Holger Schünemann, MD, MSc, PhD, FRCP(C)

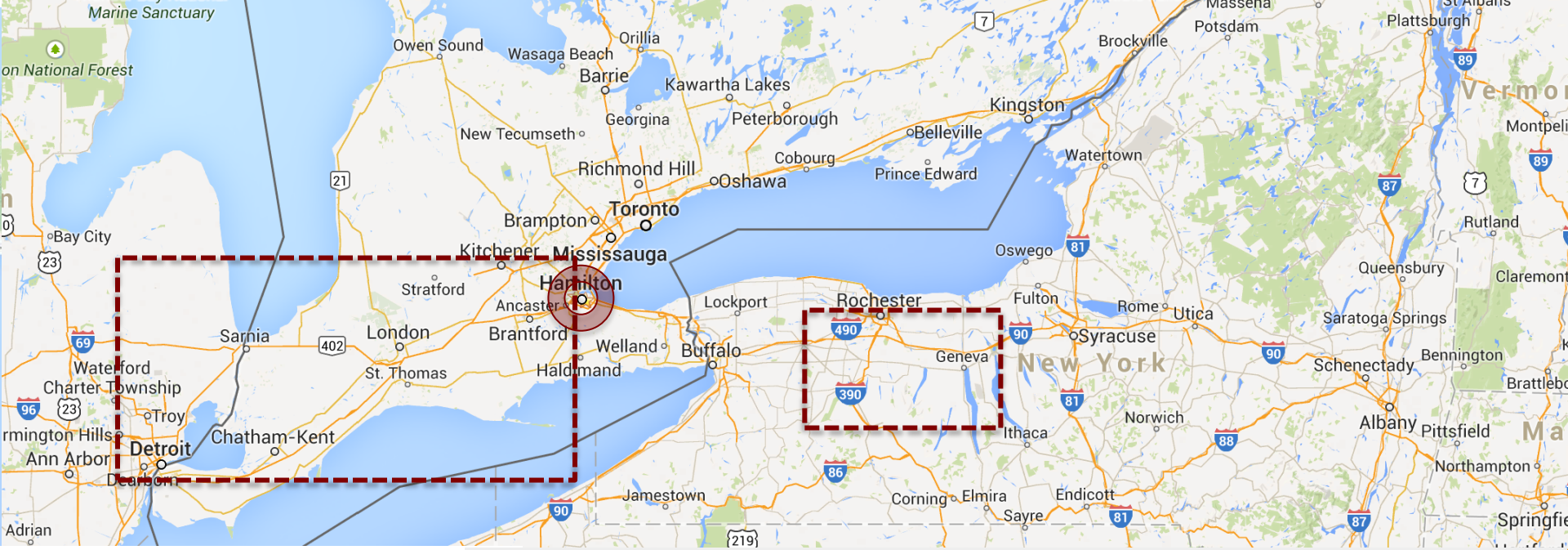
Chair and Professor

Department of Health Research Methods, Evidence and Impact

McMaster University

@schunemann_mac

Using GRADE for exposures: Question formulation and assessing the certainty of evidence using the risk of bias tool for exposure studies



“Birthplace of evidence-based medicine and problem based learning”

McMaster University

Disclosures

GRADE working group-chair

Cochrane Canada Director

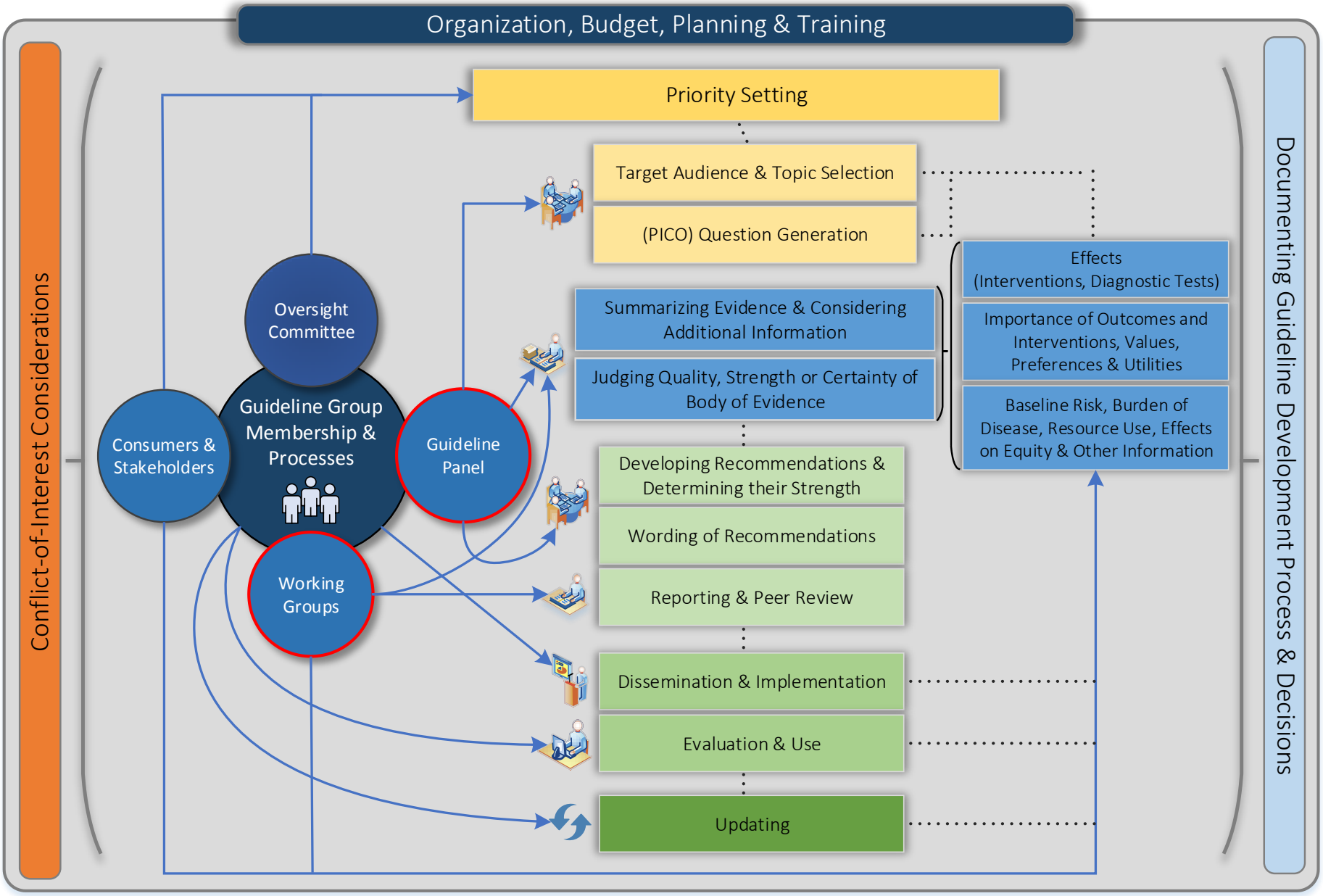
No direct financial interest

Acknowledgements for slides: Rebecca Morgan, PhD

Two topics

Question formulation in environmental and occupational health

Risk of bias assessment in the context of GRADE for studies evaluating exposure - effect relations



Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. 2014 Feb 18;186(3):E123-42.

http://cebgrade.mcmaster.ca/guidecheck.html

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions to prevent occupational noise-induced hearing loss (Review)

Tikka C, Verbeek JH, Kateman E, Morata TC, Dreschler WA, Ferrite S

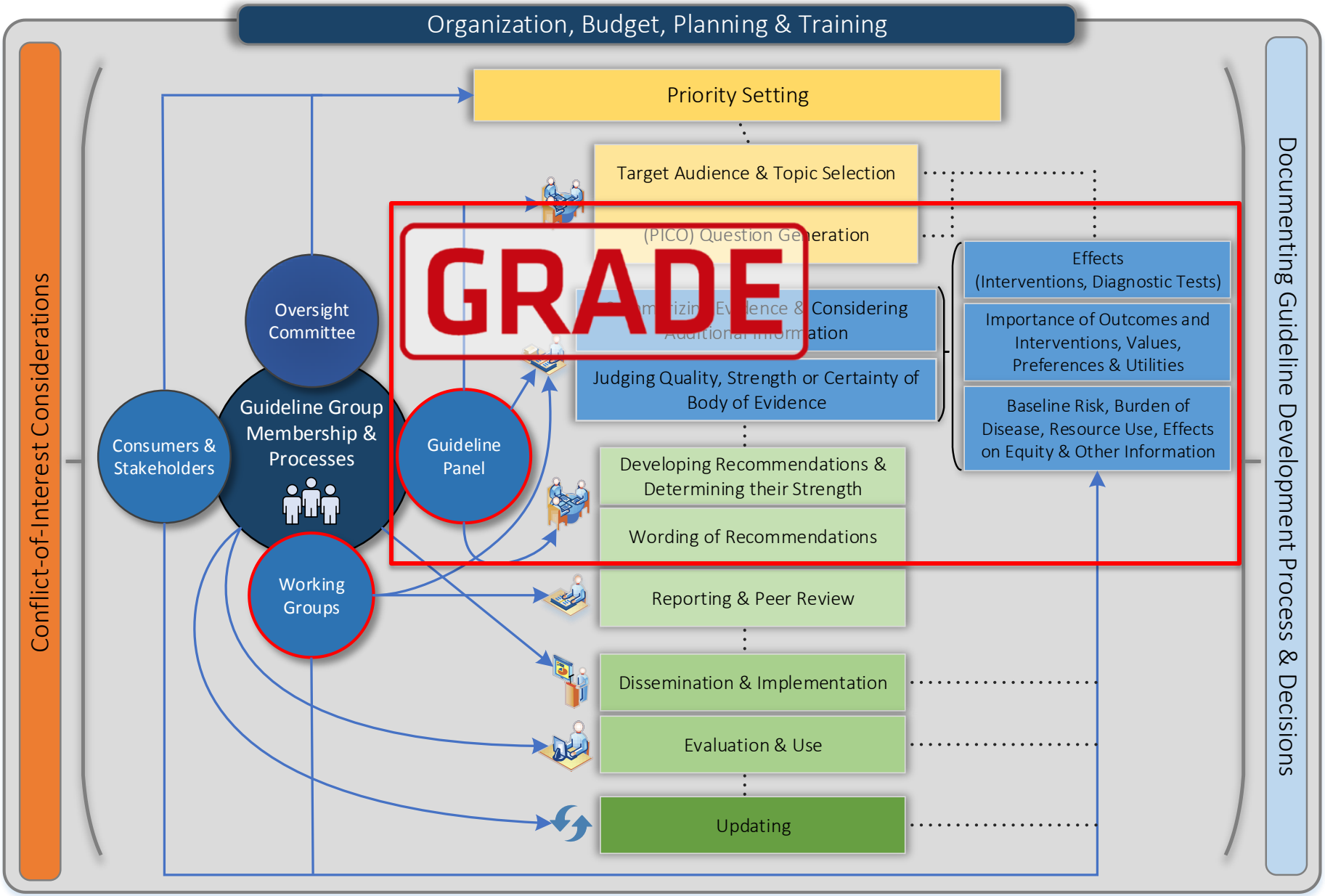
A clinically sensible question

Population: In workers exposed to noise, what is the impact of

Intervention: hearing protection devices
Comparison: compared with no devices

Outcomes: on hearing loss, hearing impairment

PICO



Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. 2014 Feb 18;186(3):E123-42.

http://cebgrade.mcmaster.ca/guidecheck.html

GRADEpro GDT

Formulate question

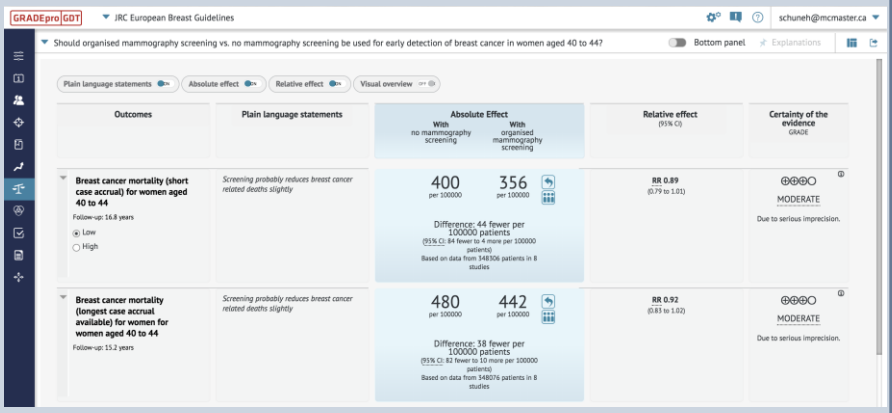
Assess single studies

Synthesize and Create **evidence profile or Summary of Findings** Table with GRADEpro

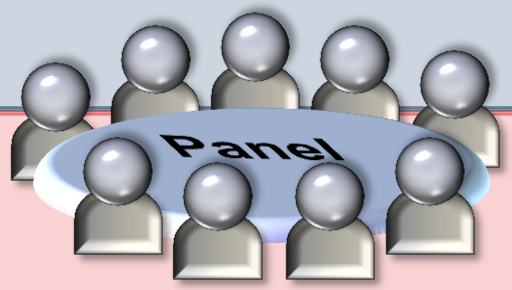
Rate certainty of evidence for each outcome

P
I
C
O

Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important



Evidence synthesis (systematic review/HTA)



Recommendation/Decision

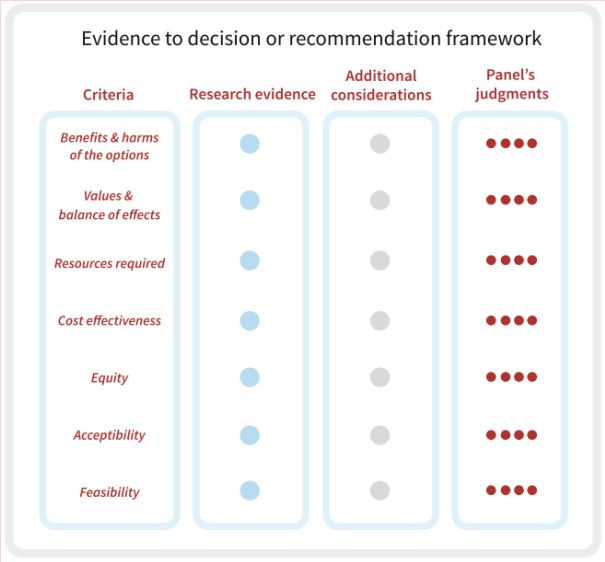
Guideline


AMERICAN GASTROENTEROLOGICAL ASSOCIATION

Colorectal Cancer Screening and Surveillance: Clinical Guidelines and Rationale–Update Based on New Evidence

Grade recommendations (Evidence to Recommendation)

- For or against (direction) ↓↑
- Strong or conditional/weak (strength)



Etiology

Is noise exposure associated with hearing impairment/loss?

Etiology

To assess the association between exposures and outcomes, including in the field of nutrition, environmental and occupational health, the concept of defining the Population (including animal species), Exposure, Comparator, and Outcomes (PECO) as pillars of the question is increasingly accepted

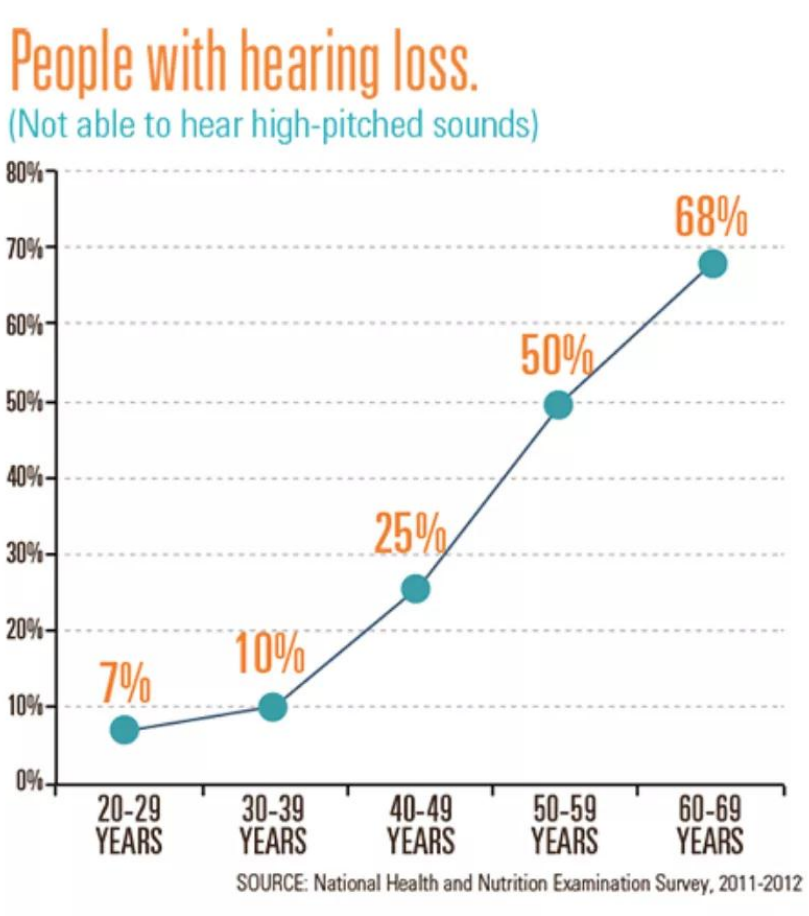
A sensible question

Population: People

Exposures: noise
Comparison: no noise, different levels of noise, exact cut offs

Outcomes: hearing loss, hearing impairment

PICO



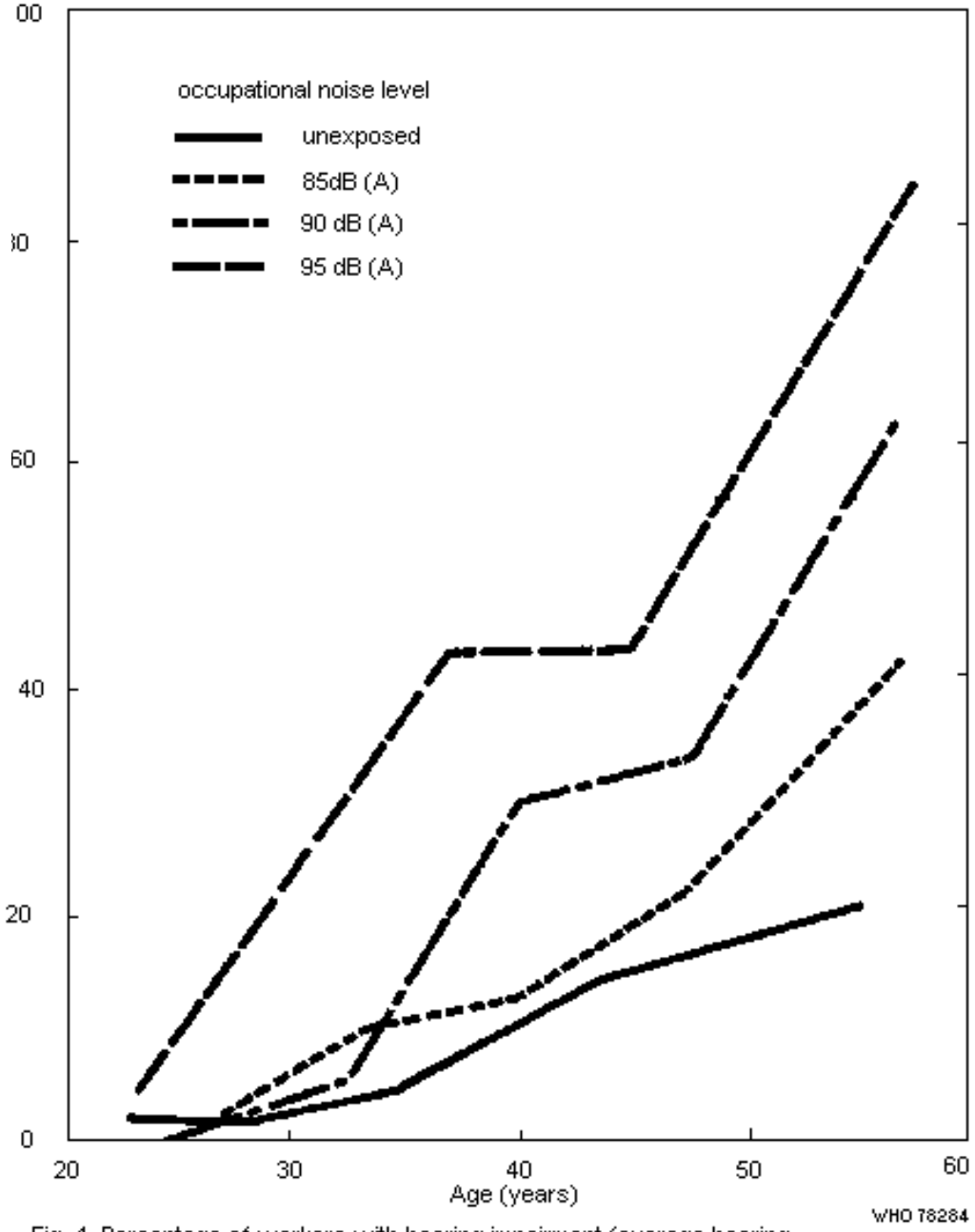


Fig. 4. Percentage of workers with hearing impairment (average hearing loss at 1, 2, and 3 kHz > 25 dB) (From: US National Institute for Occupational Safety and Health, 1972, 1973).

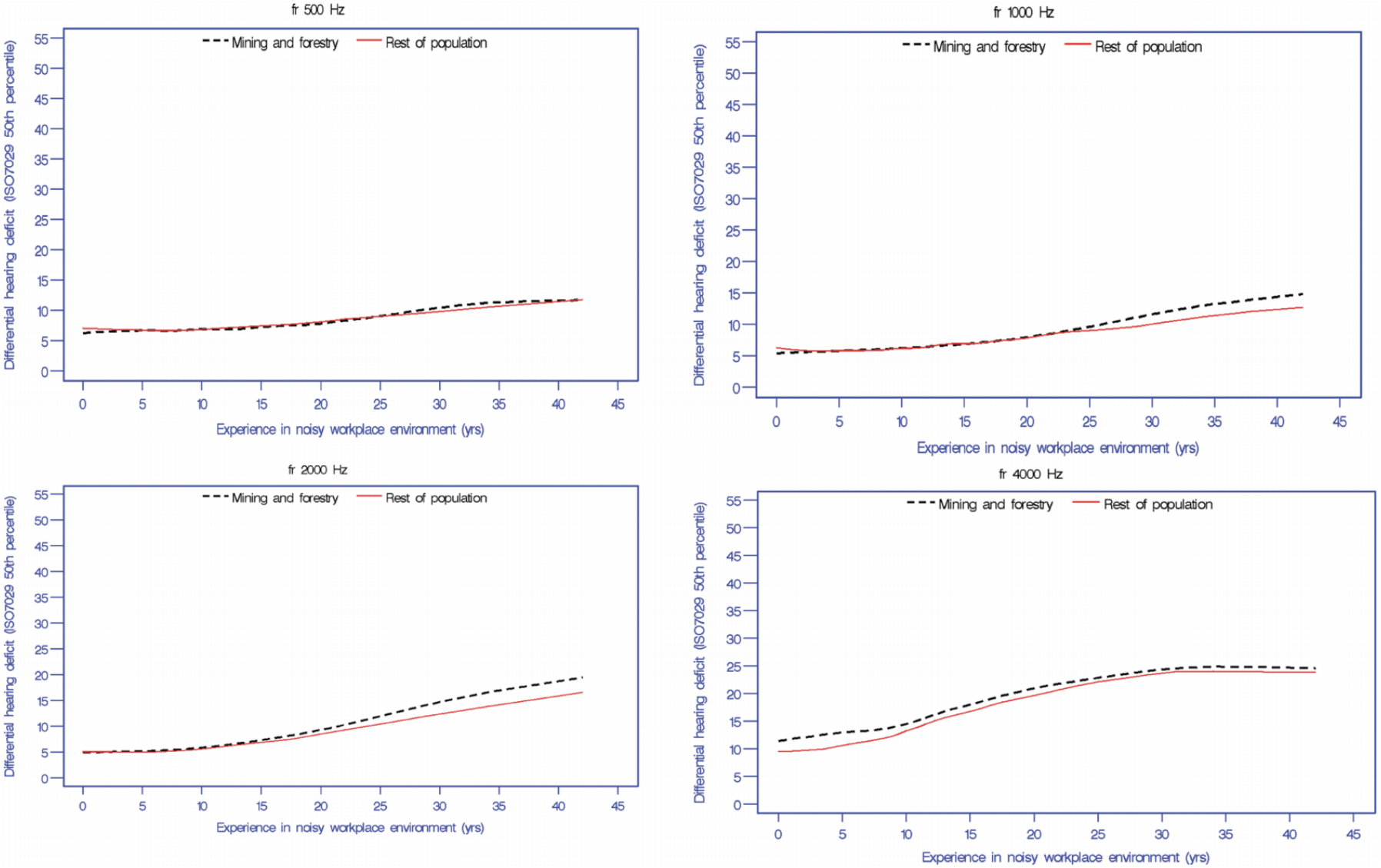
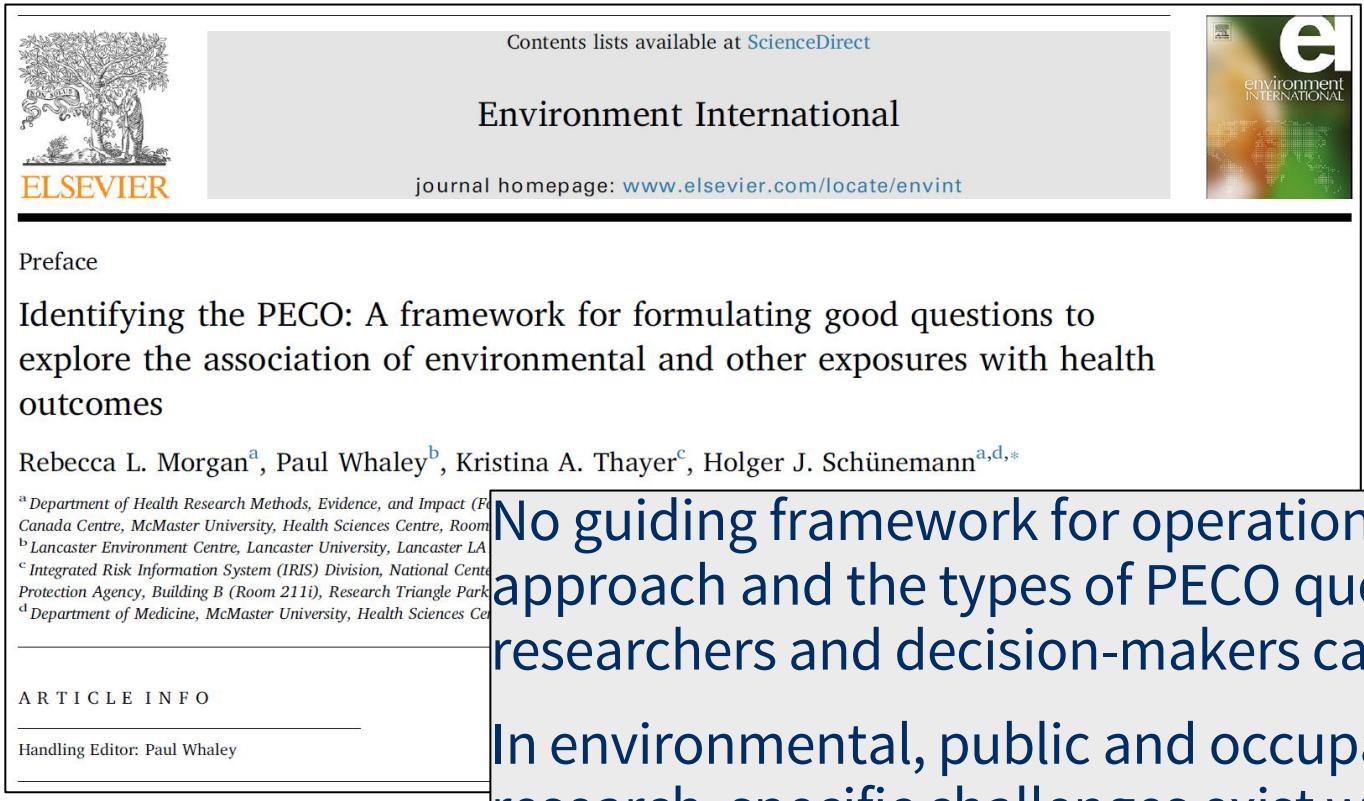


Figure 1. Comparison of DHD hearing loss between the study population and comparison group (non-mining and non-forestry population) at 500, 1000, 2000 and 4000 Hz as a function of duration of noise exposure.

Formulating Difficult PECOs



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Preface

Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes

Rebecca L. Morgan[a], Paul Whaley[b], Kristina A. Thayer[c], Holger J. Schünemann[a,d,*]

[a] Department of Health Research Methods, Evidence, and Impact (F
Canada Centre, McMaster University, Health Sciences Centre, Room
[b] Lancaster Environment Centre, Lancaster University, Lancaster LA
[c] Integrated Risk Information System (IRIS) Division, National Cent
Protection Agency, Building B (Room 211i), Research Triangle Park
[d] Department of Medicine, McMaster University, Health Sciences Ce

ARTICLE INFO

Handling Editor: Paul Whaley

No guiding framework for operationalizing the PECO approach and the types of PECO questions researchers and decision-makers can answer

In environmental, public and occupational health research, specific challenges exist with identifying the exposure and comparator within the PECO

Five paradigmatic approaches and examples for identifying the exposure and comparator in systematic review and decision-making questions.

Potential systematic-review or research context	Approach
1. Calculate the health effect from an exposure; describing the dose-effect relationship between an exposure and an outcome for risk characterization.	Explore the shape and distribution of the relationship between the exposure and the outcome in the systematic review.

Potential systematic-review or research context	Approach
1. Calculate the health effect from an exposure; describing the dose-effect relationship between an exposure and an outcome for risk characterization.	Explore the shape and distribution of the relationship between the exposure and the outcome in the systematic review.
2. Evaluate the effect of an exposure cut-off on health outcomes, when the cut-off can be informed iteratively by the results of the systematic review.	Use cut-offs defined based on distribution in the studies identified in the systematic review.

Potential systematic-review or research context	Approach
1. Calculate the health effect from an exposure; describing the dose-effect relationship between an exposure and an outcome for risk characterization.	Explore the shape and distribution of the relationship between the exposure and the outcome in the systematic review.
2. Evaluate the effect of an exposure cut-off on health outcomes, when the cut-off can be informed iteratively by the results of the systematic review.	Use cut-offs defined based on distribution in the studies identified in the systematic review.
3. Evaluate the association between an exposure cut-off and a comparison cut-off, when the cut-offs can be identified or are known from other populations.	Use mean cut-offs from external or other populations (may come from other research).

Potential systematic-review or research context	Approach
1. Calculate the health effect from an exposure; describing the dose-effect relationship between an exposure and an outcome for risk characterization.	Explore the shape and distribution of the relationship between the exposure and the outcome in the systematic review.
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3. Evaluate the association between an exposure cut-off and a comparison cut-off, when the cut-offs can be identified or are known from other populations.	Use mean cut-offs from external or other populations (may come from other research).
4. Identify an exposure cut-off that ameliorates the effects on health outcomes.	Use existing exposure cut-offs associated with known health outcomes of interest.

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1. Calculate the health effect from an exposure; describing the dose-effect relationship between an exposure and an outcome for risk characterization.	Explore the shape and distribution of the relationship between the exposure and the outcome in the systematic review.
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3. Evaluate the association between an exposure cut-off and a comparison cut-off, when the cut-offs can be identified or are known from other populations.	Use mean cut-offs from external or other populations (may come from other research).
4. Identify an exposure cut-off that ameliorates the effects on health outcomes.	Use existing exposure cut-offs associated with known health outcomes of interest.
5. Evaluate the potential effect of a cut-off that can be achieved through an intervention to ameliorate the effects of exposure on health outcomes.	Select the comparator based on what exposure cut-offs can be achieved through an intervention.

1. Is there an association or effect: Calculate the health effect from an exposure

Purpose - Identification of an association between exposure and the outcome

Approach - Explore the shape and distribution of the relationship between the exposure and the outcome in the systematic review

Example - Among newborns, what is the incremental effect of 10 dB increase during gestation on postnatal hearing impairment?

P: Among newborns, what is the effect of
E: 10 dB exposure to noise during gestation versus
C: 10 dB incremental increase on
O: Postnatal hearing impairment

2. Evaluate the effect of an exposure cut-off on health outcomes

Purpose – Do not know naturally occurring exposure levels or are unsure about which cut-offs to choose.

Approach - Use cut-offs defined based on distribution in the studies identified in the systematic review.

Example - Among newborns, what is the effect of the highest dB exposure compared to the lowest dB exposure (e.g. identified tertiles, quartiles, or quintiles) during pregnancy on postnatal hearing impairment?

P: Among newborns, what is the effect of
E: Highest noise exposure during pregnancy versus
C: Lowest noise exposure during pregnancy on
O: Postnatal hearing impairment

3. Evaluate the association between an exposure cut-off and a comparison cut-off

Purpose - Have information about a certain exposure level for a population of interest but want to compare that to the impact of a different level of exposure on a certain health outcome.

Approach - Use mean cut-offs from external or other populations (may come from other research).

Example - Among commercial pilots, what is the effect of noise corresponding to occupational exposure compared to noise exposure experienced in other occupations on hearing impairment?

P: Among commercial pilots, what is the effect of
E: Noise corresponding to their occupational exposure versus
C: Noise exposure experienced by people in low-exposure occupations on
O: Hearing impairment.

4. Identify an exposure cut-off that ameliorates the effects on health outcomes.

Purpose – Identify a permissive level of exposure based on a quantified dose-response relationship.

Approach - Use existing exposure cut-offs associated with known health outcomes of interest.

Example - Among industrial workers, what is the effect of exposure to <80 dB compared to ≥80 dB on hearing impairment?

P: Among industrial workers, what is the effect of
E: Occupational noise exposure < 80 dB versus
C: Occupational noise exposure ≥ 80 dB on
O: Hearing impairment.

5. Evaluate the potential effect of a cut-off that can be achieved through an intervention

Purpose – When the decision-maker is interested in a specific exposure cut-off that can be achieved through an intervention to mitigate the exposure.

Approach - Select the comparator based on what exposure cut-offs can be achieved through an intervention.

Example - Among the general population, what is the effect of an intervention that reduces noise levels by 20 dB compared to no intervention on hearing impairment?

P: Among the general population, what is the effect of
E: Noise levels that are 20 dB lower than
C: Current noise levels on
O: Hearing impairment.

Need for methods advancement

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

GRADE: Assessing the quality of evidence in environmental and occupational health

Rebecca L. Morgan [a], Kristina A. Thayer [b], Lisa Bero [c], Nigel Bruce [d], Yngve Falck-Ytter [e], Davina Ghersi [f,g], Gordon Guyatt [a], Carlijn Hooijmans [h], Miranda Langendam [i], Daniele Mandrioli [j], Reem A. Mustafa [a,k], Eva A. Rehfuess [l], Andrew A. Rooney [b], Beverley Shea [m], Ellen K. Silbergeld [n], Patrice Sutton [o], Mary S. Wolfe [b], Tracey J. Woodruff [o], Jos H. Verbeek [p], Alison C. Holloway [q], Nancy Santesso [a], Holger J. Schünemann [a,r,*]

"GRADE represents an untapped opportunity for environmental and occupational health to make evidence-based recommendations in a systematic and transparent manner."

Evaluate the effect of an exposure on health outcomes

Higher exposure to Bisphenol A (BPA) is associated with increased weight!

How certain can we be in this statement?

evidence

How confident in the research?

Are the research studies well done? Risk of bias

Are the results consistent across studies ? Inconsistency

How directly do the results relate to our question? Indirectness

Is the effect size precise - due to random error? Imprecision

Are these all of the studies that have been conducted? Pub. Bias

Is there anything else that makes us particularly certain? Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation

GRADE working group

After over 20 years of increasing confusion, beginning in 2000, GRADE developed a **unifying, transparent and sensible system for grading the certainty of evidence and making decisions**

- WHO, NICE, CADTH, CDC, AHRQ, professional societies, academic institutions since 2000 – over 100 use GRADE
- For systematic reviews, HTA and guidelines
- International & diverse contributors (>600)
- 2008/16 BMJ series; 2011 -? JCE series – over 30,000 cites
- Various other publications (incl. GRADE Handbook)
- IT applications GRADEpro | GDT

CMAJ 2003, BMJ 2004, BMC 2004, BMC 2005, AJRCCM 2006, Chest 2006, BMJ 2008, JCE 2011-2017

Development of the risk of bias instrument for NRS of exposures

Environment International 120 (2018) 382–387

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Evaluation of the risk of bias in non-randomized studies of interventions (ROBINS-I) and the 'target experiment' concept in studies of exposures: Rationale and preliminary instrument development

Rebecca L. Morgan[a], Kristina A. Thayer[b], Nancy Santesso[a], Alison C. Holloway[c], Robyn Blain[d], Sorina E. Eftim[d], Alexandra E. Goldstone[d], Pam Ross[d], Gordon Guyatt[a], Holger J. Schünemann[a,e,*]

[a] Department of Health Research Methods, Evidence, and Impact (formerly the Department of Clinical Epidemiology & Biostatistics), McMaster University, Health Sciences Centre, Room 2C14, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

[b] Integrated Risk Information System (IRIS) Division, National Center for Environmental Assessment (NCEA), Office of Research and Development, US Environmental Protection Agency, Building B (Room 211i), Research Triangle Park, NC 27711, USA

[c] Department of Obstetrics and Gynecology, McMaster University, Health Sciences Centre, Room 3N52A, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

[d] ICF, 9300 Lee Highway, Fairfax, VA 22031, USA

[e] Department of Medicine, McMaster University, Health Sciences Centre, Room 2C14, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

Evaluation of a new risk of bias instrument for non-randomized studies

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

- Evaluates health effects of medical interventions by comparing to the ideal RCT

Application for studies of exposures

- Need for a robust tool to assess exposure studies
- Many similarities between RoB domains

The RoB instrument for NRS of exposures

Replacement of “intervention” with “exposure”

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

Replacement of the wording for “Target Trial” with “Target Experiment”;

Fields added to address measurement of exposure and outcome

Replacement of signaling questions in “Bias in Measurement of Exposure”

Steps for applying the RoB instrument for NRS of exposures

Step I: Clarify the review question and identify topic-specific considerations (i.e., potential confounders, co-interventions, and exposure and outcome measurement accuracy information) important to assess bias;

Step II: Describe a target trial or experimental version of the study, including specific confounders and co-interventions from that study that will require consideration; and

Step III: Evaluate the study by completing signaling questions across seven RoB domains.

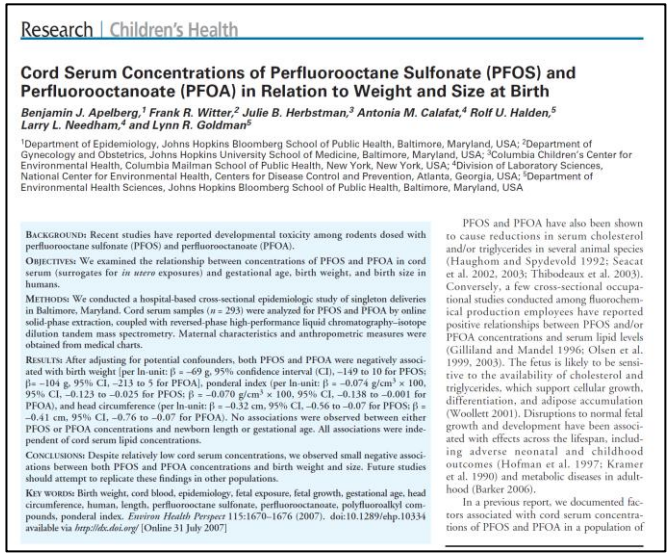
Background

Guidance needed for instruments that evaluate NRS as an ideal target trial

- GRADE Working Group approved guidance for ROBINS-I in 2017

ROBINS-I required modifications for application to NRS of exposures

- Replacement of the wording for “Target Trial” with “Target Experiment”
- Replacement of “intervention” with “exposure”
- Additional instructions and examples added to the handbook (e.g., consideration of cross-sectional studies, exposure-specific examples)
- Fields added to address measurement of exposure and outcome
- Replacement of signaling questions in “Bias in Measurement of Exposure”



Research | Children's Health

Cord Serum Concentrations of Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Weight and Size at Birth

Benjamin J. Apelberg,[1] Frank R. Witter,[2] Julie B. Herbstman,[3] Antonia M. Calafat,[4] Rolf U. Halden,[5] Larry L. Needham,[4] and Lynn R. Goldman[5]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [2]Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [3]Columbia Children's Center for Environmental Health, Columbia Mailman School of Public Health, New York, New York, USA; [4]Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [5]Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

BACKGROUND: Recent studies have reported developmental toxicity among rodents dosed with perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA).

OBJECTIVES: We examined the relationship between concentrations of PFOS and PFOA in cord serum (surrogates for *in utero* exposures) and gestational age, birth weight, and birth size in humans.

METHODS: We conducted a hospital-based cross-sectional epidemiologic study of singleton deliveries in Baltimore, Maryland. Cord serum samples ($n = 293$) were analyzed for PFOS and PFOA by online solid-phase extraction, coupled with reversed-phase high-performance liquid chromatography–isotope dilution tandem mass spectrometry. Maternal characteristics and anthropometric measures were obtained from medical charts.

RESULTS: After adjusting for potential confounders, both PFOS and PFOA were negatively associated with birth weight [per ln-unit: β = –69 g, 95% confidence interval (CI), –149 to 10 for PFOS; β= –104 g, 95% CI, –213 to 5 for PFOA], ponderal index (per ln-unit: β = –0.074 g/cm^3 × 100, 95% CI, –0.123 to –0.025 for PFOS; β = –0.070 g/cm^3 × 100, 95% CI, –0.138 to –0.001 for PFOA), and head circumference (per ln-unit: β = –0.32 cm, 95% CI, –0.56 to –0.07 for PFOS; β = –0.41 cm, 95% CI, –0.76 to –0.07 for PFOA). No associations were observed between either PFOS or PFOA concentrations and newborn length or gestational age. All associations were independent of cord serum lipid concentrations.

CONCLUSIONS: Despite relatively low cord serum concentrations, we observed small negative associations between both PFOS and PFOA concentrations and birth weight and size. Future studies should attempt to replicate these findings in other populations.

KEY WORDS: Birth weight, cord blood, epidemiology, fetal exposure, fetal growth, gestational age, head circumference, human, length, perfluorooctane sulfonate, perfluorooctanoate, polyfluoroalkyl compounds, ponderal index. *Environ Health Perspect* 115:1670–1676 (2007). doi:10.1289/ehp.10334 available via *http://dx.doi.org/* [Online 31 July 2007]

PFOS and PFOA have also been shown to cause reductions in serum cholesterol and/or triglycerides in several animal species (Haughom and Spydevold 1992; Seacat et al. 2002, 2003; Thibodeaux et al. 2003). Conversely, a few cross-sectional occupational studies conducted among fluorochemical production employees have reported positive relationships between PFOS and/or PFOA concentrations and serum lipid levels (Gilliland and Mandel 1996; Olsen et al. 1999, 2003). The fetus is likely to be sensitive to the availability of cholesterol and triglycerides, which support cellular growth, differentiation, and adipose accumulation (Woollett 2001). Disruptions to normal fetal growth and development have been associated with effects across the lifespan, including adverse neonatal and childhood outcomes (Hofman et al. 1997; Kramer et al. 1990) and metabolic diseases in adulthood (Barker 2006).

In a previous report, we documented factors associated with cord serum concentrations of PFOS and PFOA in a population of

Evaluate RoB per outcome using the RoB instrument for NRS of exposures

Domains

- Confounding
- Selection
- Measurement of Exposure
- Departures from Exposure
- Missing Data
- Measurement of Outcomes
- Reported Results

Study	Confounding	Selection	Measurement of Exposure	Departures from Exposure	Missing Data	Measurement of Outcomes	Reported Results
Apelberg et al. 2007							

Low	Moderate	Serious	Critical

RoB Matrix: Exposure to BPA on prevalent overweight and obesity

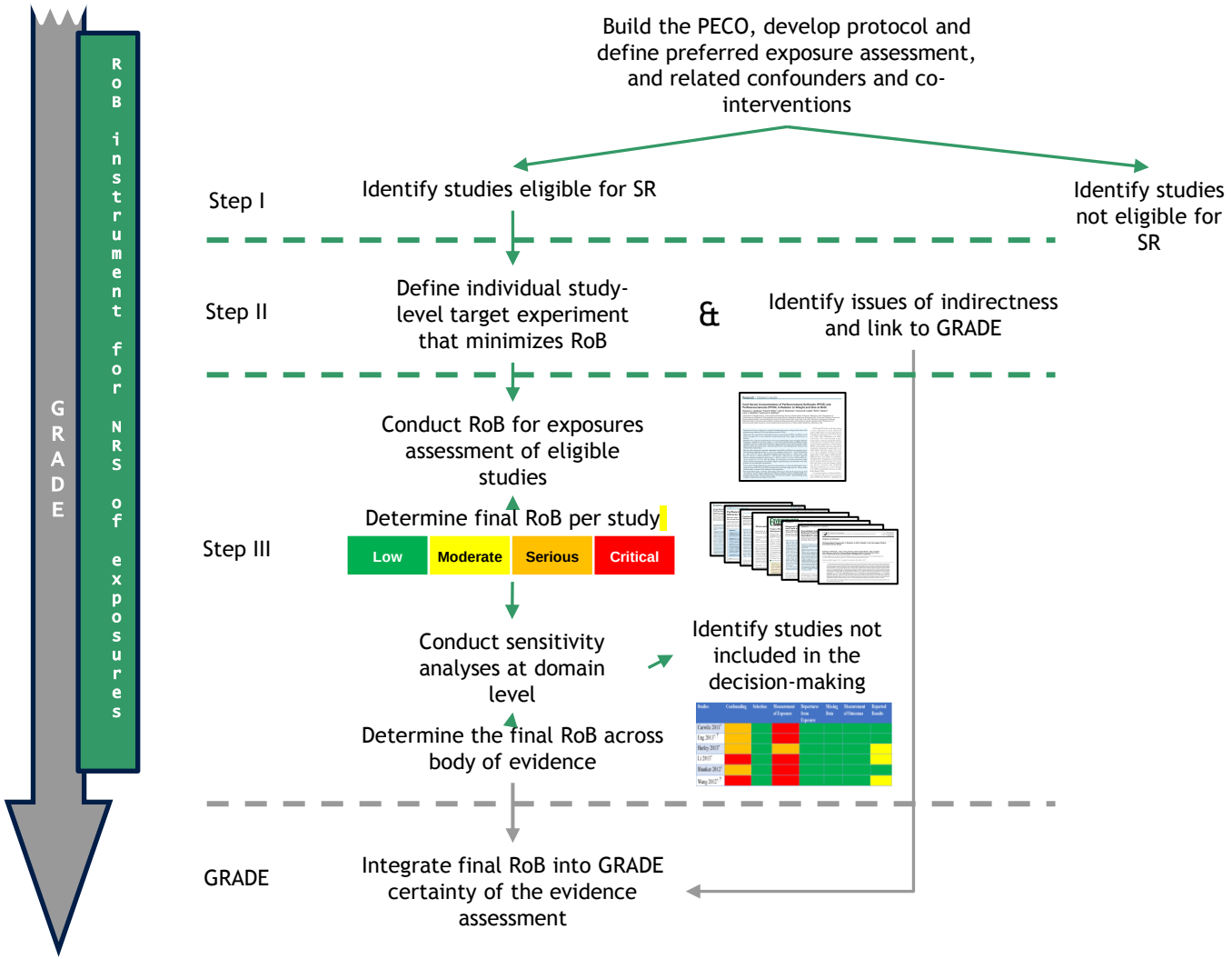
Studies	Confounding	Selection	Measurement of Exposure	Departures from Exposure	Missing Data	Measurement of Outcomes	Reported Results
Carwile 2011*							
Eng 2013*, †							
Harley 2013*							
Li 2013*							
Shankar 2012†							
Wang 2012*, †							

* Prevalent overweight
† Prevalent obesity

Low	Moderate	Serious	Critical

Ranciere, F., Lyons, J. G., Loh, V. H., Botton, J., Galloway, T., Wang, T., . . . Magliano, D. J. (2015). Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence. *Environ Health, 14*(1), 46. doi:10.1186/s12940-015-0036-5

RoB instrument integration within GRADE evidence assessment


GRADE
ROB instrument for NRS of exposures
Build the PECO, develop protocol and define preferred exposure assessment, and related confounders and co-interventions
Step I
Identify studies eligible for SR
Identify studies not eligible for SR
Step II
Define individual study-level target experiment that minimizes RoB
&
Identify issues of indirectness and link to GRADE
Conduct RoB for exposures assessment of eligible studies
Step III
Determine final RoB per study
Low
Moderate
Serious
Critical
Conduct sensitivity analyses at domain level
Identify studies not included in the decision-making
Determine the final RoB across body of evidence
GRADE
Integrate final RoB into GRADE certainty of the evidence assessment

RoB Matrix: Exposure to BPA on prevalent overweight and obesity

Studies	Confounding	Selection	Measurement of Exposure	Departures from Exposure	Missing Data	Measurement of Outcomes	Reported Results
Carwile 2011*							
Eng 2013*, †							
Harley 2013*							
Li 2013*							
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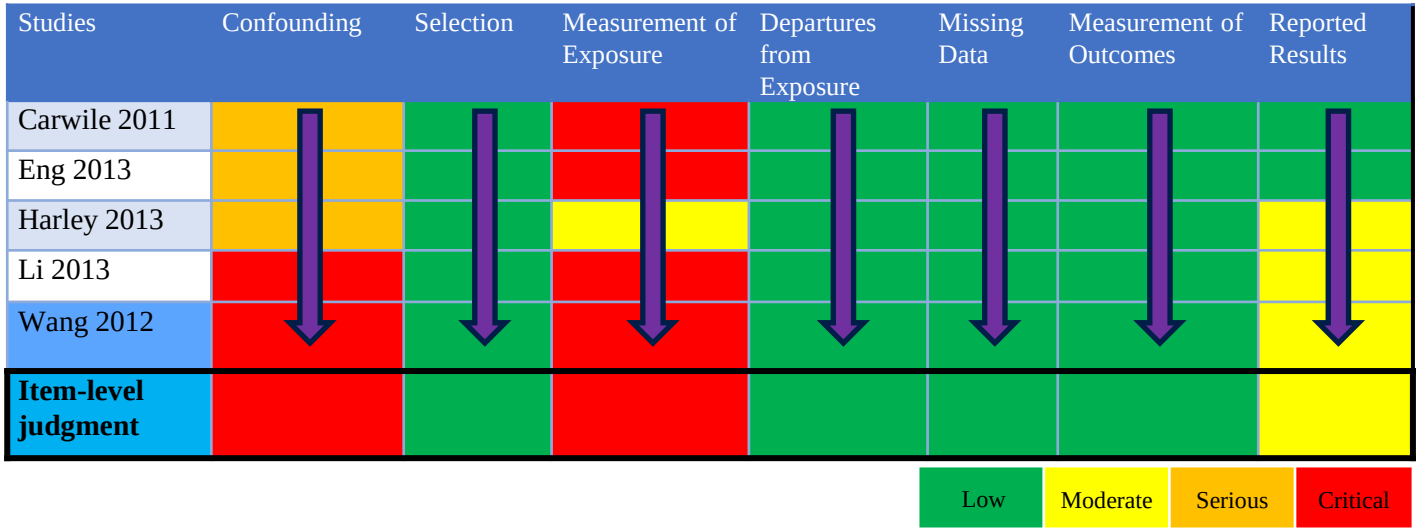
* Prevalent overweight
† Prevalent obesity

Low	Moderate	Serious	Critical

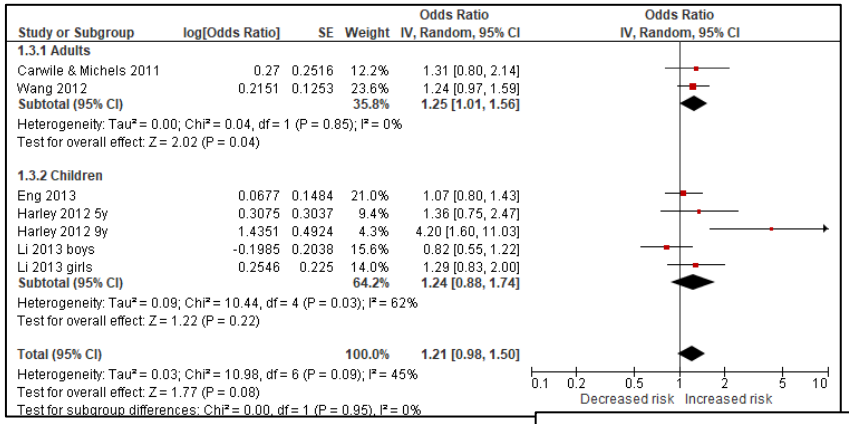
Ranciere, F., Lyons, J. G., Loh, V. H., Botton, J., Galloway, T., Wang, T., . . . Magliano, D. J. (2015). Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence. *Environ Health, 14*(1), 46. doi:10.1186/s12940-015-0036-5

RoB judgment across the body of evidence: Part 1

RoB judgment across the body of evidence (prevalent overweight): Part 2



Prevalent overweight



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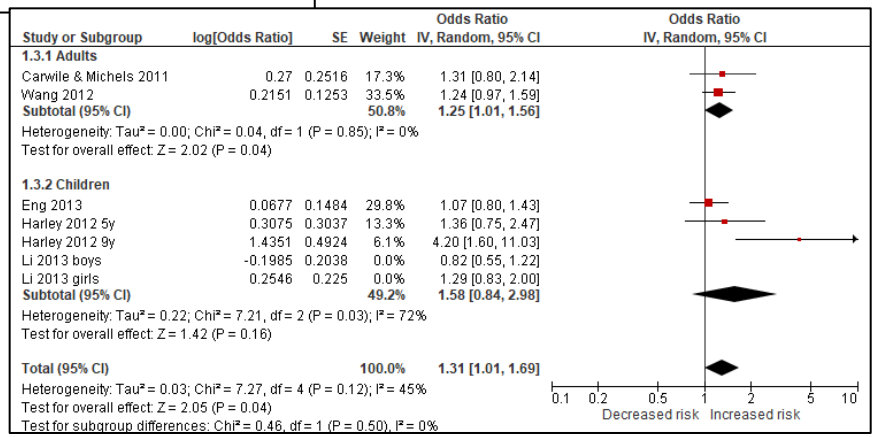
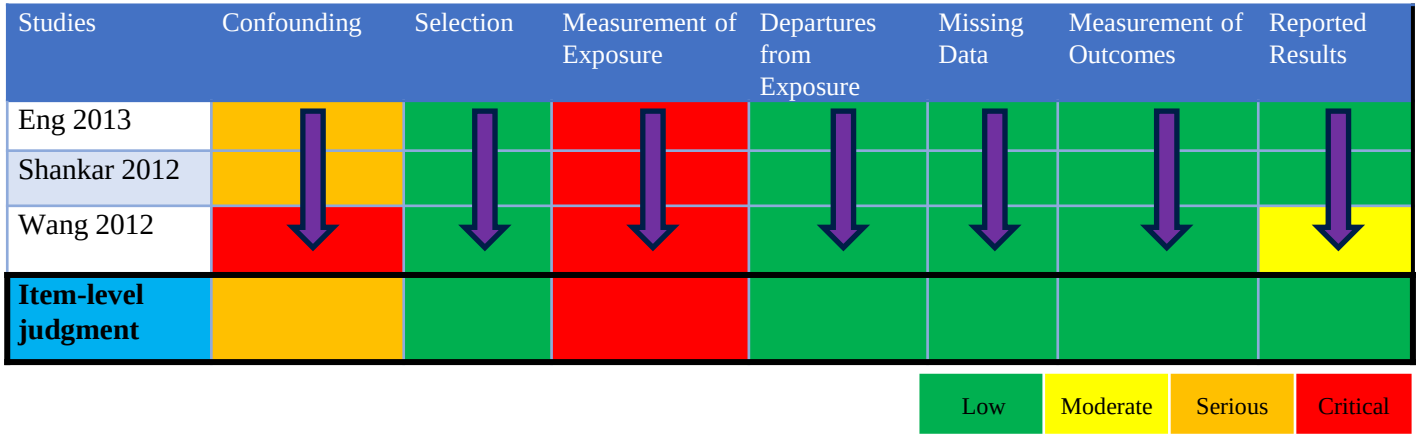
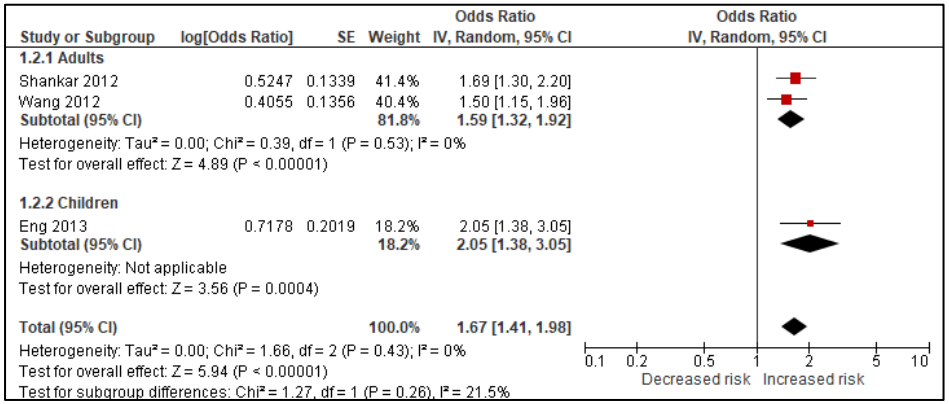


RoB judgment across the body of evidence (prevalent obesity): Part 2



Prevalent obesity



1

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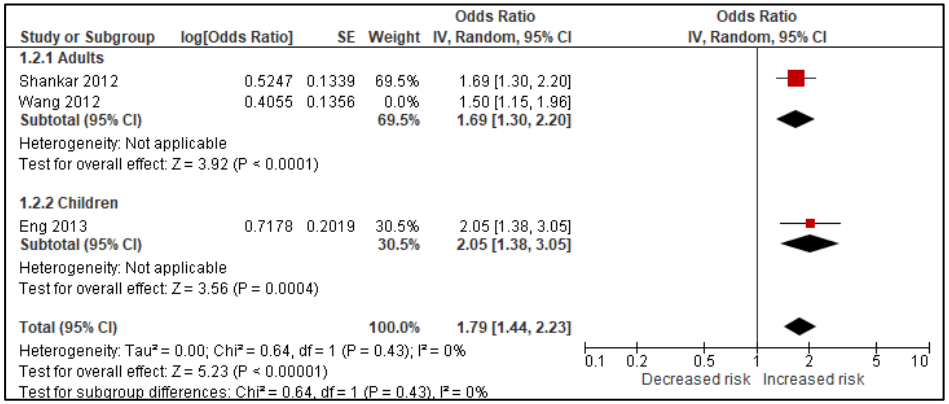

Transparency within the Evidence Profile: GRADE assessment

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	exposure to BPA (CAS# 80-05-7)	exposure to lower levels of BPA	Relative (95% CI)	Absolute (95% CI)	
Prevalent overweight (assessed with: BMI ≥85th percentile for age/gender in children; BMI 18.5-25/30 kg/m2)											
5	studies	very, very	not serious [b]	not serious	serious	none	1774/5403	1584/5657	OR 1.21	40 more per	⊕◯◯◯
Prevalent obesity											
3	studies										

CI: Confide

a. **Most studies adjusted for known confounders** of body composition (age, ethnicity, gender, height, race), and diet; however, **two studies did not account for caloric intake or diet which is relevant for evaluating weight-related outcomes**, **there is some risk of unmeasured confounding**; BPA measurement present potential for bias as the **chemical is non-persistent with a short half-life** and exposure measurements were not repeated (except in one study), one study measures BPA three months post-BMI measurement, remaining studies measure BPA and BMI at the same time; potential risk of reporting bias because **three studies did not report prior publication of a protocol**; however, all studies present outcome measures and analyses consistent with *a priori* plan outlined in the manuscript.

b. The I^2 value = 45% and exploration of the forest plot suggests some inconsistency introduced by one outlying study contributing 4.3% of the weight to the analysis of children.

c. Imprecision is present because the width of the confidence interval is consistent with both important benefit and harm.

Summary

Formulating good questions: PECO

Guidance when evaluating RoB of exposure studies using a target experiment approach

Conceptualization of RoB integration of studies of exposures into GRADE

GRADE as a decision-making framework for research on environmental exposures

 @schunemann_mac

Eskerrik asko – Thank you