“Evolution of and Current Issues in Evidence Synthesis and Integration in Air Pollution and Health”

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A short history of causal inference in Biomedical research and public health (I)

Causation cannot be observed directly

Philosophers developed constructs & heuristics to define a "cause" operationally.

These constructs typically have two components:

- an associational one, determined empirically from variations in the probability of disease occurrence, and
- an explanatory one, based on a proposed underlying mechanism.

All causal claims rest on these twin pillars.

- For biomedical research, the first criteria came following the discovery of bacteria during the nineteenth century.
- Method needed for judging if an organism caused a particular disease.

Henle-Koch Postulates

1. The parasite occurs in every case of the disease in question and under circumstances that can account for the pathologic changes of the disease.
2. It occurs in no other disease as a fortuitous and non-pathogenic parasite.
3. After isolation from the body and grown in pure culture, it can induce the disease

A short history of causal inference in Biomedical research and public health (II)

Criteria are necessarily different for **chronic diseases**, with **multiple causes**, heterogeneous clinical features and much longer induction periods than in infectious diseases.

Bradford Hill: "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non."

Rather, in support of causal explanations, or

as evidence against, competing non-causal explanations,
- chance;
- selection bias;
- errors in measurement of exposure, confounders, or outcome.
- residual or unmeasured confounding

5 of these viewpoints also used in 1964 Surgeon General's report, as the criteria for causal judgment

Bradford Hill's Viewpoints for assessing causality

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

Problematic developments in systematic review methodology and causal inference

Systematic review and causal inference concepts, e.g., as developed by the IARC Monographs, have matured as an authoritative reference of cancer hazard identification well before risk assessment paradigms evolved.

Approaches more recently developed in clinical medicine (e.g., Cochrane Collaboration, 1993; GRADE, 2000) now try to impose their methodology on evidence synthesis in public health.

Annals of Internal Medicine IDEAS AND OPINIONS

GRADE Methods for Guideline Development: Time to Evolve?

Susan L. Norris, MD, MPH, MSc, and Lisa Bero, PhD

"not currently applicable to many questions that guideline developers face, including those about assessing risk and causality, establishing risk thresholds, or assessing animal studies."

"have low interrater reliability when assessing complex bodies of evidence consisting of different study designs".

Randomized controlled vs observational studies (I)

RCTs rarely used in natural sciences, such as physics; likewise, most important public health questions (e.g. global climate change, smoking) cannot be studied

Observational studies have potential to suffer from biases theoretically avoided by RCTs

GRADE states : “Evidence from randomized controlled trials starts at high quality and, because of residual confounding, evidence that includes observational data starts at low quality.”

RCTs may be a useful theoretical starting point to think about potential bias, but they do NOT provide the gold standard for environmental studies

Randomized controlled vs observational studies (II)

- RCTs typically involve limited sample sizes and a short follow-up time, inadequate for observing chronic disease or rare outcomes.
- Observational studies often involve rare outcomes with long latencies
- RCTs deliver the exposure (e.g., medication) at the beginning of follow-up, typically in a limited number of dose levels
- Yet, in real life exposures are often present before follow-up begins, occur at many different levels, and often change over time
- RCT may involve highly selective study groups, which have little generalizability to other populations

Risk of bias (ROB)

- Increasing use of various tools for evaluating epidemiological studies
- Here, risk of bias (ROB) assessments tools, such as various ROBINS, or within GRADE
- ROB assessments typically focus on whether specific biases (confounding, selection bias, and information bias) are present, but do not usually assess the direction, magnitude, or overall importance of the various types of bias.
- Information bias unlikely to explain positive findings of studies with non-differential exposure misclassification
- ROB tools typically evaluate bias in individual studies and consider individual studies out of context.
- Assessments often used to exclude "low-quality" studies from evidence synthesis.

A risk of bias instrument for non-randomized studies of exposures: A users' guide to its application in the context of GRADE

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], Mohammed Ansari[e], Elie A Akl[a,f], Tommaso Filippini[g], Anna Hansell[h,i,j], Joerg J. Meerpohl[k], Reem A. Mustafa[a,l], Jos Verbeek[m],

Assessing risk of bias in human environmental epidemiology studies using three tools: different conclusions from different tools

Stephanie M. Eick[1], Dana E. Goin[1], Nicholas Chartres[1], Juleen Lam[1,2] and Tracey J. Woodruff[1*]

For each tool, assess usability and inter-rater reliability of human observational studies

	Use of biomarker of exposure	Comparison group	Measurement of exposure	Method Requirements	Temporality	Matrix Adjustment	Reporting bias	Participant selection	Covariate characterization	Outcome measurement or characterization	Reproducibility of analyses	Co-exposure confounding	Method Sensitivity	Sample Contamination	Covariate adjustment	Exposure levels	Study design and methods	Attrition	Biomarker Stability	Statistical models	Effect Biomarker	Statistical power	**Overall Score**
Adgent et al. 2014	1	1	1	1	1	2	1	2	2	1	2	3	2	3	3	2	2	3	3	3	NA	4	4
Eskenazi et al. 2013	1	1	1	1	2	2	1	2	2	2	2	2	3	3	1	2	2	3	3	3	NA	4	4
Chao et al. 2011	1	1	1	1	1	2	3	2	2	3	2	3	2	2	3	3	2	3	3	3	NA	4	4
Chen et al. 2014	1	1	1	1	1	2	1	1	3	1	2	2	2	3	3	2	2	3	3	3	NA	4	4
Gascon et al. 2012	1	1	1	2	1	2	1	1	2	2	2	2	3	2	3	3	2	2	3	3	NA	4	4
Gascon et al. 2011	1	1	1	2	2	3	1	1	1	2	2	2	3	3	3	3	2	3	3	3	NA	4	4
Herbstman et al. 2010	1	1	1	1	1	2	1	2	1	2	2	3	3	3	3	2	2	3	3	3	NA	4	4
Hoffman et al. 2012	1	1	1	1	1	1	1	2	2	2	2	3	3	3	3	2	2	3	3	3	NA	4	4
Sagiv et al. 2015	1	2	2	1	1	2	1	2	2	2	2	2	3	3	3	2	2	2	3	3	NA	4	4
Roze et al. 2009	1	1	1	2	1	2	3	1	3	2	3	3	2	2	3	3	2	1	3	3	NA	4	4
Zhang et al. 2017	1	1	1	1	1	2	3	1	2	2	2	2	3	3	3	3	2	3	3	3	NA	4	4
Shy et al. 2011	1	1	1	1	1	2	2	3	2	3	3	3	2	2	3	4	2	3	3	3	NA	4	4
Gump et al. 2014	1	1	2	1	3	1	2	3	1	2	3	2	2	2	3	3	4	3	3	3	NA	4	4
Cowell et al. 2015	1	1	1	1	1	2	3	2	2	2	2	3	3	2	3	3	4	4	3	3	NA	4	4
Lin et al. 2010	1	1	1	1	1	2	3	3	3	3	3	3	3	3	3	4	4	3	3	3	NA	4	4

Fig. 4 Summary of risk of bias judgments (high, medium, low, unacceptable) using the TSCA framework for the human studies included in our case series. The justification for risk of bias designations for individual studies are provided in Tables S3-S17. Kappa value was 54% (95% confidence interval 47-61%). Note: 1 indicates high, 2 indicates medium, 3 indicates low, 4 indicates unacceptable study quality. Abbreviations: NA, not applicable

Randomized trials of interventions	Non-randomized/observational studies of interventions	Non-randomized/observational studies of exposures
Cochrane RoB (2008)	ROBINS-I *V1* (2016)	ROBINS-E for follow-up studies

Commentary

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP6980.

Risk of Bias Assessments and Evidence Syntheses for Observational Epidemiologic Studies of Environmental and Occupational Exposures: Strengths and Limitations

Kyle Steenland,[1] M.K. Schubauer-Berigan,[2] R. Vermeulen,[3] R.M. Lunn,[4] K. Straif,[5,6] S. Zahm,[7] P. Stewart,[8] W.D. Arroyave,[9] S.S. Mehta,[4] and N. Pearce[10]

- Although RCTs may provide a useful starting point to think about bias, they do not provide a gold standard for environmental studies. Observational studies should not be considered inherently biased vs. a hypothetical RCT.
- Rather than a checklist approach when evaluating individual studies using risk of bias tools, we call for identifying and quantifying possible biases, their direction, and their impacts on parameter estimates.
- As is recognized in many guidelines, evidence synthesis requires a broader approach than simply evaluating risk of bias in individual studies followed by synthesis of studies judged unbiased…

Study Sensitivity or Informativeness

- Ability to show a true association, if there is one, and the lack of an association, if no association exists.
- Key determinants include: precise estimates of effect; sufficient elapsed time from exposure to measurement of outcome;
- Adequate exposure contrast (intensity, frequency, and/or duration);
- Biologically relevant definitions of exposure & relevant & well-defined time windows for exposure and outcome.

Conflict of Interests

At level of development of frameworks for SR

- ROB tool, **Definitely Low-risk (Ideal Study) "**Authors state that there are no conflicts of interests OR state that the funders did not have a say in the methods, analysis and reporting of results"

At level of assessment of individual agents

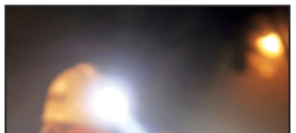
- Blocking publication of NCI/NIOSH studies on carcinogenicity of Diesel Engine Exhaust
- Withdrawal of accepted studies after take-over of journal by stakeholders with vested interests
- Weakness of Conflict of Interest procedures (eg, Gamble, DEE) and Committee on Publication Ethics (COPE)

Industry group "threatens" journals to delay publications

Several scientific journals, including *The Lancet* titles, have received letters from the industry-funded Mining

Annals of Occupational Hygiene (which also received MARG's letter) and the *Journal of the National Cancer Institute*,

for publication, except through normal peer review", said Vincent Cogliano, a former IARC Monographs Programme



Carcinogenicity of consumption of red and processed meat

In October, 2015, 22 scientists from ten countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of the consumption of red meat and processed meat. These assessments will be published in

more than 200 g per person per day.[4] Less informatio consumption of p

The Working (than 800 epid that investigate cancer with cons

day of red meat and an 18% increase per day of

for more r. Positive n cohort sed case-

Congratulations, Kurt!

Your article reached 5,000 reads

Achieved on May 4, 2021

Article: Carcinogenicity of consumption of red and processed meat

FINANCIAL TIMES

November 24, 2015 5:55 pm

A false alarm on red meat and cancer

Gordon Guyatt

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Two large trials have tested for evidence and the WHO ignored both of them, writes Gordon Guyatt

"So the WHO leaned heavily on the third source: epidemiological data. ... Unless relative risks are greater than five, epidemiological studies typically provide only low-quality evidence."

REVIEW

Annals of Internal Medicine

Patterns of Red and Processed Meat Consumption and Risk for Cardiometabolic and Cancer Outcomes

A Systematic Review and Meta-analysis of Cohort Studies

Robin W.M. Vernooij, PhD*; Dena Zeraatkar, M

CLINICAL GUIDELINE

Annals of Internal Medicine

Unprocessed Red Meat and Processed Meat Consumption: Dietary Guideline Recommendations From the Nutritional Recommendations (NutriRECS) Consortium

Bradley C. Johnston, PhD; Dena Zeraatkar, MSc; Mi Ah Han, PhD; Robin W.M. Vernooij, PhD; Claudia Valli, MSc;

thebmj

NEWS

New red meat guidelines are undermined by undisclosed ties and faulty methods, say critics

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

New “guidelines” say continue red meat consumption habits, but recommendations contradict evidence

Red and processed meat still pose cancer risk, warn global health experts

World Cancer Research Fund International

So-called "guidelines" on meat consumption

Weighting evidence from **RCTs** more heavily than observational studies, but

- small exposure contrasts and short follow-up of the trials
- combined red meat and processed meat

Observational studies categorized as providing low or very low "certainty"

- despite showing strong evidence of dose-response gradient,
- selection of most-adjusted parameter estimate (overadjustment)
- RoB approach, all sources of bias considered as equally important,
- high RoB if 2 or more elements rated as having high RoB, regardless of the direction or impact of the likely bias
- Risk estimates for consumption of red meat and processed meat and overall cancer similar to those used by authoritative health organizations

However, estimates considered as of low-to-very low certainty due to their origin in observational studies

Principles of Evidence Synthesis

1. Comprehensive **subject matter expertise** covering the different aspects and perspectives of expertise involved in a specific question, as well as of Systematic Review (SR) methods.
2. SR methodology and expert reasoning should be thoroughly documented and made **transparent**, given the inevitable subjectivity of expert opinions.
3. Proper and transparent management of real and perceived **conflicts of interest,** (COI), from the protocol development to the peer review process and editorial handling. As recommended by the National Academy of Sciences, financial COI should be a risk of bias evaluated in the primary studies used in the SR.
4. The **inclusion of pertinent studies** should be **comprehensive** with all studies judged based on their scientific merit, as opposed to outright exclusion of studies only on the basis of selected attributes.

Principles of Evidence Synthesis

5. As recommended by the NAS, **ROB tools** that use a domain-based approach that are **not too prescriptive** should be used to evaluate the internal validity of a study.
6. Evidence synthesis should start by **listing the possible biases in a structured approach** and then, for each possible bias, consider **how the available evidence can inform the likely existence, strength, direction of the potential bias and its overall impact**.
7. In assessing possible biases, a **triangulation approach** is particularly valuable; this involves identifying populations and studies where one would expect a particular bias to be in different directions (e.g. populations with different confounding structures).
8. SR may include quantitative meta-analyses (MA), but MA **need to be critically assessed** similarly to the individual studies and do **not necessarily provide higher certainty of evidence**.

Our Planet, Our Future, 26-28 April 2021 (virtual)

- The **First Nobel Prize Summit** brought together Nobel Prize laureates, scientists, policy makers, business leaders, and youth leaders to explore the question: What can be achieved in this decade to put the world on a path to a more sustainable, more prosperous future for all of humanity?
- **Our Planet, Our Future. An Urgent Call for Action.**

Statement inspired by the discussions at the 2021 Nobel Prize Summit, issued by the Steering Committee and co-signed by almost 100 Nobel Prize laureates

Our future, A Decade of Action and 7 proposals for Planetary stewardship

- **EDUCATION**: Education at all ages should include a **strong emphasis on the nature of evidence, the scientific method, and scientific consensus** to ensure future populations have the grounding necessary to drive political and economic change.
- **INFORMATION TECHNOLOGY**: Special interest groups and highly partisan media can amplify misinformation and accelerate its spread through social media… Societies must urgently act to counter the industrialization of misinformation…