Various Forms of Bias Analysis for Uncontrolled Confounding in Observational Research

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Outline

- Background
- State of the Art

- Future Directions
- Conclusion

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Background

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- Key sources of bias or systematic error:
  - Confounding
  - Selection bias

- Measurement error (misclassification)

- These sources of bias are often neglected in large studies or meta-analyses where they matter most

- Recent advancements in methods and computing have made it easier to conduct bias analysis

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Data we want but do not have id U X Y

1

2

3

:
.

:
.

N

Data we have

id U (X) X* Y

1

2

3

:
.

:
.

N

Missing data

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- Bias sources can occur singly, jointly or be repeated over time

- Models for the bias must address the above single or multiple bias scenarios and their appropriate sequence

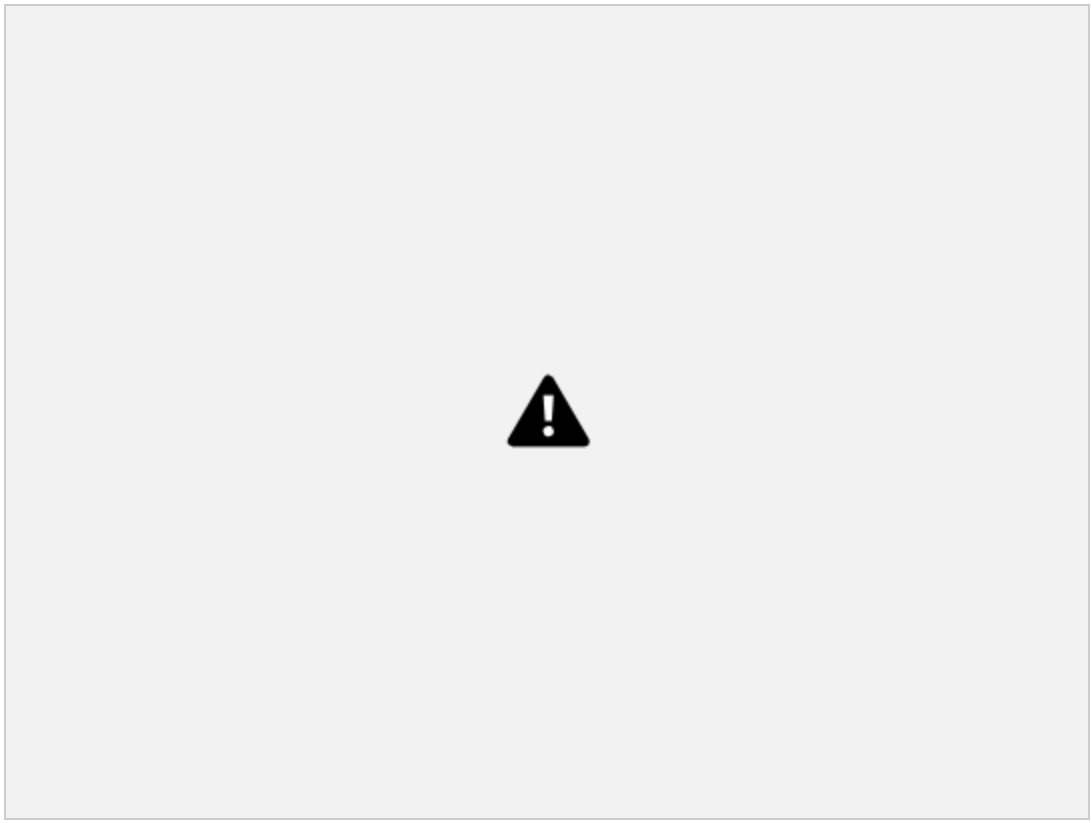
- Bias sources can be seen as inducing missing data and can be

depicted in directed acyclic graphs (DAGS)

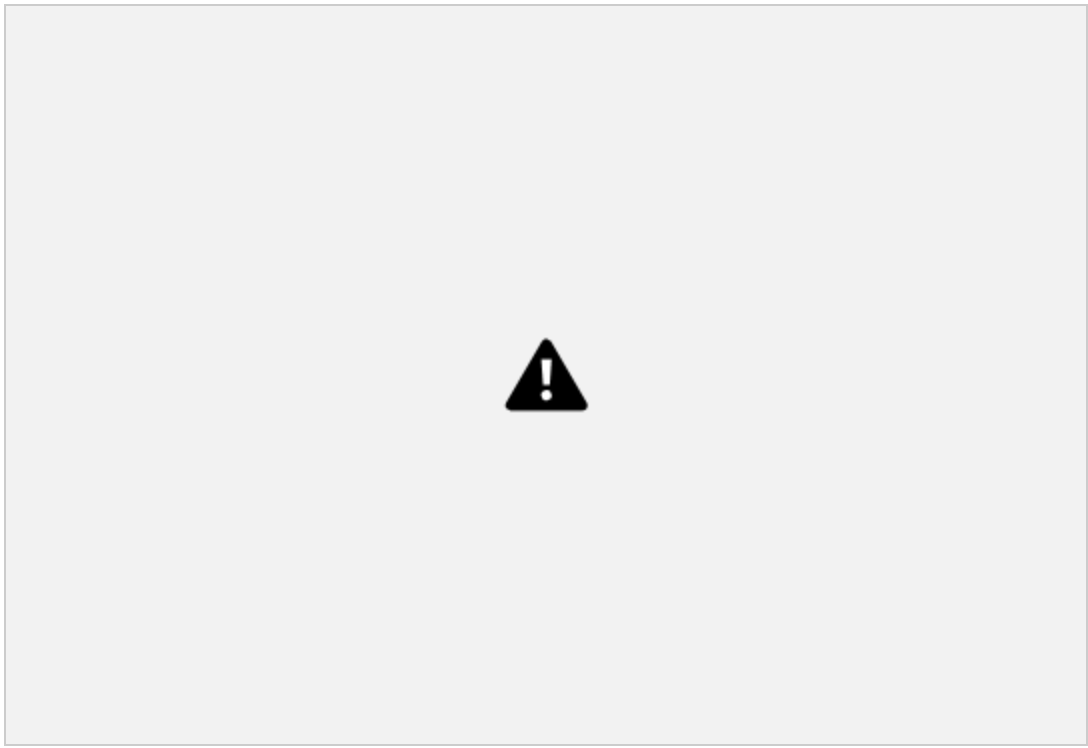
C U


X


Y



C U



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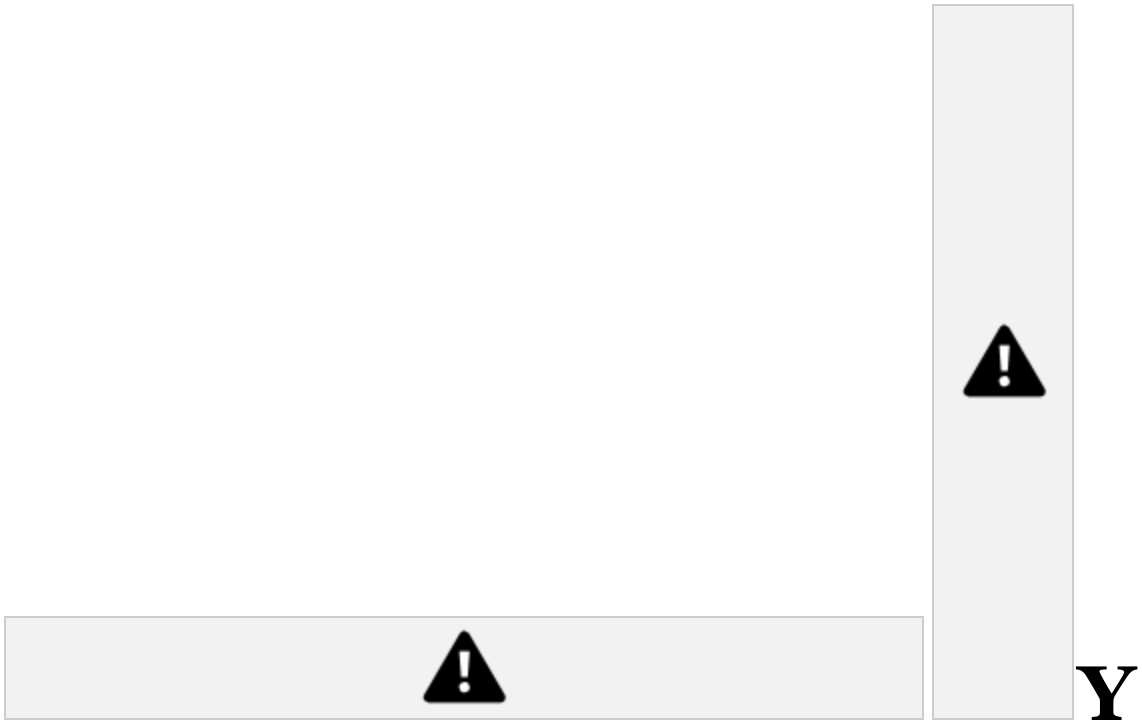

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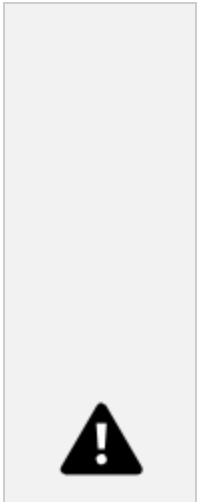

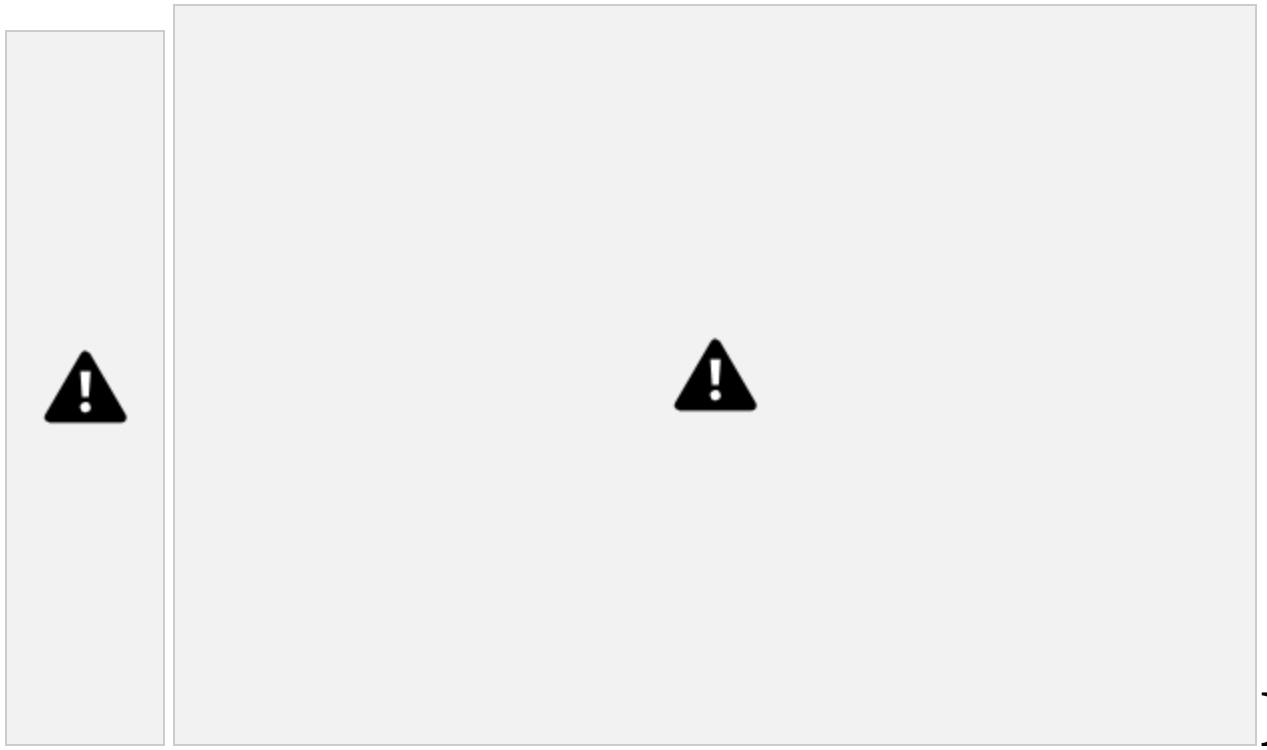

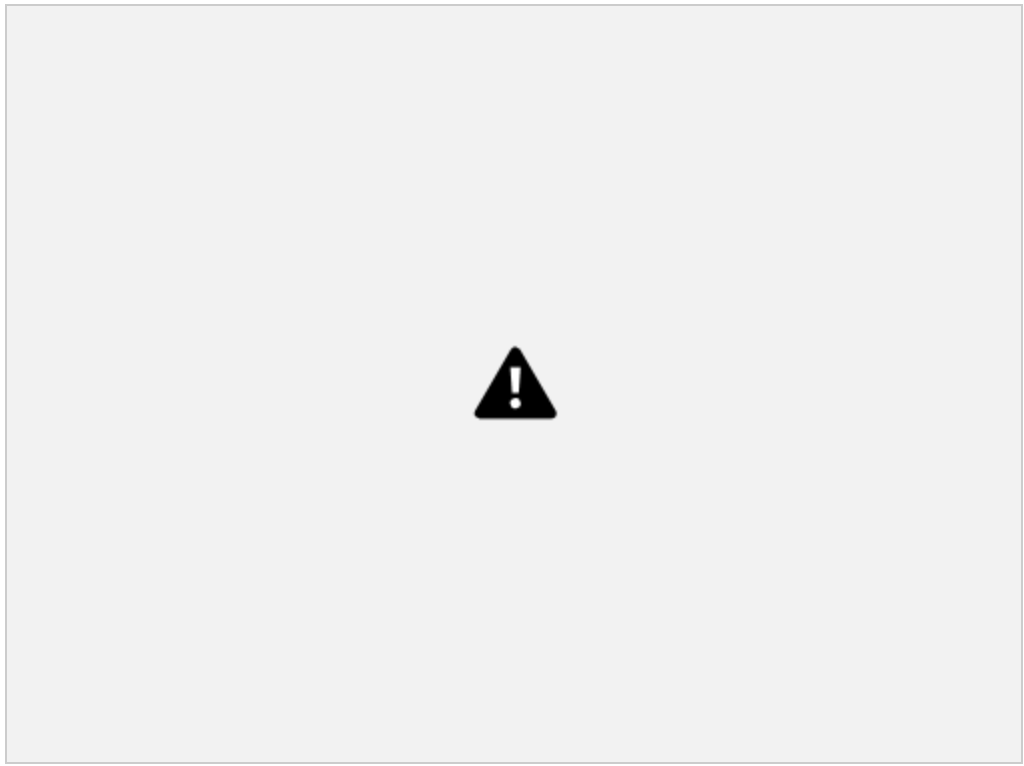

Y

• Not adjusting for *U* leads to

– **Uncontrolled confounding** of conditional and marginal effects of *X* on *Y*

– **Collider-stratification bias** in the association of *C* and *Y* (hence, the so-called **table 2 fallacy**)

– **Amplification of bias** in *X*□*Y* association if we additionally adjust for an instrumental variable (i.e. a variable associated only with *X* but not *U* or *C*, and with *Y* only through *X*)

State of the Art

- Current methods for bias analysis of uncontrolled confounding (typically based on the back door

criterion) fall into one of these broad categories:

– **Bias formula methods**

– **Missing data methods**

– **Negative control methods**

– **Bounding methods**

Bias Formulas

International Journal of Epidemiology 2009;38 :1175–1191
doi:10.1093/ije/dyp289

REPRINTS AND REFLECTIONS

Smoking and lung cancer: recent evidence and a discussion of some questions!

Jerome Cornfield,[1] William Haenszel,[2] E. Cuyler Hammond,[3] Abraham M. Lilienfeld,[4] Michael B. Shimkin[5] and Ernst L. Wynder[6]

Summary This report reviews some of the more recent epidemiologic and experimental findings on the relationship of tobacco smoking to lung cancer, and discusses some criticisms directed against the conclusion that tobacco smoking, especially cigarettes, has a causal role in the increase in broncho-genic carcinoma. The magnitude of the excess lung-cancer risk among cigarette smokers is so great that the results can not be interpreted as arising from an indirect asso ciation of cigarette smoking with some other agent or characteristic, since this hypothetical agent would have to be at least as strongly

associated with lung cancer as cigarette use; no such agent has been found or suggested. The consistency of all the epidemiologic and experimental evidence also supports the conclusion of a causal relationship with cigarette smoking, while there are serious incon sistencies in reconciling the evidence with other hypotheses which have been advanced. Unquestionably there are areas where more research is necessary, and, of course, no single cause accounts for all lung cancer. The information already available, however, is sufficient for planning and activating publ

– J. Nat. Cancer Inst. 22:173–203, 1959.

In 1957 a Study Group[1], appointed by the NationalConcurrently, a report from the Medical Research 2 u. , u u or conditional estimate.

Bias Formulas for External Adjustment and Sensitivity Analysis

RESULTS: All the bias expressions can be given parallel formulations as the difference or ratio of (i) the sum across confounder strata of each exposure-stratified confounder-outcome effect measure multiplied by of Unmeasured Confounders

the confounder prevalences among the exposed and (ii) the sum across confounder strata of the same effect measure multiplied by the confounder prevalences among the unexposed. The basic formulas can be applied to scenarios with a polytomous confounder, exposure, or outcome.

CONCLUSIONS: In addition to aiding design and analysis strategies for confounder control, the bias for ONYEBUCHI A. ARAH, MD, PHD,

YASUTAKA CHIBA, PHD,

mulas provide a link between classical standardization decompositions of demography and classical bias for AND SANDER GREENLAND, DRPH
mulas of epidemiology. They are also useful in constructing general programs for sensitivity analysis and more elaborate probabilistic risk analyses.
Ann Epidemiol 2008;18:637–646.

KEY WORDS: Bias, Bias Adjustment, Confounding, Epidemiologic Methods, Odds Ratio, Risk Difference,
Submitted 4 March 2010; accepted 10 August 2010.
From the Departments of [a]Epidemiology and [b]Biostatistics, Harvard Scof Public Health, Boston, MA; [c]Department of Epidemiology, SchoPublic Health, University of California, Los Angeles (UCLA),Angeles, CA; and [d]Department of Public Health, Academic MeCenter, University of Amsterdam, Amsterdam, The Netherlands.
Supported by National Institutes of Health grant R03 HD060696 – 0(to T.J.V.). Supported by a career grant (VENI number 916.96.

ORIGINAL ARTICLE

from the Netherlands Organization for Scientific Research (NWOO.A.A.).

Supplemental digital content is available through direct URL citatin the HTML and PDF versions of this article (www.epidem.coCorrespondence: Tyler J. VanderWeele, Departments of Epidemiology

Bias Formulas for Sensitivity Analysis of Unmeasured

PURPOSE: Uncontrolled confounders are an important source of bias in epidemiologic studies. risk ratio, and

The au Risk Ratio, Sensitivity Analysis, Unmeasured Confounders.

thors review and derive a set of parallel simple formulas for bias factors in the risk difference,

Biostatistics, Harvard School of Public Health, 677 Huntington Ave

Confounding for General Outcomes, Treatments,

and Confounders

studies with an unmeasured polytomous confounder and a dichotomous exposure and outcome.

METHODS: The authors show how the bias formulas are

UCTION

odds ratio related to and are sometimes simpler than earlier (RR) in

from cohort studies and the odds ratio (OR) in case-con

formulas. The article contains three examples, including a Monte Carlo sensitivity analysis of a preadjusted

Boston, MA 02115. E-mail: tvanderw@hsph.harvard.edu.

e central problems in causal inference from obser

trol studies can be given a common conceptual framework. We show how the basic formulas can be straightforwardly

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DOI: 10.1097/EDE.0b013e3181f74493

Tyler J. VanderWeele[a,b] *and Onyebuchi A. Arah*[c,d]

or conditional estimate.

RESULTS: All the bias expressions can be given parallel formulations as the difference or ratio of (i) the

ata is uncontrolled confounding (1). This problem ~~expo~~

applied to scenarios with a polytomou~~s confounder,~~

sum across confounder strata of each exposure-stratified confounder-outcome effe~~ct~~ hensive review, a number of the existing techniques are

~~measure multiplied by~~

s from insufficient knowledge of important con

Abstract: Uncontrolled confounding in observational studies

restricted to simple or very particular settings. There is

the confounder prevalences among the exposed and (ii) the sum across confounder

are re

strata of the same effect sure, or outcome. We also describe how the formulas

gives rise to biased effect estimates. Sensitivity analysis tech

measure multiplied by the confounder prevalences among the unexposed. The basic

formulas can be applied

also a literature on bounds for causal effects or "partial

or lack of data on known potential confounders. lated to previously published work and illustrate their use identification"[23–27] that makes fewer assumptions than

niques can be useful in assessing the magnitude of these biases. in

to scenarios with a polytomous confounder, exposure, or In this paper, we use the potential outcomes framework to derive
outcome.

earchers discuss potential bias from failing to ad for sensitivity-analysis techniques, but that thereby effectively

Monte Carlo sensitivity analysis. We will discuss cohort a general class of sensitivity-analysis formulas for outcomes,

CONCLUSIONS: In addition to aiding design and analysis strategies for confounder control, the bias for

confounder, they usually do so only qualitatively. mulas in terms of risk differences and risk ratios, although considers extreme scenarios which in some settings give

treatments, and measured and unmeasured confounding variables

mulas provide a link between classical standardization decompositions of demography and classical bias for

onvincing approach uses external data in adjust that may be categorical or continuous. We give results for ratios

the same formulas apply to rate differences and rate

bounds that include the null irrespective of the data.

mulas of epidemiology. They are also useful in constructing general programs for sensitivity more elaborate probabilistic risk analyses.

analysis and by interpreting the denominators as person time, provided

additive, risk-ratio and odds-ratio scales. We show that these

results encompass a number of more specific sensitivity-analysis

ias formulas (1, Chapter [Ch.] 19). These formulas In this paper, we extend the bias-modeling and sen sitivity-analysis literature on uncontrolled confounding.

to Cornfield et al. (2) and Bross (3, 4), have been reserved.

Ann Epidemiol 2008;18:637–646. ! 2008 Elsevier Inc. All rights methods in the statistics and epidemiology literature. The

the impact of exposure on the person-time is negligible (1 Using the potential outcomes framework, we derive a

applicability, usefulness, and limits of the bias-adjustment for

extensively since (5–15) and are often [Ch. 3], 4, 19). doi: 10.1111/ppe.12049

used as mulas are discussed. We illustrate the sensitivity-analysis tech general class of formulas for sensitivity analysis of uncon

KEY WORDS: Bias, Bias Adjustment, Confounding, Epidemiologic Methods, Odds Ratio, Risk Difference,

dern bias-analysis techniques (1, Ch. 19; e show that the equations for biases from uncon formulas are particularly simple and

16–18). Commentary trolled confounding with outcomes, treatments, and mea sured and unmeasured

Risk Ratio, Sensitivity Analysis, Unmeasured Confounders. niques that follow from our results by applying them to 3 different studies. The bias confounders that may be categorical

Marginal Structural Models, Doubly Robust Estimation, and

nfounding in the risk difference (RD) and easy to use in settings in which the unmeasured confounding ~~variable~~ many previous results in the literature and give rise

risk ratio ~~is binary with constant~~ effect on the outcome across

METHODS AND RESULTS

(2 or more categories) or continuous. The formulas gen eralize

treatment levels.

Bias Analysis in Perinatal and Paediatric Epidemiology

INTRODUCTION

Research

Notation

Department of Social Medicine, Academic Medical Center,

Let A_{xz} represent cases, B_{xz} controls or noncases where D

f Amsterdam, The Netherlands (O.A.A.); Department of Ep

represents disease or outcome, X the exposure, and Z the un

vational data is uncontrolled confounding (1). This problem

follows from our results and is summarized in the discus

University of California, Los Angeles School of Public Health,

applied to scenarios with a polytomous confounder, expo

(O.A.A., Y.C., S.G.); Department of Biostatistics, Kyoto Uni

measured confounder. Also, we use N_{xz} to represent the sum

often stems from insufficient knowledge of important con

ol of Public Health, Japan (Y.C.); and Department of Statistics,

sure, or outcome. We also describe how the formulas are re

of A_{xz} and B_{xz}, that is, the total number exposed to X Z x

founders or lack of data on known potential confounders.

f California, Los Angeles College of Letters and Science (S.G.).

and bias-modeling techniques have now been developed to

orrespondence to: Onyebuchi A. Arah, MD, PhD, Department

within the stratum Z Z z. The prevalence of each stratum

When researchers discuss potential bias from failing to ad

edicine, Academic Medical Center, University of Amsterdam,

just for a confounder, they usually do so only qualitatively.

(RR) in cohort studies and the odds ratio (OR) in case-con

(*Epidemiology* 2011;22: 000 – 000)

Onyebuchi A. Arah,[a,b] Madhuri Sudan,[a] Jørn Olsen[a,c] and Leeka Kheifets[a]

One of the central problems in causal inference from obser

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RESEARCH

Unmeasured confounders in observational studies result

[b]*Department of Public Health, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

sion section.

[c]*Institute of Public Health, University of Aarhus, Aarhus, Denmark*

in biased effect estimates. Several sensitivity-analysis

of A_{xz} and B_{xz}, that is, the total number exposed to X Z x

lated to previously published work and illustrate their use

in We thank Ahrens and Schisterman (henceforth, A&S)

handle uncontrolled confounding.[1–22] Although the litera

Monte Carlo sensitivity analysis. We will discuss cohort for

for their commentary[1] on our article.[2] Although it was

ture is large and it would be difficult to provide a compre

of Z given exposure X is notated as P_{zx}. For any measure re

mulas in terms of risk differences and risk ratios,

very flexible sensitivity-analysis techniques that can be

used in a wide range of applications. We also describe a particularly easy-to-use sensitivity-analysis technique that

trol studies can be given a common conceptual framework.

We show how the basic formulas can be straightforwardly

can be used under some simplifying assumptions and that

door or when the exposure under study is cause

NOTATION, DEFINITIONS, AND ASSUMPTIONS

collider that also lies on an open back-door path

although

Severe hypoglycaemia and cardiovascular disease~~:~~

systematic review and meta-analysis with bias analysis

Atsushi Goto *senior researcher* [1 2], Onyebuchi A Arah *professor* [3 4], M~~aki Goto *researcher* [1 2],~~ ~~Yasuo~~

September 14, 2007; accepted April 2, 2008.

From the Departments of [a]Epidemiology and [b]Biostatistics, Harvard School of Public Health, Boston, MA; [c]Department of Epidemiology, School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, CA; and [d]Department of Public Health, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

Supported by National Institutes of Health grant R03 HD060696 – 01A1 (to T.J.V.). Supported by a career grant (VENI number 916.96.059) from the Netherlands Organization for Scientific Research (NWO) (to T.J.V.).

Correspondence: Tyler J. VanderWeele, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115. E-mail: tvanderw@hsph.harvard.edu.

Received 4 March 2010; accepted 10 August 2010.

~~A more convincing approach uses external data in~~ ~~adjust~~ ~~ratios~~

~~lating exposure to outcome, the general not~~ation is R_{dxz} ~~arah@ucla.edu.~~

~~We agree with A&S on the need for multipl~~

~~not our original intention, we are grateful for the~~

~~00, 1100 DE Amsterdam, The Netherlands. Tel.: þ31 20 526~~

~~31 20 697 2316. E-mail: o.a.arah@amc.uva.nl,~~

We will use the potential outcomes or counterfactual framework.[28–30] Let treatment A denote the treatment

the same formulas apply to rate differences and rate

modelling.[5] We expect to see more of it in the

invited discussion on the place of causal inference in

where the first subscript represents t~~he 'outcome' (in this~~ ment or bias formulas (1, Chapter [Ch.] 19). These formulas by interpreting the denominators as person time, provided

received by a particular individual. Let Y be the observed perinatal and paediatric epidemiology. In response, post-treatment outcome of that individual. Let Y_a denote

date back to Cornfield et al. (2) and Bross (3, 4), have been we briefly offer some clarifications and extensions. accepted by journals, large data become more

the impact of exposure on the person-time is negligible (1 [Ch. 3], 4, 19). A&S claim that we did not adjust for reduced able, and investigators routinely use bias form

developed extensively since (5–15) and are often used as part of modern bias-analysis techniques (1, Ch. 19; 16–18).

OPEN ACCESS

hearing at age 18 months (Y_1) in our analysis of the impact of postnatal cellphone exposure (X_2) on that bias analysis must be preceded by 'placem

and simulation techniques. We disagree with hearing loss at age 7 years (Y_2). In fact, we adjusted for the unmeasured confounder in the DAG'[1] an

Herein we show that the equations for biases from uncon other individuals. This assumption is sometimes referred individual does not depend on the treatments received by

ture as probabilistic bias analysis is increa

evier Inc. All rights reserved. 1047-2797/08/$–see front matter

the potential outcome Y for an individual if the treatment A, perhaps contrary to fact, had been set to value a. Note that we assume that the potential outcome Y_a for an

trolled confounding in the risk difference (RD) and risk ratio

~~O.A.A.).~~

to as SUTVA, the stable unit treatment value assumption[30]

METHODS AND RESULTS

Y_1 and other variables listed in the footnotes of Tables

such placement can reveal when 'the potential

Terauchi *professor* [2], Mitsuhiko Noda *director* [1]

Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

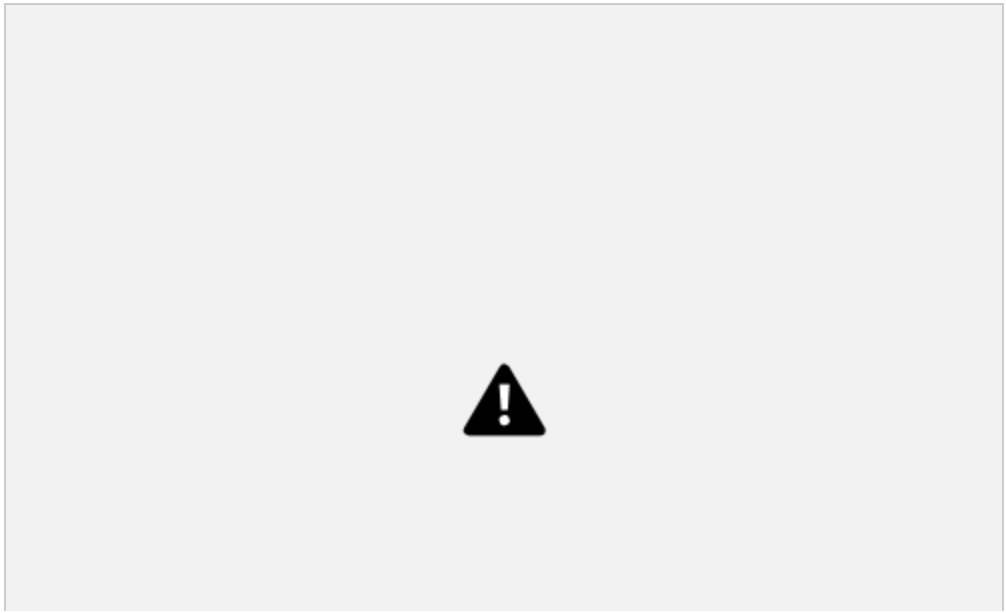
or as a no-interference assumption.[31] Furthermore, we

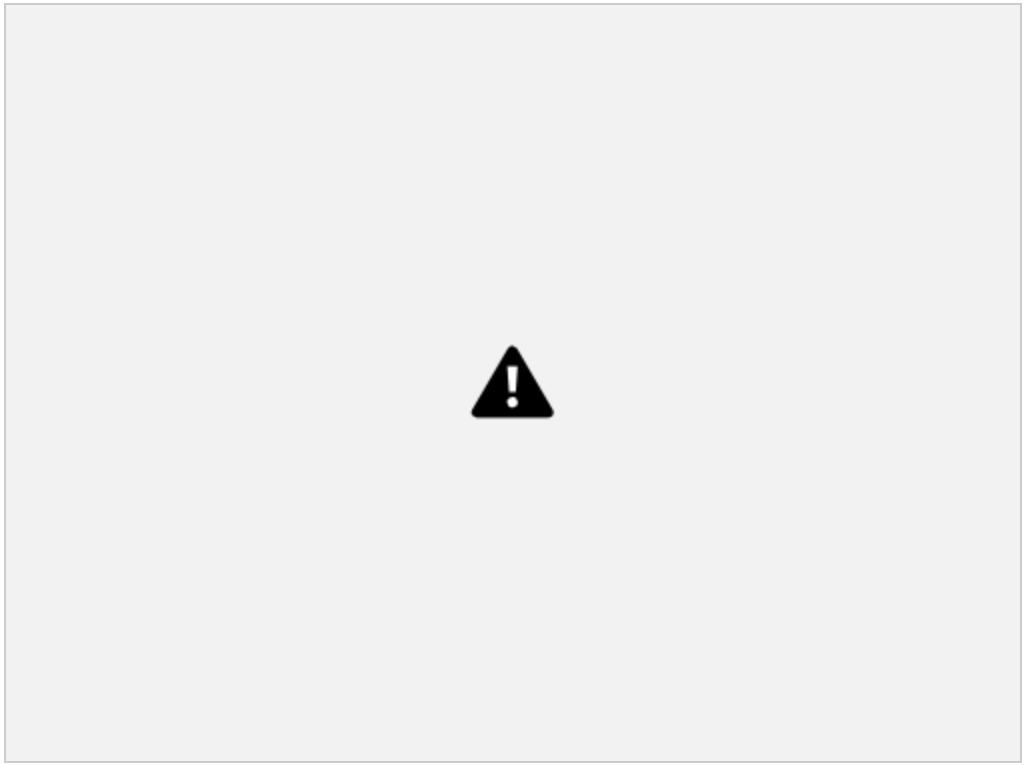
3 and 4 in our article.[2] In applying directed acyclic

no longer a concern'.[1] A known but unmeasure

Bias formula methods trace and quantify the open back door path due to unmeasured U: $X \perp U \perp Y$ conditional on C

[C] **U**





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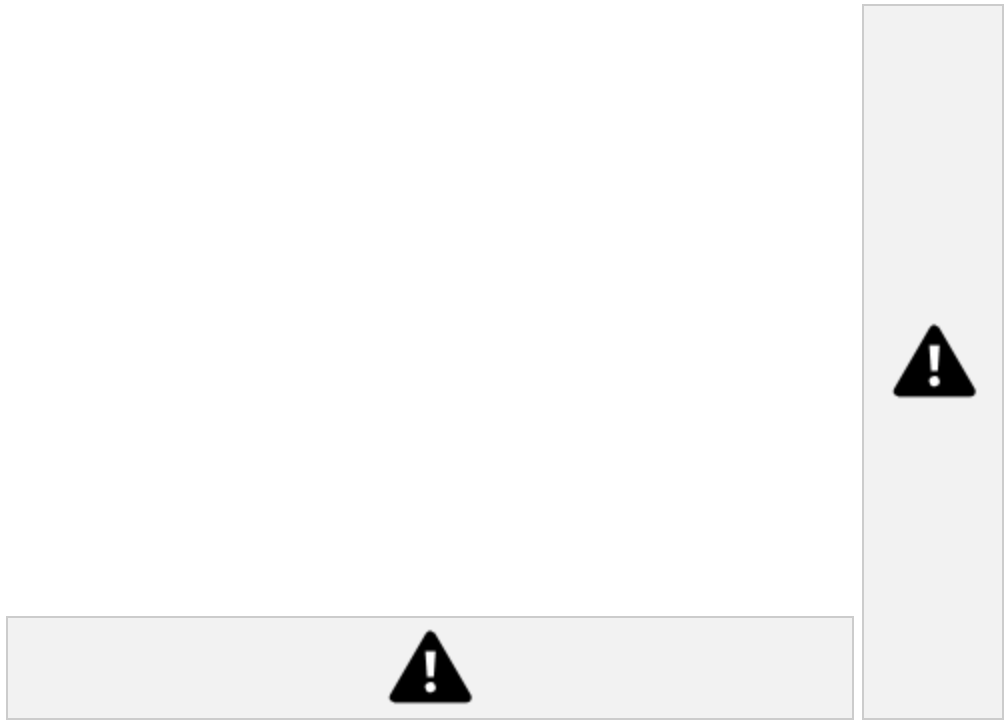

• At the core of bias analysis are the following expressions with the unknown part in gray, parts from observed data

highlighted in yellow, and what we want is in **bold blue**:

***P*(*Y*, *U*, *X*, *C*)**

= $P(Y \mid X, C, U)P(U \mid X, C)P(X, C)$ □ Bias formula methods =

$P(U \mid Y, X, C)P(Y \mid X, C)P(X, C)$ □ Missing data methods

- External adjustment of crude or pre-adjusted association measures can be done using bias formulas for the bias model:

$RD_{+} - RD_{adj} = Bias_{RD}$

$RR_{+} / RR_{adj} = Bias_{RR}$

$OR_{+} / OR_{adj} = Bias_{OR}$

where RD_+, RR_+ and OR_+ are respectively the crude or biased risk difference, risk ratio and odds ratio respectively; RD_{adj}, RR_{adj} and OR_{adj} are their unknown "true" or confounding adjusted versions;

$Bias_{RD}$, $Bias_{RR}$, and $Bias_{OR}$ are the respective *bias formulas* containing the **bias parameters** as shown on the following slides

• For conditional risk differences (i.e. conditioned on measured confounder *C*), we have the following respective bias formulas:

• For marginal risk differences, we have the following respective bias formulas:

- Bias formulas can also be applied to record-level data by using a **bias offset** method
- Bias offset method computes an offset variable from the appropriate form of the bias formula and for the appropriate link function

– Identity bias offset for risk difference and mean difference models:

- Compute *BiasOffset* = $RD_{X \square U} \times RD_{U \square Y} \times X$
- Regress Y on X and C with *BiasOffset* set as an offset variable – Log

bias offset for risk ratio and odds ratio models 

Missing Data Methods

- Uncontrolled confounding is a special case of missing data: missing data on *U* for all study subjects

- While **bias formula methods** aim to compute the amount of bias

using exposure-U and U-outcome relations, **missing data methods** aim to impute or simulate the missing (unmeasured) confounding variable *U*

• Missing data methods are usually internal adjustment methods that simulate the missing data on *U* using validation study data or externally obtained information combined with the observed data on exposure, outcome and measured confounders or using propensity or disease risk scores

For example: $P(Y, U, X, C) = P(U \mid Y, X, C)P(Y, X, C)$ 

International Journal of Epidemiology 2009;38:1662–1673
doi:10.1093/ije/dyp278

Bayesian perspectives for epidemiologic research: III. Bias analysis via missing-data methods

Sander Greenland

Accepted 30 June 2009

American Journal of Epidemiology Advance Access published March 28, 2007

American Journal of Epidemiology

DOI: 10.1093/aje/kwm074

I present some extensions of Bayesian methods to situations in which biases are of concern. First, a basic misclassification problem is illustrated using data from a study of sudden infant death syndrome. Bayesian analyses are then given. These analyses can be conducted directly, or by converting actual-data records to incomplete records and prior distributions to complete-data records, then applying missing-data techniques to the augmented data set. The analyses can easily incorporate any complete ('validation' or second-stage) data that might be available, as well as adjustments for confounding and selection bias. The approach illustrates how conventional analyses depend on implicit certainty that bias parameters are null and how these implausible assumptions can be replaced by plausible priors for bias parameters.

Practice of Epidemiology

Performance of Propensity Score Calibration—A Simulation Study

Til Stu¨rmer[1,2], Sebastian Schneeweiss[1,3], Kenneth J. Rothman[1,4,5], Jerry Avorn[1], and Robert J. Glynn[1,2,6]

American Journal of Epidemiology Advance Access published June 24, 2014

Keywords Bayesian methods, bias, biostatistics, epidemiology, missing data,
American Journal of Epidemiology
Women's Hospital, Harvard Medical School,
[1] Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and

DOI: 10.1093/aje/kwu130

observational studies, odds ratio, relative risk, risk analysis, risk
Boston, MA.

assessment, sensitivity analysis, validation
[2] Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
[3] Department of Epidemiology, Harvard School of Public Health, Boston, MA.

Practice of Epidemiology

Introduction

There is a growing literature on accounting for uncer

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Boston, MA. [5] Research Triangle Institute, Research Triangle Park, NC.

Adjustment for Missing Confounders in Studies Based on Observational

tainties in epidemiologic studies by using prior distri butions (priors) for parameters that govern bias.[1–26]

Received for publication November 1, 2005; accepted for publication July 13, 2006.

below are available at http://www.ph.ucla.edu/epi/

Databases: 2-Stage Calibration Combining Propensity Scores From Primary

Bayesian methods are a natural approach to use of

and Validation Data

priors, but epidemiologists have gravitated to more informal simulation methods. I here provide one approach to Bayesian uncertainty assessment, focuss ing on data priors in order to recast bias analysis as a missing-data problem. This approach shows how bias analysis is complementary to validation-study and two-phase (two-stage) analyses, and how all

faculty/greenland/index.htm.

recently introduced propensity score calibration (PSC), which combines propensity scores and regression calibration to address

exposure misclassification

confounding by variables unobserved in the main study by using variables observed in a validation study. Here,

Conventional analyses

the authors assess the performance of PSC using simulations in settings with and without violation of the key

Table 1 presents a study of the relation of sudden

assumption of PSC: that the error-prone propensity score estimated in the main study is a surrogate for the gold

A case–control study with

Confounding can be a major source of bias in nonexperimental research. The authors

Hui-Wen Lin* and Yi-Hau Chen*

infant death syndrome (SIDS) to maternal antibiotic

standard propensity score (i.e., it contains no additional information on the outcome). The assumption can be

Creating U from X, Y (and C):

$$g[\mathrm{P}(U|Y, X, C)]$$

$$= \theta_o + \theta_Y Y + \theta_X X + \theta_{YX} YX + \theta_C C$$

for some link function g

id U C X Y

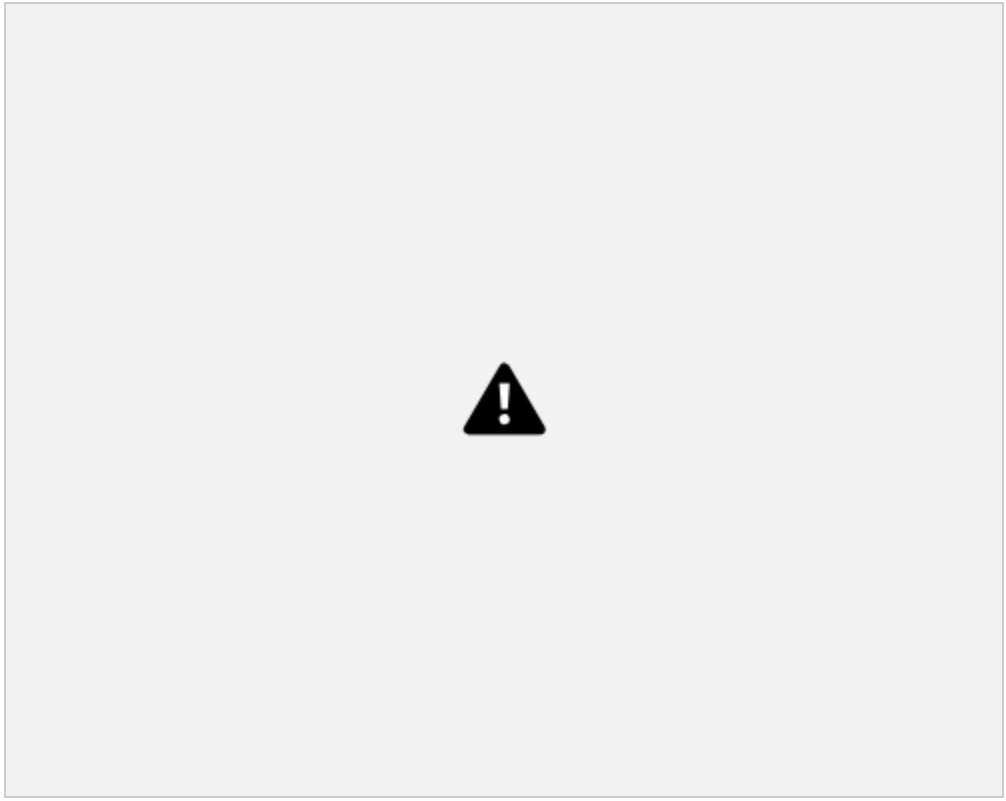
1

N

Model for *U*

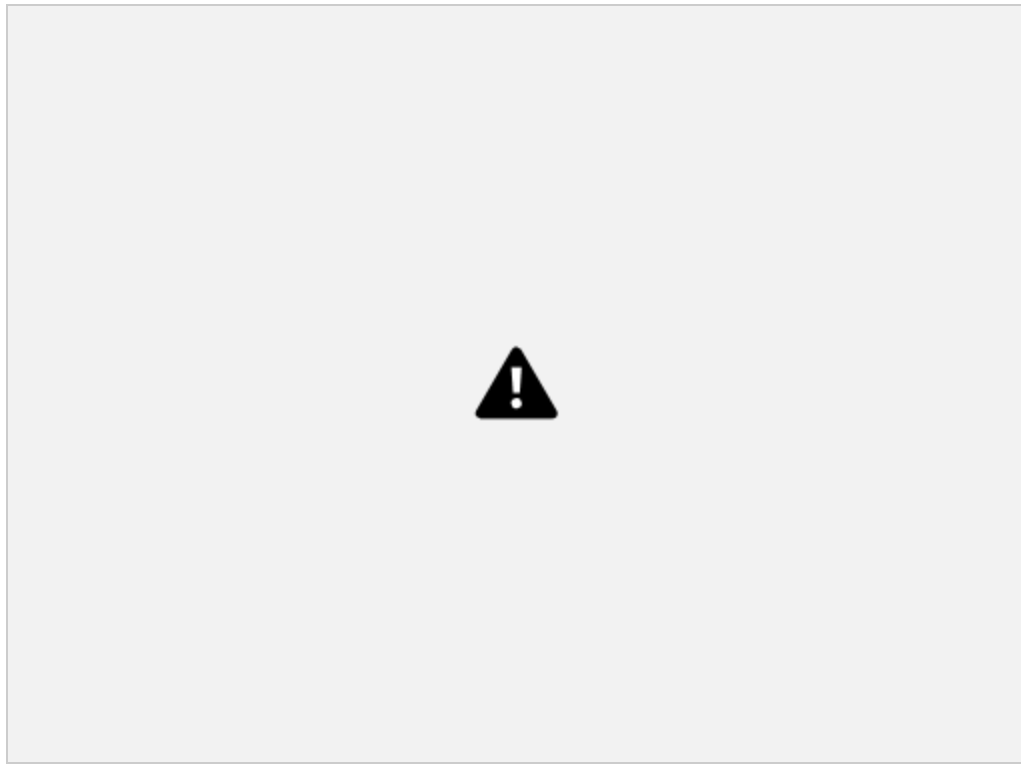
Missing data methods recreate *U* or some quantity representing adjustment for U using validation study data or external information

[C]



U

[X]



[Y]

Many techniques have been developed for study design and analysis to identify and eliminate such errors. Such problems are not ex pected to compromise experimental studies, where careful standard ization of conditions (for laboratory work) and randomization (for

Negative Controls

population studies) should, if applied properly, eliminate most such noncausal associations. We argue, however, that a routine precau tion taken in the design of biologic laboratory experiments—the use

of "negative controls"—is designed to detect both suspected and unsuspected sources of spurious causal inference. In epidemiology, analogous negative controls help to identify and resolve confound ing as well as other sources of error, including recall bias or analytic flaws. We distinguish 2 types of negative controls (exposure controls

Negative Controls

A Tool for Detecting Confounding and Bias in Observational Studies

Marc Lipsitch,[a,b,c] *Eric Tchetgen Tchetgen,*[a,c,d] *and Ted Cohen*[a,c,e]

(*Epidemiology* 2010;21: 383–388)

EXPERIMENTAL BIOLOGY: THRECAUSAL INFERENCE AND THE UNEGATIVE CONTROLS

Abstract: Noncausal associations between exposures and outcomes are a threat to validity of causal inference in observational studies.

In experimental biology, the manipulation of experi

One might imagine that the experimental

Many techniques have been developed for study design and analysis

tions that arise in observational studies. Nonetheless, exper

Epidemiologists seek to distinguish the causal effect of

that occur in observational studies. For example

to identify and eliminate such errors. Such problems are not ex pected to compromise experimental studies, where careful standard

imental biologists routinely question whether they have

exposure A on outcome Y from associations due to other

hypothesis that a particular cytokine—a chemic

correctly inferred causal relationships from the results of their

signaling in the immune system— enhances th

mental conditions prevents many of the noncausal associa

circumvent most threats to the validity of ca

and outcome controls), describe examples of each type from the epidemiologic literature, and identify the conditions for the use of

tions that arise in observational studies. Nonetimental biologists routinely question whethcorrectly inferred causal relationships from the rexperiments.

Biologists employ “negative cmeans of ruling out possible noncausal interpretresults. We describe the use of negative contrments, highlight some examples

of their use in studies, and define the conditions under wcontrols can detect confounding in epidemioAlthough the particular threats to causal infereent in

experimental and observational sciencenegative controls is a valuable means of idecausal associations and can complement other methods for improving

causal inference.

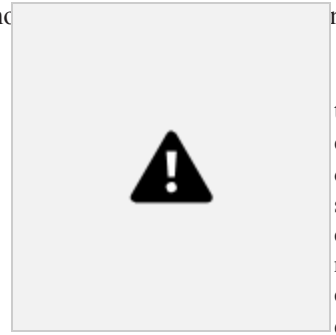
such negative controls to detect confounding. We conclude that

negative controls should be more commonly employed in observa

tional studies, and that additional work is needed to specify the

conditions under which negative controls will be sensitive detectors

of other sources of error in observational studies.

ization of conditions (for laboratory work) and randomization (for
between A and N does not prove unequivocally that the A-Y
population studies) should, if applied properly, eliminate most such
association is biased. In the example of using death or
noncausal associations. We argue, however, that a routine precau
ho

tion taken in the design of biologic laboratory
experiments—the use
of "negative controls"—is designed to detect both
suspected and unsuspected sources of spurious
causal inference. In epidemiology, analogous
negative controls help to identify and resolve
confound
death or pneumonia/influenza hospitalization,
one could ar
ments, highlight some examples of their use in epidemiologic
the cytokine is added, and in condition 2, so
ing as well as other sources of error, including recall bias or analytic
compared between conditions 1 and 2.
not think of a plausible one) would create an association in
ent in experimental and observational sciences, the use of
mechanisms. Noncausal associations may be classified into 3
categories (in addition to chance)[1]: mismeasurement (eg,
recall bias), confounding, and biased selection of individuals
into the analysis.
negative control outcome for

Submitted 19 March 2009; accepted 12 October 2009.

From the [a]Department of Epidemiology, [b]Department of Immunology and Infectious Diseases, [c]Center for Communicable Disease Dynamics, and

experiments. Biologists employ "negative controls" as a
species of bacteria by neutrophils, a class o
means of ruling out possible noncausal interpretations of their
cells.[2] An experiment is devised in which neu
results. We describe the use of negative controls in experi
teria, and growth medium are mixed together. I
gue that there may be some common causes of vaccination
studies, and define the conditions under which negative
stance such as saline solution is added. After i
and injury that are not causes of all-cause death or pneumo
~~controls can detect confounding in epide~~miologic studies.
bacteria are enumerated and the number of
can
nia/influenza hospitalization. Such common causes (we
Although the particular threats to causal inference are differ
flaws. We distinguish 2 types of negative controls (exposure controls
If the investigator finds fewer live bacteri
the negative control analysis of vaccination and injury, even

negative controls is a valuable means of identifying non

[d]Department of Biostatistics, Harvard School of Public Health, Boston,

and outcome controls), describe examples of each type from the the primary analyses of vaccination and death or pneumo

1 than in condition 2, the finding is consisif

MA; and [e]Division of Global Health Equity, Brigham and Women's

epidemiologic literature, and identify the conditions for the use of

causal associations and can complement other epidemiologic

Hospital, Boston, MA.

unconfounded—thus mak

hypothesis that the cytokine enhanced

neutronia/influenza hospitalization were

such negative controls to detect confounding. We conclude methods for improving causal inference.
that

Supported by NIH 5U01GM076497 and 1U54GM088558 (Models of Infec

killing. Nonetheless, concern remains that so

FIGURE 2. Causal diagram showing an ideal negative control

negative controls should be more commonly employed in observa
tious Disease Agent Study) to ML.

neutrophil-mediated killin

However, if N is associated only with some, but not all, of the

outcome N for use in evaluating studies of the causal relation

ing the negative control detect bias even where none exists. than cytokine-aided,

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tional studies, and that additional work is needed to specify the

ship between exposure A and outcome Y. N should ideally

in the HTML and PDF versions of this article (www.epidem.com).

EXPERIMENTAL BIOLOGY: THREATS TO

sponsible. For example, perhaps there is a cont

conditions under which negative controls will be sensitive detectors

CAUSAL INFERENCE AND THE USE OF

have the same incoming arrows as Y, except that A does not

Y, it is possible that A and N will appear unassociated despite

uncontrolled confounders of the association between A and

cytokine preparation that directly kills bacteri

of other sources of error in observational studies.

Correspondence: Marc Lipsitch, Department of Epidemiology, Harvard

cause N; to the extent this criterion is met, N is called

School of Public Health, 677 Huntington Avenue, Boston, MA 02115.

NEGATIVE CONTROLS

(*Epidemiology* 2010;21: 383–388)
E-mail: mlipsitc@hsph.harvard.edu.
U-comparable to Y.

ISSN: 1044-3983/10/2103-0383

DOI: 10.1097/EDE.0b013e3181d61eeb

Epidemiologists seek to distinguish the causal effect of

exposure A on outcome Y from associations due to other

Practice of Epidemiology

Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II

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Frequent maternal use of acetaminophen in pregnancy has been linked to attention-deficit/hyperactivity disorder (ADHD) in children, but concerns regarding uncontrolled confounding remain. In this article, we illustrate use of the negative control exposure (NCE) approach to evaluate uncontrolled confounding bias in observational studies on pregnancy drug safety and explain the causal assumptions behind the method. We conducted an NCE analysis and evaluated the associations between maternal acetaminophen use during different exposure periods and ADHD among 8,856 children born in 1993–2005 to women enrolled in the Nurses' Health Study II cohort. Information on regular maternal acetaminophen use was collected prospectively in biennial questionnaires. A total of 721 children (8.1%) in the cohort had been diagnosed with ADHD as reported by the mothers. Our NCE analysis suggested that only acetaminophen use at the time of pregnancy was associated with childhood ADHD (odds ratio = 1.34, 95% confidence interval: 1.05, 1.72), and the effect estimates for the 2 NCE periods (about 4 years before and 4 years after the pregnancy) were null. Our findings corroborate those of prior reports suggesting that prenatal acetaminophen exposure may influence neurodevelopment. The lack of an association between acetaminophen

use in the pre- and postpregnancy exposure periods and ADHD provides assurance that uncontrolled time invariant factors do not explain this association.

acetaminophen; attention-deficit/hyperactivity disorder; negative control exposure analysis; neurological development; pregnancy; prenatal exposure delayed effects; uncontrolled confounding

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; NCE, negative control exposure; NHS II, Nurses' Health Study II.

sure and the confounder on the outcome, or having only one unmeasured confounder. Without imposing any assumptions on the unmeasured confounder or confounders, we derive a bounding factor and a sharp inequality such that the sensitivity analysis parameters must satisfy the

Bounding

inequality if an unmeasured confounder is to explain away the observed effect estimate or reduce it to a particular level. Our approach is easy to

implement and involves only two sensitivity parameters. Surprisingly, our bounding factor, which makes no simplifying assumptions, is no more conservative than a number of previous sensitivity analysis techniques that do make assumptions. Our new bounding factor implies not only the traditional Cornfield conditions that both the relative risk of the

4FOTJUJWJUZ "OBMZTJT 8JUIPVU "TTVNQUJPOT

exposure on the confounder and that of the confounder on the outcome must satisfy but also a high threshold that the maximum of these relative risks must satisfy. Furthermore, this new bounding factor can be viewed as a measure of the strength of confounding between the exposure and

Peng Ding[a] *and Tyler J. VanderWeele*[b]

the outcome induced by a confounder.

(*Epidemiology* 2016;27: 368–377)

.also often assume a homogeneity assumption thatinteraction between the effects of the exposure afounder on the outcome.[5–9] Some sensitivity anniques only allow one to assess how strong an confounder would have to be to completely expleffect[1–3,10,11] but do not allow one to assess whaestimate might be under weaker unmeasured cscenarios (i.e., do not allow one to do sensitiviunder alternative hypotheses). Performing sensitivunder alternative hypotheses can be quite challenmore parameters needed in the sensitivity analysisfield et al. early study[1] on sensitivity analysis for tsmoking and lung cancer association, which helthe entire field of sensitivity analysis, in fact masimplifying assumptions: a single binary confinteraction, and only sensitivity analysis for the n

Abstract: Unmeasured confounding may undermine the validity of causal inference with observational studies. Sensitivity analysis pro

esis of no causal effect. Although some sensitiv

causal inferences even without full control of the confounders of

the relationship between the exposure and outcome.

Although

Causal inference with observational studies is of great

results exist for general confounders,[8,12] they are

inter

est and importance in many scientific disciplines.

vides an attractive way to partially circumvent this issue by assessing the potential influence of unmeasured confounding on causal conclusions. However, previous sensitivity analysis approaches often make strong

influence of the unmeasured confounding on the causal con

Sensitivity analysis plays a central role in assessing the

In this article, we propose a new bounding

clusions. However, many sensitivity analysis techniques often

implement under some of the above simplifying as

unmeasured confounding between the exposure and the outcome

sensitivity analysis technique without any a

and untestable assumptions such as having an unmeasured confounder

require additional untestable assumptions. For instance, some

Sensitivity Analysis in Observational Research: Introducing the E-Value

Submitted 10 October 2014; accepted 28 January 2016.

Tyler J. VanderWeele, PhD, and Peng Ding, PhD

From the [a]Department of Statistics, University of California, Berkeley, CA; and [b]Department of Epidemiology and Biostatistics, Harvard School of Public Health, Boston, MA.

Sensitivity analysis is useful in assessing how robust an association is to potential unmeasured or uncontrolled confounding. our bounding factor, which makes no simplifying assumptions, is no

may bias the estimation of the true causal effect, an approach

that is binary, or having no interaction between the effects of the expo

authors assume a single binary confounder.[1–6] Researchers

often called "sensitivity analysis" or "bias analysis" over a range

sure and the confounder on the outcome, or having only one unmeasured

of sensitivity parameters sometimes allows researchers to make

confounder. Without imposing any assumptions on the unmeasured

confounder or confounders, we derive a bounding factor and a sharp inequality such that the sensitivity analysis parameters must satisfy the

interaction between the effects of the exposure and the con

niques only allow one to assess how strong an unmeasured

inequality if an unmeasured confounder is to explain away the observed

effect estimate or reduce it to a particular level. Our approach is easy to

implement and involves only two sensitivity parameters.

Surprisingly,

This work was partly supported by National Institutes of Health Grant R01 ES017876.

about the unmeasured confounder or confounde

the assumptions of the null hypothesis, a single

also often assume a homogeneity assumption that there is no

founder, or no interaction is required for using th

factor. Nonetheless, our new bounding factor, w

~~founder on the outcome.[5–9] Some sensit~~ivity analysis tech

no simplifying assumptions, is no more conser

many previous sensitivity analysis techniques th

confounder would have to be to completely explain away an

assumptions and is furthermore easy to implement

effect[1–3,10,11] but do not allow one to assess what the effect

The authors propose that in all observational studies intended to

we show that the new bounding factor implies n

This article introduces a new measure called the "E-value," which more conservative than a number of previous sensitivity analysis tech

produce evidence for causality, the E-value be reported or some

estimate might be under weaker unmeasured confounding scenarios (i.e., do not allow one to do sensitivity analysis other sensitivity analysis be used. They suggest calculating the

classical Cornfield conditions[1] that both the rela

The authors report no conflicts of interest.

is related to the evidence for causality in observational studies E-value for both the observed association estimate (after adjust

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the exposure on the confounder and that of the

niques that do make assumptions. Our new bounding under alternative hypotheses). Performing sensitivity analysis factor implies not that are potentially subject to ments for measured confounders) and the limit of the confi confounding. The E-value is de

in the HTML and PDF versions of this article (www.epidem.com).

on the outcome must satisfy but also a stronger co

only the traditional Cornfield conditions that both the relative risk of dence interval closest to the null. If this were to become the fined as the minimum strength of association, on the risk standard ratio

under alternative hypotheses can be quite challenging due to

Correspondence: Peng Ding, Department of Statistics, University of California,
exposure on the confounder and that of the confounder on the outcome the maximum of these relative risks must satisf

more parameters needed in the sensitivity analysis. The Corn

425 Evans Hall, Berkeley, CA 94720. E-mail: pengdingpku@berkeley.edu.

scale, that an unmeasured confounder would need to have with must satisfy but also a field et al. early study[1] on sensitivity analysis for the cigarette high threshold that the maximum of these relative both the treatment and the outcome dence from observational studies would improve considerably,

to fully explain away a spe risks must satisfy. Furthermore, this new bounding factor can be viewed

practice, the ability of the scientific community to assess evi

bounding factor can be viewed as a measure of the confounding between the exposure and the outco

cific treatment–outcome association, conditional on the mea and ultimately, science would be strengthened.

smoking and lung cancer association, which helped initiate

as a measure of the strength of confounding between the exposure and

sured covariates. A large E-value implies that considerable un

the entire field of sensitivity analysis, in fact made all three

the outcome induced by a confounder.

from the confounder. We begin by considering ou

measured confounding would be needed to explain away an

simplifying assumptions: a single binary confounder, no

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effect estimate. A small E-value implies little unmeasured con

For author affiliations, see end of text.

are binary and extend our results further to time-t

(*Epidemiology* 2016;27: 368–377)

interaction, and only sensitivity analysis for the null hypoth

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non-negative count or continuous outcomes. We co

founding would be needed to explain away an effect estimate.

esis of no causal effect. Although some sensitivity analysis

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ratio and difference scales.

~~results exist for general confounders,[8,12] they are only easy to~~ implement under some of the above simplifying assumptions.

Causal inference with observational studies is of great inter

est and importance in many scientific disciplines. Although

Much empirical research is concerned with estab

lishing causation. It is well-known, however, that

unmeasured confounding between the exposure and the outcome may bias the estimation of the true causal effect, an approach with observational data,

association (1–11) need not im “”“”

In this article, we propose a new bounding factor and

feeding may be confounded by smoking behavior or

sensitivity analysis technique without any assumptions

by socioeconomic status. In a population-based case– about

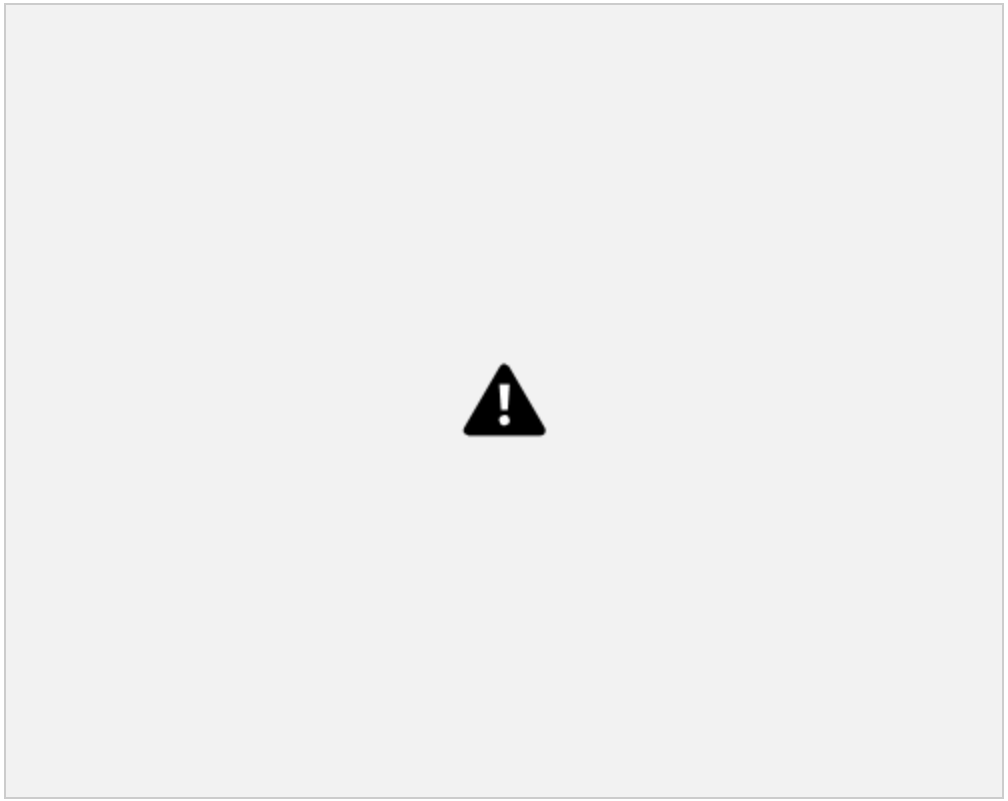
the unmeasured confounder or confounders. None of

control study, Victora and colleagues (23) examined as

Bounding methods aim to provide the limit(s) that the bias due to not

controlling for U never exceeds, by using a combination of the parameters captured by the red dashed arrows

[C]



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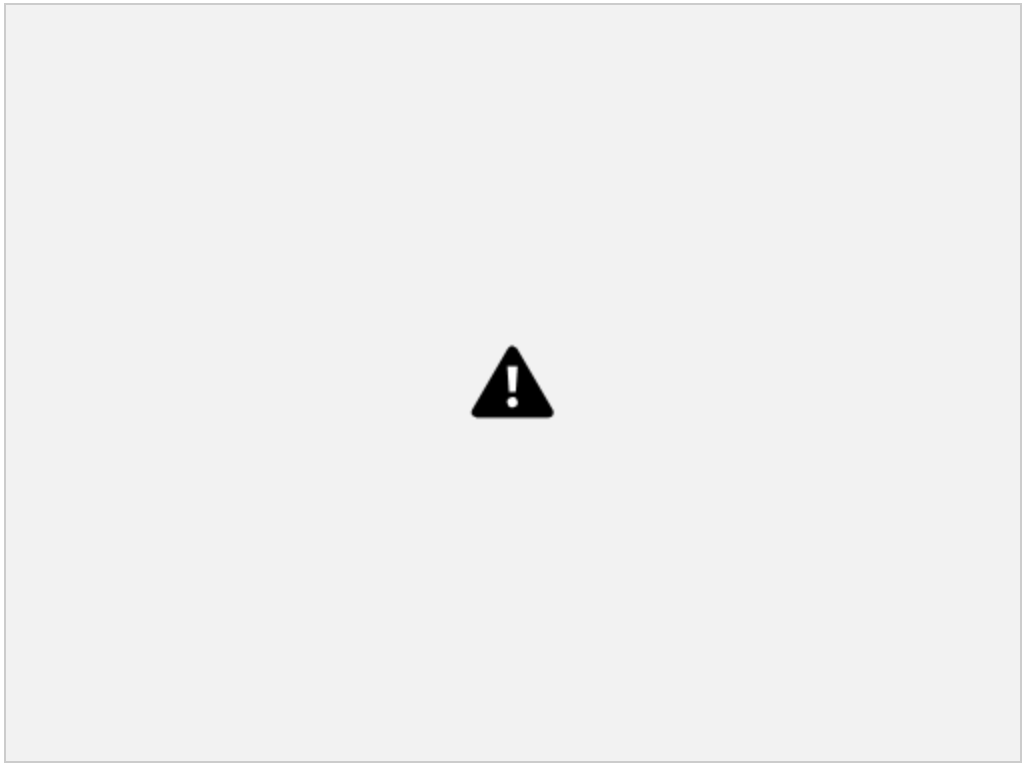


[X]

Future Directions

- Some challenges that need addressing

– Making existing and future methods more user-friendly

– Reasoning about and how to obtain bias parameters and their –

Extension to time-varying confounding settings and g-methods –

Different sources of bias: need for multiple-bias modeling

– How to integrate bias analysis into routine regression procedures –

How to conduct, interpret and report quantitative bias

– How to get journals to accept more nuanced analysis of observational data that incorporates bias analysis

– How to train epidemiologists to see bias analysis as an integral part of any serious causal modeling, not as an after-thought

- Some unfolding and expected future directions

– Extending Pearl's front door formula: somewhat like using mediating instrumental variable(s) (Pearl 1994, 1995, 2000)

– Use of a general bias simulation framework: DAG out the data generating process and use it to simulate how much confounding by *U* under the causal null (Arah 2017)

– Data fusion: combining multiple datasets and information within a causal framework (Bareinboim 2016; 2019)

– New clever designs: e.g. use of multiple synthetic exposure controls with increasingly richer confounder information

– Extending negative control methods to complex exposures and outcomes

DAG: Uncontrolled confounding of $X \rightarrow Y$ due to unmeasured U

Front-door criterion:

M d-separates X and Y

Can identify the total effect of X on Y provided

(i) M completely d-separates the

conditional on U

Can be extended to allow for multiple M and direct arrow from X to Y: total unidentified but the effect of X on Y through M would be

causal path(s) from X to Y

(ii) no uncontrolled confounding of confounders

X□M

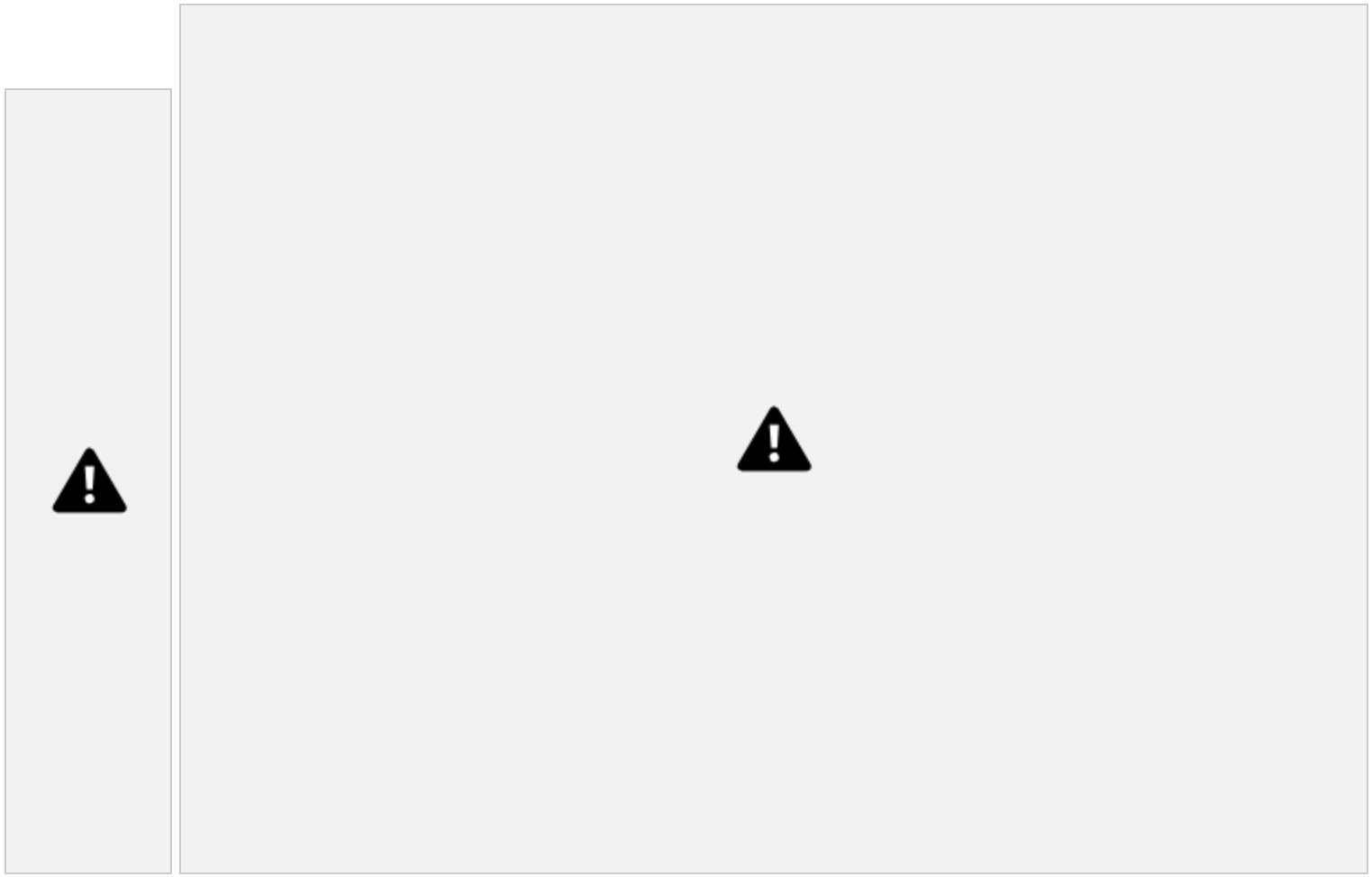
(ii) no uncontrolled confounding of M□Y given X

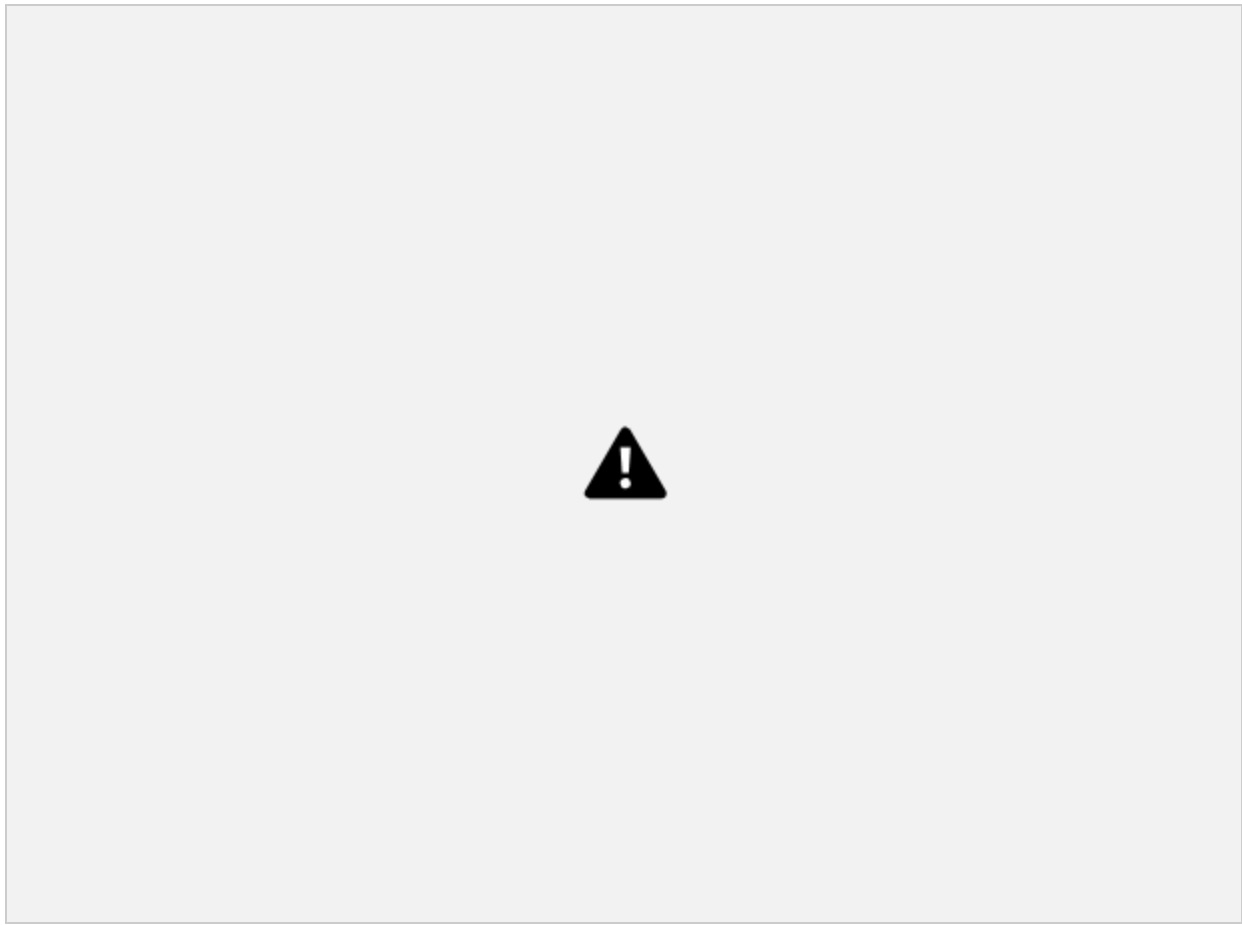
(Pearl 1994, 1995, 2009)

Modified (i): M d-separates a specific causal path from X to Y

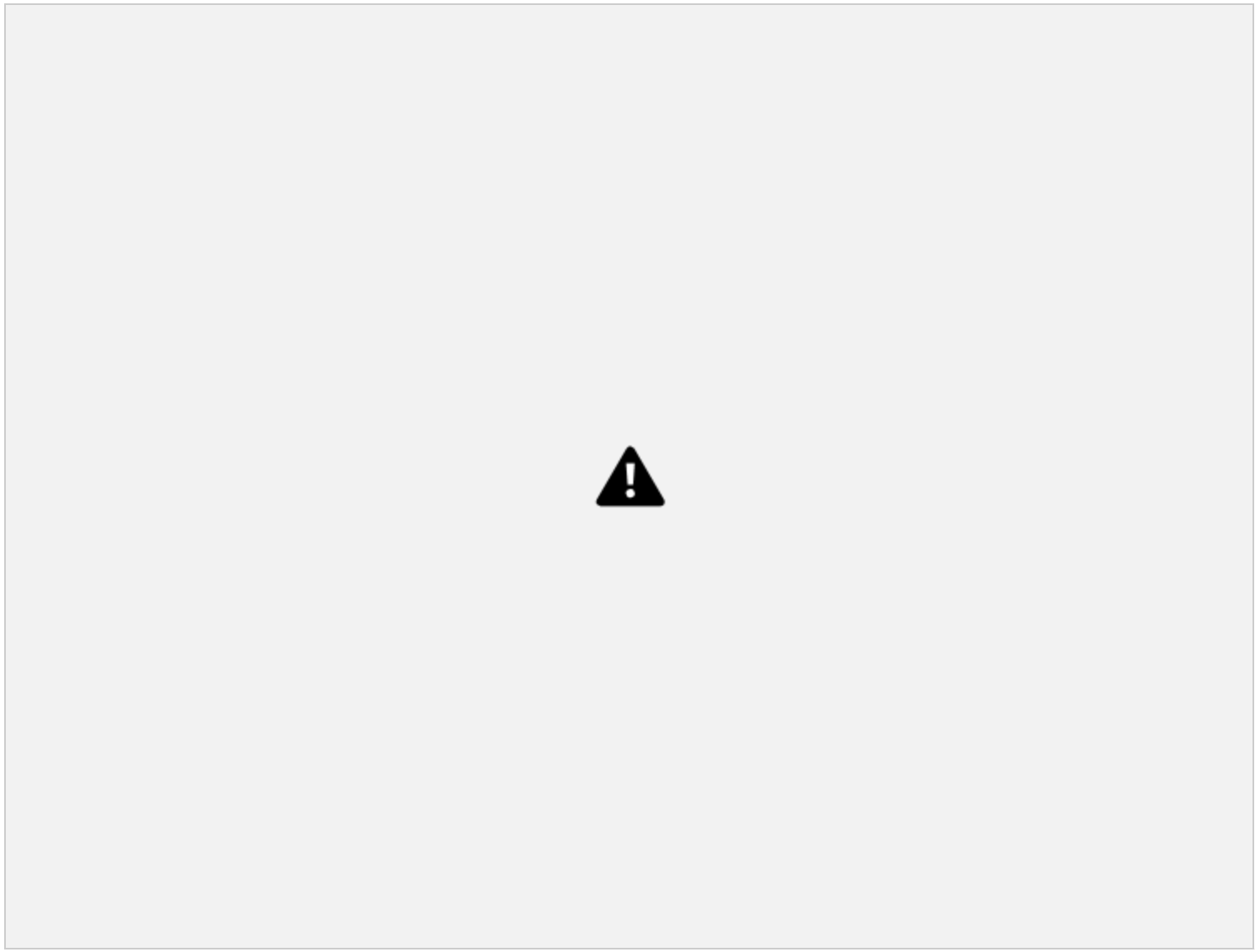
Modified (i) and (**ii**): Both conditional on measured

C U





Y



Arah

Conclusion

- Bias analysis is becoming more important given the rise of big data, cheap computing and automated algorithms (including AI), new bias methods, and causal inference

- Given the increased use of very large datasets in epidemiology, we need methods for **reducing the chances of being precisely wrong:** we need **sophisticated and transparent quantitative bias analysis**

• **Bias analysis is a stress test for credible causal inference:** *What else could explain our results from observational studies?* 

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