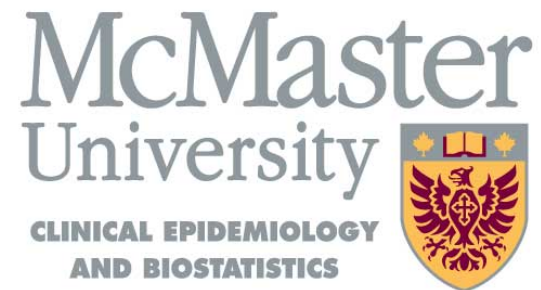# Applicability of ROBINS-I to Studies of Environmental Exposures

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for Chemical Risk Assessment

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CLINICAL EPIDEMIOLOGY
AND BIOSTATISTICS

Disclosures

- GRADE Working Group member/U.S. GRADE Network chair

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Overview

- Application of ROBINS-I to studies of environmental/occupational exposure

- Comparison of ROBINS-E with other tools used to assess RoB of environmental/occupational exposure

- Impact of using ROBINS-E on GRADE's certainty in the evidence assessment

Project #1

APPLICATION OF ROBINS-I TO STUDIES OF ENVIRONMENTAL/ OCCUPATIONAL EXPOSURE

Background

- 2014: Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I)

- Evaluates health effects (benefits/harms) of medical interventions by comparing to the ideal RCT

- Outcomes for environmental and occupational health typically are a result of exposure instead of planned intervention

- There is a need for a robust tool to assess risk of bias of exposure studies

- Many similarities between domains included in ROBINS-I and other bias assessment tools used in environmental/ occupational health

Objectives

- Determine the usability of ROBINS-I when applied to studies of environmental/occupational exposure

- If indicated, adapt tool to facilitate assessment of bias in environmental/occupational health

- Use adapted tool for future method development work when conducting systematic reviews of environmental/occupational health topics

Methods

- Usability assessed by pilot testing & modifications made after each round, as indicated

- Three rounds of pilot testing
  - 2-3 raters independently applied ROBINS-I to 3 case topics:
    - Bisphenol-A (BPA) and development of obesity
    - Perflourooctanoic acid (PFOA) and birth weight
    - Polybrominated diphenyl ethers (PBDEs) and thyroid function
  - Feedback collected from raters on each question and overall tool
  - Subject matter experts applied ROBINS-I & provided input on domains

Results

- Modifications to facilitate usage included:

  - Replacement of "intervention" with "exposure"

  - Additional instructions and examples added to the handbook (e.g., consideration of cross-sectional studies, etc.)

  - Fields added to the protocol to address measurement of exposure and outcome

  - Content expertise is needed when developing guidance for each assessment

  - Replacement of signaling questions in "Bias in Measurement of Intervention/Exposure"

Results: Measurement of Exposure

ROBINS-I (Classification of Intervention)	ROBINS-E (Measurement of Exposure)
3.1 Is the intervention well defined?	3.1 Is exposure status well defined?
3.2 Was information on intervention status recorded at the time of intervention?	3.2 Did entry into the cohort begin with start of the exposure?
3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome?	3.3 Was information on exposure status recorded prior to outcome assessment?
	3.4 Could classification of exposure status have been affected by knowledge of the outcome or risk of the outcome?
	3.5 Are the levels, duration, or range of exposure of the population at risk sufficient or adequate to detect an effect of exposure?
	3.6 Is the follow-up period adequate to allow for the development of the outcome of interest?
	3.7 Were exposure methods robust (including methods used to input data)?

Conclusions

- Modifications increased understanding of items and agreement across raters

- Sufficient variations to recommend: ROBINS-E (<u>E</u>xposure)

Project #2

COMPARISON OF ROBINS-E WITH OTHER TOOLS USED TO ASSESS ROB AND STUDY QUALITY OF ENVIRONMENTAL/ OCCUPATIONAL EXPOSURE

Study Objectives

- Four tools: ROBINS-E, ORoC, OHAT, Newcastle-Ottawa Scale (NOS)
  - ORoC considered representative of EPA-IRIS
  - OHAT considered representative of Navigation Guide

- Compare the results of risk of bias assessment across the tools
  - How similar are tools in identifying low and high risk of bias studies?
  - Hypothesis is they will be similar given overlap in content across tools

- Assess the inter-rater and the test-retest reliability of each tool using 7 case-study topics (already conducted systematic reviews), each topic composed of 5-to-6 individual studies, reviewed by 3 raters.

- For the sub-set of individual studies, compare the tool ratings with unstructured expert assessment to help assess the validity each tool and provide suggestions to improve accuracy in measurement of bias.

Study-level Responses

ROBINS-E	OROC	OHAT	NOS
Low risk of bias	High (low/minimal concerns)	Tier 1 (definitely/probably low bias)	Stars for each domain-level response (meets criteria)
Moderate risk of bias	Moderate (low/minimal or some concerns)	Tier 2	Stars for some domains
Serious risk of bias	Moderate/low (some or major concerns)	Tier 2	Stars for some domains
Critical risk of bias	Low (major concerns) & Inadequate (critical concerns or variability)	Tier 3 (definitely/probably high bias)	No stars (does not meet criteria)
No information			

Carcinogens., O.o.t.R.o. Handbook for Preparing Report on Carcinogens Monographs 2015. NTP. OHAT Risk of Bias Rating Tool for Human and Animal Studies - January 2015. in: Office of Health Assessment and Translation, ed. National Toxicology Program. RTP, NC; 2015. Wells, G.; Shea, B.; O'connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000. Sterne, J.A.C.; Higgins, J.P.T.; Reeves, B.C.; on behalf of the development group for ACROBAT-NRSI. ACROBAT-NRSI: A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions. https://sites.google.com/site/riskofbiastool/ [accessed 24 September 2014]. 2014

Case Topics

Topic for RoB Comparison	Systematic Review Studies (n selected for comparison)	Systematic Review
PFOA and birth weight	18 (6)	Johnson et al., 2014
BPA and obesity	14 (6)	Thayer et al., 2013
PFOA and cancer	10 (5)	EPA-IRIS Monograph
Outdoor particulate matter and lung cancer	18 (6)	Hamra et al., 2014
Phthalate and pre-term birth	5 (5)	Ferguson et al., 2013
Cobalt and cancer	9 (5)	NTP, 2015
Pentachlorophenol (PCP) and cancer	11 (5)	NTP, 2014

Preliminary Results

- 3 reviewers independently applied all tools to 6 studies examining PFOA and birth weight
- Some consistency of ratings between tools

	ROBINS-E	ORoC	OHAT	NOS
Apelberg 2007	Moderate	High	Tier 1	9
Hamm 2010	Moderate	High & Moderate	Tier 1	8
Kim 2011	Serious	Moderate/Low	Tier 2	4
Maisonet 2012	Moderate	High	Tier 1	9
Nolan 2009	Serious	Moderate	Tier 2	8
Whitworth 2012	Moderate	High	Tier 1	9

Project #3

IMPACT OF USING ROBINS-E ON GRADE'S CERTAINTY IN THE EVIDENCE ASSESSMENT

The GRADE Approach

1) Certainty in the evidence: ⊕⊕⊕⊕ (High), ⊕⊕⊕◯ (Moderate), ⊕⊕◯◯ (Low), ⊕◯◯◯ (Very low)
   – methodological quality of evidence
   – likelihood of bias
   – by outcome and across a body of evidence

2) Recommendation: weak/strong (strength) or for/against (direction)
   – Certainty in the evidence only one factor
   – Balance of benefits and harms, values and preferences, resource use, inequity, acceptability, feasibility

Guyatt, G.H.; Oxman, A.D.; Akl, E.A.; Kunz, R.; Vist, G.; Brozek, J.; Norris, S.; Falck-Ytter, Y.; Glasziou, P.; Debeer, H.; Jaeschke, R.; Rind, D.; Meerpohl, J.; Dahm, P.; Schunemann, H.J. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 64:383-394; 2011

Determining the Certainty in the Evidence: GRADE

Table: GRADE's approach to rating quality of evidence (aka certainty in effect estimates)

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1.
Establish initial level of certainty

2.
Consider lowering or raising level of certainty

3.
Final level of certainty rating

Study design	*Initial certainty in an estimate of effect*	*Reasons for considering lowering or raising certainty*		*Certainty in an estimate of effect across those considerations*
		⬇ **Lower if**	⬆ **Higher if***	
Randomized trials ➜	**High certainty**	**Risk of Bias** **Inconsistency** **Indirectness** **Imprecision** **Publication bias**	**Large effect** **Dose response** **All plausible confounding & bias** • would reduce a demonstrated effect **or** • would suggest a spurious effect if no effect was observed	**High** ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies ➜	**Low certainty**			**Low** ⊕⊕◯◯
				Very low ⊕◯◯◯

*upgrading criteria are usually applicable to observational studies only.

Objective & Methods

- Proposed comparison of ROBINS-E used within GRADE approach with initial certainty in the evidence as "High" vs. current approach with initial certainty in the evidence as "Low" with other RoB tool

- >8 potential systematic reviews proposed for initial certainty in the evidence study

- Assess the impact on final confidence rating of using all start high + ROBINS-E approach

Case Topics

Topics for CiE Study	Systematic Review Studies	Systematic Review
BPA-obesity	14	Thayer et al., 2013
PFOA-birth weight	18	Johnson et al., 2014
PFOA-Cancer	10	IARC Monograph
Outdoor particulate matter and lung cancer	18	Hamra et al., 2014
PBDE and thyroid	17	Zhao et al., 2015
Folic acid and twinning	27	NTP
Wind turbines	9	Merlin et al., 2015
Air pollution and autism	23	USCF

Summary

- Working version of ROBINS-E to apply to studies of environmental/occupational exposure

- Current analyses will demonstrate consistency between tools

- Next steps will be to apply ROBINS-E as the RoB tool within GRADE assessment of the certainty in the evidence

QUESTIONS?

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