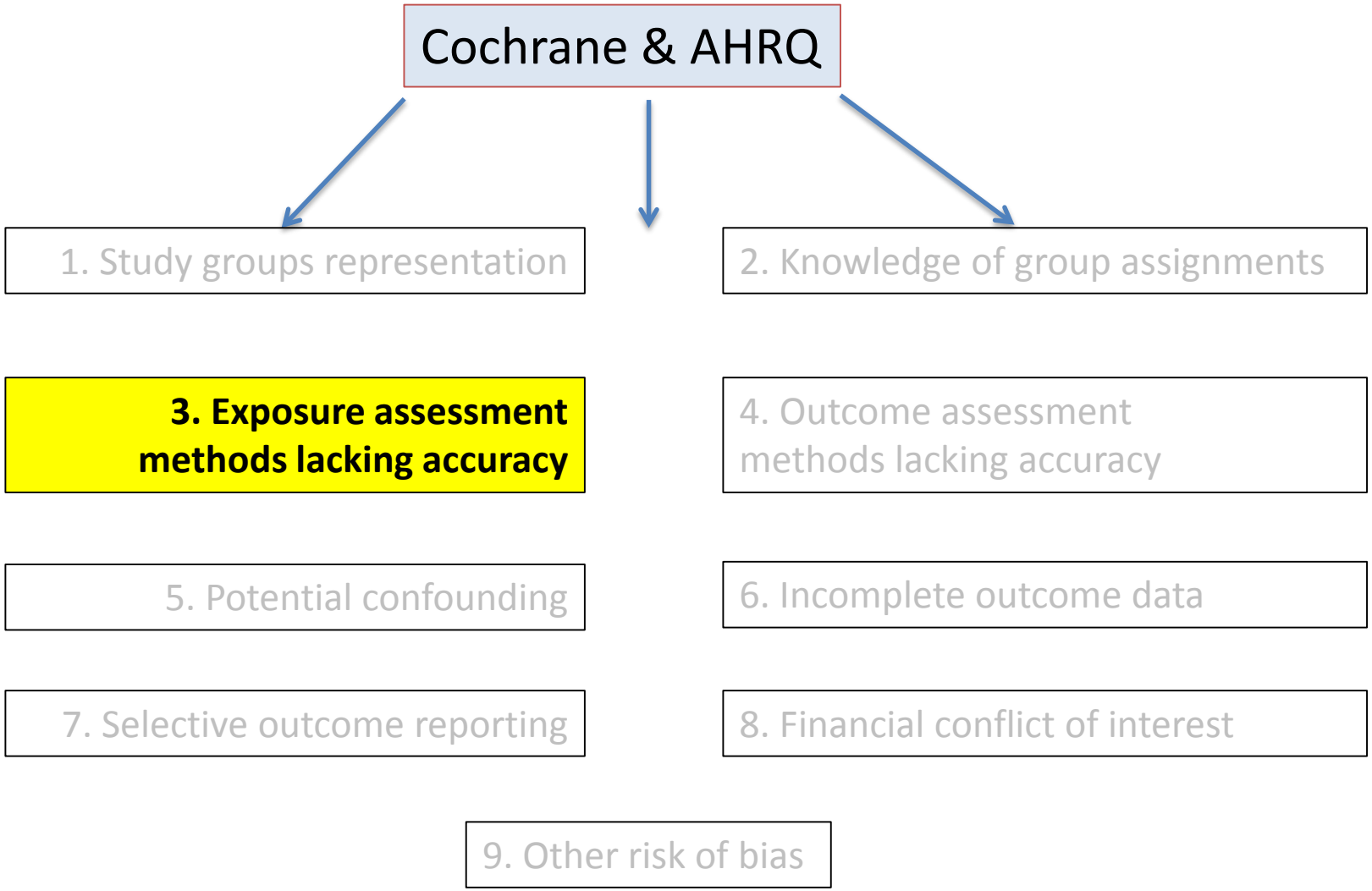
2. Random Error



Rating Risk of Bias



Rating Risk of Bias



Exposure Assessment Risk of Bias

The reviewers judge that there is low risk of exposure misclassification if:

- There is high confidence in the accuracy of the exposure assessment methods, such as methods that have been tested for validity and reliability in measuring the targeted exposure; or
- Less-established or less direct exposure measurements are validated against well-established or direct methods

Exposure Assessment RoB

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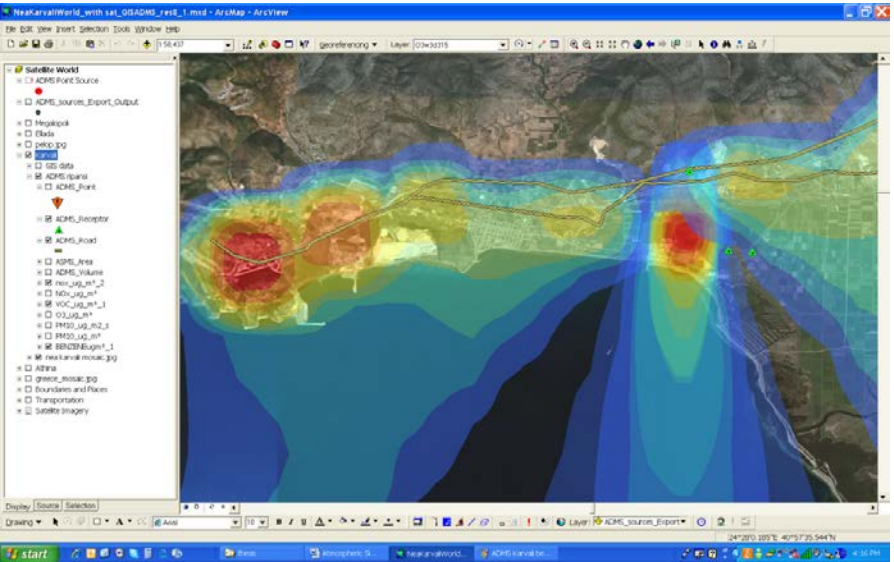
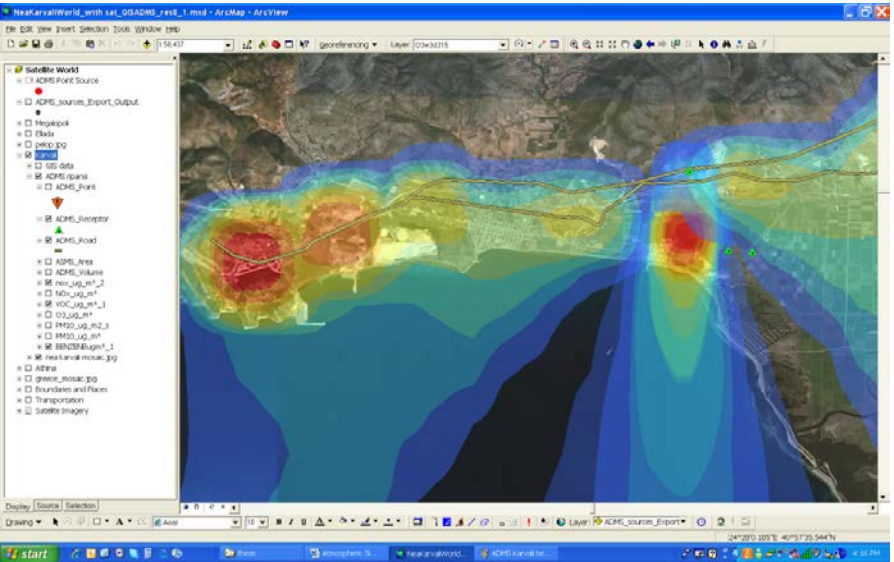
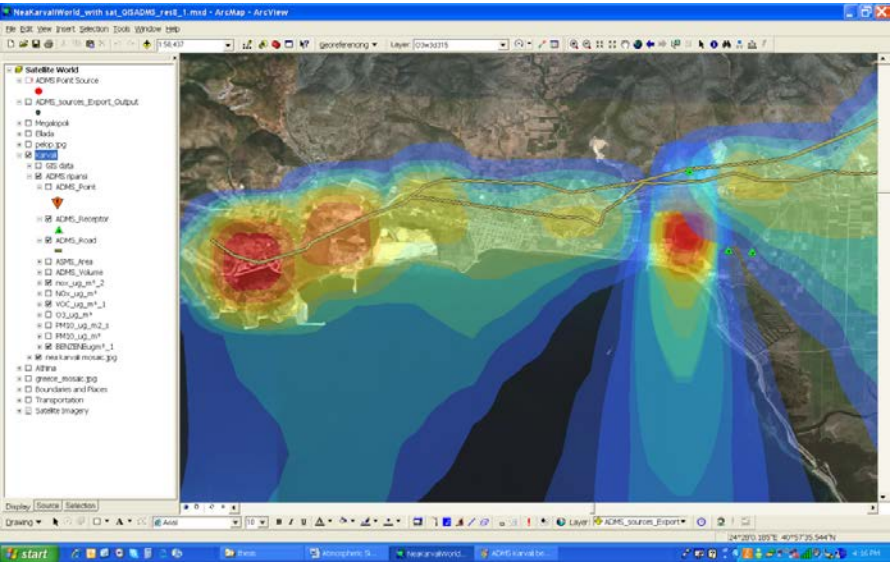


Exposure Assessment RoB



Exposure Assessment RoB



Exposure Assessment RoB

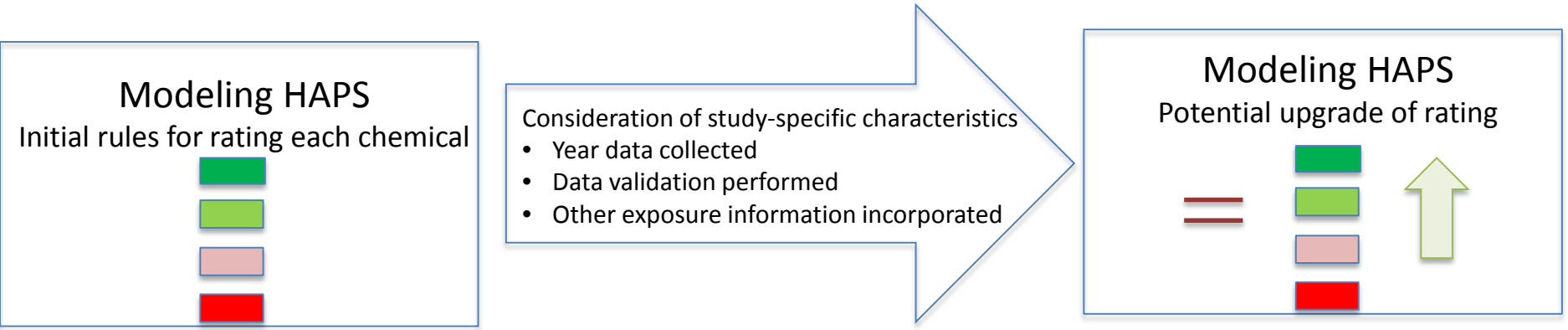
- Separately evaluated each chemical

- List of considerations by metric, identified by epidemiologists and air pollution experts:
  - Quality of input data for computer model
  - Was exposure a surrogate for air pollution (i.e., distance to freeway)?
  - Has metric been validated for scenario of use?
  - Temporal coverage in study
  - Handling of missing data
  - Address completeness (models)

- NOT a checklist—but used to guide reviewer's decisions on rating risk of bias for each data set
  - Justification and comparison among reviewers
  - Standardized ratings across studies with similar metrics/chemicals subsequent to discussion

Exposure Assessment RoB

- Developed initial ratings for certain metric/chemicals
  - US EPA evaluation of confidence in NATA data by chemical based on ASPEN modeling, Rosenbaum (2011)
- Discussion/consensus among review authors to develop initial ratings (i.e., TRI data, distance to freeway)
- Study-specific design considerations potentially bumped up ratings



RoB Ratings

RefID	Author	Source population representation	Blinding	Outcome assessment	Potential confounding	Incomplete outcome data	Selective outcome reporting	COI	Other
1598	Becerra 2013								
1600	Blanchard 2011								
1614	Gong 2014								
1620	Jung, 2013								
1622	Kalkbrenner 2010								
1624	Kalkbrenner 2014								
1629	Lewandowski 2010								
1632	McCanlies 2012								
1643	Roberts 2014								
1648	Roberts 2007								
1656	Shelton 2014								
1665	Trousdale 2010								
1666	Volk 2011								
1667	Volk 2014								
1668	Volk 2013								
1669	von Ehrenstein 2014								
1672	Windham 2007								
1674	Windham 2013								
1675	Windham 2006								
1684	Dickerson 2015								
1685	Dickerson 2015								
1686	Raz 2015								
1639	Pino-Lopez 2013	*	*	*	*	*	*	*	*

KEY:

- No
- Probably No
- Probably Yes
- Yes

**Will be confirmed after translation*

RoB Ratings—Exposure Assessment

1598	O3	NO2	PM10	PM2.5														
1600					Mercury													
1614			PM10															
1620		NO2	PM10															
1622					Mercury	Arseni	Benzen	Cadmiu	chromiu	ethyl benzene	Lead	manganes	Methylene	Nickel	perchloroethylen	trichloroethylen	vinyl	
1624			PM1															
1629					Mercury		Benzen			ethyl benzene	Lead	Manganese		Nickel		trichloroethylene		
1632					Mercury				chromiu		Lead			Nickel				Solvents
1639																		
1643					Mercury	Arsenic		Cadmium	chromiu		Lead	manganes	Methylene	Nickel		trichloroethylen	vinyl	
1648																		
1656																		
1665																		
1666																		
1667	O3	NO2	PM1	PM2.														Traffic related air pollution
1668	O3	NO2	PM10	PM2.5														Traffic related air pollution
1669							benzen		chromiu	ethylbenzene	lead	manganes	methylene	nickel	perchloroethylen	trichloroethylen		
1672																		
1674																	Solvents	Exhaust
1675					mercury	arsenic		cadmiu	chromiu		lead	manganes	methylene	nickel	perchloroethylen		vinyl	Aromatic
1684					mercury	arsenic					lead							
1685					mercury	arsenic					lead							
1686			PM10	PM2.5														

KEY:

No
Probably No
Probably Yes
Yes

RoB Ratings—Exposure Assessment PM_{10}

- 7 studies
- All exposure involves ambient monitoring data
- Initial rating assigned as “probably low”
- One study changed to “probably high”
  - No temporal accuracy of time to conception
  - No person-level data; analyzed in quartiles
  - Based on estimates from CALINE4 modeling

1598	PM10
1614	PM10
1620	PM10
1624	PM10
1667	PM10
1668	PM10
1686	PM10

RoB Ratings—Exposure Assessment $PM_{2.5}$

- 4 studies
- Initial rating assigned as “probably low”
- Same study changed to “probably high”

1598	PM2.5
1667	PM2.5
1668	PM2.5
1686	PM2.5

RoB Ratings—Exposure Assessment NO_2

- 4 studies
- Exposure based on:
  - Air quality monitoring data (“probably low”)
  - Land Use Regression (LUR) modeling (“probably high”)
- Same study from PM changed to “probably high”

1598	NO2
1620	NO2
1667	NO2
1668	NO2

RoB Ratings—Exposure Assessment Mercury

- 8 studies
- Exposure based on:
  - Modeling from US EPA NATA (“high”)
  - Modeling from TRI (“probably high”)
  - Surrogate measure based on occupation (“high”)
- No additional info from studies warranted changing ratings

1600	Mercury compounds
1622	Mercury
1629	Mercury
1632	Mercury
1643	Mercury
1675	mercury
1684	mercury
1685	mercury

Lessons Learned

- Developed exposure assessment tool sufficient for this case study, but modifications likely needed for broader application
- Standard approaches to measure and report air pollution data
- Determining/availability of combinable data challenging
- Expert elicitation is time consuming and can be difficult, but is worth it
  - Expert opinion a necessity; systematic review process makes these decisions transparent and documented
  - Process of training new review authors was very informative to understand the complexity of assessing the overall body of literature

Timeline

Human Data

"PECO" Statement → Systematic search → Select Studies → Extract Data & Data Analysis → Rate Quality of Evidence → Rate the Strength of Evidence → Overall Conclusion

- Finalizing evidence ratings with review authors
- Drafting manuscript for submission
- Additionally drafting a manuscript on exposure assessment risk of biases based on the new tool
  - Currently publically available on PROSPERO

http://www.crd.york.ac.uk/PROSPERO/

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