Control of Confounding and Reporting of Results in Causal Inference Studies

Lederer, David J.; Bell, Scott C.; Branson, Richard D.; Chalmers, James; Marshall, Rachel; Maslove, David M.; Ost, David E.; Punjabi, Naresh M.; Schatz, Michael; Smyth, Alan R.; Stewart, Paul W.; Suissa, Samy; Adjei, Alex A.; Akdis, Cezmi A.; Azoulay, Élie; Bakker, Jan; Ballas, Zuhair K.; Bardin, Philip G.; Barreiro, Esther; Bellomo, Rinaldo; Bernstein, Jonathan A.; Brusasco, Vito; Buchman, Timothy G.; Chokroverty, Sudhansu; Collop, Nancy A.; Crapo, James D.; Fitzgerald, Dominic A.; Hale, Lauren; Hart, Nicholas; Herth, Felix J.; Iwashyna, Theodore J.; Jenkins, Gisli; Kolb, Martin; Marks, Guy B.; Mazzone, Peter; Moorman, J. Randall; Murphy, Thomas M.; Noah, Terry L.; Reynolds, Paul; Riemann, Dieter; Russell, Richard E.; Sheikh, Aziz; Sotgiu, Giovanni; Swenson, Erik R.; Szczesniak, Rhonda; Szymusiak, Ronald; Teboul, Jean-Louis; Vincent, Jean-Louis

Published in:
Annals of the American Thoracic Society

DOI:
10.1513/AnnalsATS.201808-564PS

Publication date:
2019

Document Version
Peer reviewed version

Link to publication in Discovery Research Portal

Citation for published version (APA):
Control of Confounding and Reporting of Results in Causal Inference Studies: Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals

David J Lederer, MD, MS* ORCID 0000-0001-5258-0228
Departments of Medicine and Epidemiology
Columbia University Irving Medical Center
New York, New York, United States
Editor-in-Chief, Annals of the American Thoracic Society

Scott C Bell, MBBS, MD, FRACP* ORCID 0000-0001-8651-7139
Department of Thoracic Medicine
The Prince Charles Hospital
Brisbane, Australia
Editor-in-Chief, Journal of Cystic Fibrosis

Richard D Branson, MSc, RRT* ORCID 0000-0002-0912-3360
Department of Surgery
University of Cincinnati
Cincinnati, Ohio, United States
Editor-in-Chief, Respiratory Care

James D Chalmers, MD, PhD*
University of Dundee
Dundee, Scotland
Deputy Chief Editor, European Respiratory Journal

Rachel Marshall, BSc*
London, England
Deputy Editor, The Lancet Respiratory Medicine

David M Maslove, MD, MS* ORCID ID 0000-0002-0765-7158
Department of Medicine
Queen’s University
Kingston, Ontario, Canada
Associate Editor for Data Science, Critical Care Medicine

David E Ost, MD, MPH*
Department of Pulmonary Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas, United States
Editor-in-Chief, Journal of Bronchology and Interventional Pulmonology

Naresh M Punjabi, MD, PhD*
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University
Baltimore, Maryland, United States
Deputy Editor-in-Chief, SLEEP

Michael Schatz, MD, MS*
Department of Allergy
Kaiser Permanente Medical Center
San Diego, California, United States
Editor-in-Chief, The Journal of Allergy & Clinical Immunology: In Practice

Alan R Smyth, MA MBBS MRCP MD FRCPCH*
Division of Child Health, Obstetrics & Gynecology
University of Nottingham
Nottingham, England
Joint Editor-in-Chief, Thorax

Paul W Stewart, PhD*
Department of Biostatistics
University of North Carolina
Chapel Hill, North Carolina, United States
Associate Editor, Pediatric Pulmonology

Samy Suissa, PhD*
Department of Epidemiology, Biostatistics, and Occupational Health
McGill University
Montreal, Quebec, Canada
Advisor, COPD: Journal of Chronic Obstructive Pulmonary Disease

Alex A Adjei, MD, PhD
Department of Oncology
Mayo Clinic
Rochester, Minnesota, United States
Editor-in-Chief, Journal of Thoracic Oncology

Cezmi A Akdis, MD ORCID 0000-0001-8020-019X
Swiss Institute of Allergy and Asthma Research
University of Zurich
Davos, Switzerland
Editor-in-Chief, Allergy

Élie Azoulay, MD, PhD
St Louis Hospital
University of Paris
Paris, France
Editor-in-Chief, *Intensive Care Medicine*

Jan Bakker, MD, PhD, FCCM, FCCP  ORCID 0000-0003-2236-7391  
Department of Pulmonology and Critical Care  
Columbia University Irving Medical Center and NYU Langone Health, New York, United States  
Department of Intensive Care Adults, Erasmus MC University Medical Center, Rotterdam, Netherlands  
Department of Intensive Care, Pontificia Universidad Católica de Chile, Santiago, Chile  
Editor-in-Chief, *Journal of Critical Care*

Zuhair K Ballas, MD  
Department of Internal Medicine  
University of Iowa and the Iowa City VA Medical Center  
Iowa City, Iowa, United States  
Editor-in-Chief, *The Journal of Allergy & Clinical Immunology*

Philip G Bardin, FRACP, PhD  
Monash Lung & Sleep  
Monash Hospital and University  
Melbourne, Victoria, Australia  
Co-Editor-in-Chief, *Respirology*

Esther Barreiro, MD, PhD  
Pulmonology Department-Muscle & Lung Cancer Research Group  
Research Institute of Hospital del Mar and CIBERES (ISC-III)  
Barcelona, Spain  
Editor-in-Chief, *Archivos de Bronconeumologia*

Rinaldo Bellomo, MD, PhD  
Department of Intensive Care Medicine  
Austin Hospital and University of Melbourne  
Melbourne, Australia  
Editor-in-Chief, *Critical Care & Resuscitation*

Jonathan A Bernstein, MD  
Department of Internal Medicine  
University of Cincinnati College of Medicine  
Cincinnati, Ohio, United States  
Editor-in-Chief, *Journal of Asthma*

Vito Brusasco, MD  
Department of Internal Medicine  
University of Genoa  
Genoa, Italy
Editor-in-Chief, *COPD: Journal of Chronic Obstructive Pulmonary Disease*

Timothy G Buchman, PhD, MD  
Departments of Surgery, Anesthesiology, and Biomedical Informatics.  
Emory University School of Medicine  
Atlanta, Georgia, United States  
Editor-in-Chief, *Critical Care Medicine*

Sudhansu Chokroverty, MD, FRCP  
JFK NJ Neuroscience Institute  
Hackensack Meridian Health-JFK Medical Center  
Edison, New Jersey 08820, USA  
Editor-in-Chief, *Sleep Medicine*

Nancy A Collop, MD  
Departments of Medicine and Neurology  
Emory University School of Medicine  
Atlanta, Georgia, United States  
Editor-in-Chief, *Journal of Clinical Sleep Medicine*

James D Crapo, MD  
Department of Medicine  
National Jewish Hospital  
Denver, Colorado, United States  
Editor-in-Chief, *Journal of the COPD Foundation*

Dominic A Fitzgerald, MBBS, PhD, FRACP  
The Children’s Hospital at Westmead  
Sydney Medical School  
University of Sydney  
Sydney, Australia  
Editor in Chief, *Paediatric Respiratory Reviews*

Lauren Hale, PhD  
Program in Public Health  
Department of Family, Population and Family Medicine  
Stony Brook University  
Stony Brook, New York, United States  
Editor-in-Chief, *Sleep Health*

Nicholas Hart, MB, BS, BSc, MRCP, PhD, FFICM  
Lane Fox Respiratory Service  
Guy’s & St Thomas' Hospital  
London, United Kingdom
Joint Editor-In-Chief, Thorax

Felix J Herth MD, PhD
Department of Pneumology and Critical Care Medicine
University of Heidelberg
Heidelberg, Germany
Editor-in-Chief, Respiration

Theodore J Iwashyna, MD, PhD
Department of Internal Medicine
University of Michigan
VA Center for Clinical Management Research, VA Ann Arbor Health System.
Ann Arbor, Michigan, United States
Innovation Editor, Annals of the American Thoracic Society

Gisli Jenkins, BM, PhD
Department of Experimental Medicine
University of Nottingham
Nottingham, England
Joint Editor-In-Chief, Thorax

Martin Kolb, MD, PhD
Department of Medicine
McMaster University
Hamilton, Ontario, Canada
Chief Editor, European Respiratory Journal

Guy B. Marks, MB, BS, PhD ORCID 0000-0002-8976-8053
South Western Sydney Clinical School
University of New South Wales
Sydney, Australia
Joint Editor-in-Chief (Lung Diseases), International Journal of Tuberculosis and Lung Disease

Peter Mazzone, MD, MPH
Department of Pulmonary Medicine
Cleveland Clinic
Cleveland, Ohio, United States
Incoming Editor-in-Chief, CHEST

J Randall Moorman, MD
Departments of Medicine, Physiology, Engineering
University of Virginia
Charlottesville, Virginia, United States
ORCID 0000-0002-5772-1648
Editor-in-Chief, *Physiological Measurement*

Thomas M Murphy, MD  
Division of Pulmonary & Sleep Medicine  
Mass General Hospital for Children  
Harvard Medical School  
Boston, Massachusetts, United States  
Editor-in-Chief, *Pediatric Pulmonology*

Terry L Noah, MD  
Department of Pediatrics, Division of Pulmonology  
University of North Carolina  
Chapel Hill, North Carolina, United States  
Deputy Editor, *Pediatric Pulmonology*

Paul Reynolds, MBBS, PhD, MD  
Department of Thoracic Medicine  
Royal Adelaide Hospital  
University of Adelaide  
Adelaide, Australia  
Co-Editor-in-Chief, *Respirology*

Dieter Riemann, PhD  
Department of Psychiatry & Psychotherapy  
Freiburg University Medical Center  
Freiburg, Germany  
Editor-in-Chief, *Journal of Sleep Research*

Richard E Russell, MD, PHD  
Senior Clinical Researcher Nuffield Dept of Medicine, University of Oxford  
Consultant Physician, Lymington New Forest Hospital, Hampshire, UK  
Editor-in-Chief, *International Journal of COPD*

Aziz Sheikh, MD, MSc  
Usher Institute of Population Health Sciences and Informatics  
The University of Edinburgh  
Edinburgh, Scotland, United Kingdom  
Editor-in-Chief, *npj: Primary Care Respiratory Medicine*

Giovanni Sotgiu, MD, PhD  
Clinical Epidemiology and Medical Statistics Unit  
Department of Medical, Surgical and Experimental Sciences  
University of Sassari  
Sassari, Italy
Associate Editor, *European Respiratory Journal*
Advisor, *COPD: Journal of Chronic Obstructive Pulmonary Disease*

Erik R Swenson, MD
Department of Medicine
University of Washington
VA Puget Sound Health Care System
Seattle, Washington, United States
Editor-in-Chief, *High Altitude Medicine & Biology*

Rhonda Szczesniak, PhD
Division of Biostatistics & Epidemiology
Cincinnati Children’s Hospital Medical Center
Department of Pediatrics
University of Cincinnati
Cincinnati, Ohio, United States
Statistical Editor, *Thorax*

Ronald Szymusiak, PhD
Departments of Medicine and Neurobiology
David Geffen School of Medicine at UCLA
Los Angeles, California, United States
Editor-in-Chief, *SLEEP*

Jean-Louis Teboul, MD, PhD
CHU Bicêtre,
Le Kremlin-Bicêtre, France
Editor-in-Chief, *Annals of Intensive Care*

Jean-Louis Vincent, MD, PhD
Bicêtre Hospital, AP-HP
University Paris South
Le Kremlin-Bicêtre, France
Editor-in-Chief, *Critical Care*

*Writing group*

**Corresponding Author:**
David J Lederer, MD, MS
Associate Professor of Medicine and Epidemiology
Columbia University Irving Medical Center
161 Fort Washington Ave, Rm 3-321A
New York, NY 10032; Phone: 212-305-8203
DL427@cumc.columbia.edu
Funding: None

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Running Head: Guidance for Authors

MeSH Headings: Epidemiology, Causality, Research Design, Confounding Factors

Word Count: 3,119
The 21st century has brought with it a welcome call for increased rigor in observational research methods (1, 2). It is not that observational research methods are inherently flawed – they are not (3, 4). Observational studies can contribute valuable evidence supporting causal associations when designed and conducted using rigorous methods. The “flaws” are a result of reliance on outdated methodology, inadequate attention to threats to validity (such as confounding), opaque reporting of results, lack of replication, and a failure to interpret findings within the context of the limitations of observational research methodology.

Aware of this situation and influenced by our experience as journal editors, we convened an ad hoc group of 47 editors of 35 respiratory, sleep, and critical care journals to offer guidance to authors, peer reviewers, and researchers on the design and reporting of observational causal inference studies. This guidance takes the form of a call for investigators to consider making major changes to their approach to such studies. This document represents our current best understanding of approaches to causal inference, an active area of research. We anticipate that best practice in this, as in any scientific endeavor, will continue to evolve, requiring this document to be updated every 5 to 10 years. We believe these changes will increase the rigor, validity, and value of the work we publish in our journals.

What Is Causal Inference?

We first wish to make a distinction between causal inference and prediction modeling. Causal inference is the examination of causal associations to estimate the causal effect of an exposure on an outcome. We use causal inference to answer questions about etiology: Does long-term
Does caffeine intake protect against pulmonary arterial hypertension? Do anti-depressants reduce the risk of the ARDS in adults with community-acquired pneumonia? Both experimental studies (e.g., randomized clinical trials) and observational studies (e.g., cohort, case-control, and cross-sectional studies) can be used to examine causal associations. We encourage authors to design observational studies that emulate the clinical trial they would have designed to answer the causal question of interest (5, 6). Causal inference studies require a clearly articulated hypothesis, careful attention to minimizing selection and information bias, and a deliberate and rigorous plan to control confounding. The latter is addressed in detail later in this document.

Prediction models are fundamentally different than those used for causal inference (7). Prediction models use individual-level data (predictors) to estimate (predict) the value of an outcome. For example, one might wish to predict an adult’s 10-year risk of developing lung cancer. Investigators might use machine learning methods, penalized estimation, or one of many other available methods to develop a prediction model using a dataset containing both the predictors of interest and lung cancer event data. A risk score calculator (or other clinically useful tool) could then be developed, validated, disseminated, and implemented in practice. This document does not address development, validation, or reporting of prediction model.

With this background, we offer three key principles to guide authors in the analysis and reporting of causal inference studies (Table 1):
Key Principle #1: Causal Inference Requires Careful Consideration of Confounding

Herein, we focus on how one should define and select confounders in observational studies that attempt to make causal inferences. Based on our experience, we have identified 5 approaches commonly used by authors (Table 1). Only two of these methods (the “historical” approach and causal modeling), however, aid in causal inference. The others, those based on statistical hypothesis testing or model fit, do not. We detail each approach below:

**Historical Approach to Defining a Confounder**

A confounder has long been defined as any third variable that is associated with the exposure of interest, is a cause of the outcome of interest, and does not reside in the causal pathway between the exposure and outcome (Figure 1A) (8). We find this definition reasonable, and we regard it as an acceptable approach to address confounding in studies of causal inference. Importantly, as clarified later, we expect authors to *purposefully* select variables that plausibly fit these criteria based on prior knowledge rather than selecting those variables associated with the exposure or outcome using the available data.

**Using Causal Models to Identify Confounding**

While the historical approach described above is acceptable for simple causal structures, it is often inadequate to describe the more commonly encountered causal networks. Hence, we urge authors to consider using causal models when testing causal associations.
The scientific, mathematical, and theoretical underpinnings of causal inference, developed by Judea Pearl, James Robins, Miguel Hernán, and others, have evolved sufficiently to permit the everyday use of causal models (9-17). Causal models can be represented visually using directed acyclic graphs (DAGs). A DAG is a graph in which unidirectional arrows are used to represent known causal effects (based on prior knowledge). While investigators often feel some discomfort in deciding what causal effects do and do not exist based on prior knowledge, the advantage of this approach is that it makes these assumptions explicit (and hence transparent). In fact, all other methods of controlling for confounding involve implicit assumptions about causal effects, which are not transparent to the reader.

Four simple DAGs are shown in Figure 1. Within a DAG, a “path” is a set of arrows connecting any two variables (regardless of arrow direction). The causal path of interest is the hypothesized association between the exposure and outcome. A “back-door path” is an alternate path between the exposure and the outcome. Confounding is defined as the presence of at least one “open” back-door path between exposure and outcome. Variables that naturally open back-door paths are called confounders. An association will exist between any two variables connected by an open path. When an investigator “controls” for a confounder, the back-door path will be “closed,” and the association between the exposure and outcome will no longer be observed.

As an example, suppose an investigator is testing whether exercise is associated with a reduced risk of lung cancer. In Figure 1A, there is one causal path: exercise → lung cancer, and one back-door path: exercise ← smoking → lung cancer. This open back-door path indicates the presence of confounding, and therefore smoking is a confounder of the causal association.
between exercise and lung cancer. Note that we define a confounder here as a variable that, when controlled for, closes a back-door path.

When more than one variable lies along a back-door path, control of a single confounder on the path is sufficient to close the back-door path. In a fully developed DAG with many paths, control of a small number of variables (a “minimum set” of confounders) will often close all back-door paths. We recommend using this approach in causal inference studies. DAGitty.net offers authors a simple interface with which to construct DAGs and identify back-door paths and minimum sets of confounders (18).

Figure 1B adds another type of variable -- a mediator -- to the DAG. A mediator is a variable that lies along the causal path (not a back-door path) between the exposure and disease. Mediators are, of course, of great interest, since they are causes and mechanisms of disease. In Figure 1B, the mediator is “immune function.” At least some of the causal effect of exercise on lung cancer risk is mediated by exercise-induced changes: exercise → immune function → lung cancer. A path that includes a mediator is often called an indirect effect or indirect causal path. In contrast, the arrow directly connecting exercise and lung cancer represents the direct causal effect of exercise on lung cancer not due to changes in immune function.

Mediators naturally leave the indirect causal path open. Control of a mediator (through adjustment or other means) will close the indirect causal path, preventing or limiting the ability to observe an association between the exposure and outcome (if indeed one exists). Mediators therefore require special attention (if they are to be examined at all) and should not be treated
as confounders. Use of a DAG can aid investigators in identifying mediators, thereby avoiding control of these variables in testing causal effects.

A discussion of “collider bias” further illustrates the value of using DAGs. A “collider” is a variable with two or more antecedent causes that lie within a pathway of interest. A collider can be identified on a DAG when two arrows along a path both point to a variable (Figure 1C). When both the exposure and outcome are causes of the collider, one may be tempted to control for the collider. However, *colliders naturally block back-door paths*. Controlling for a collider will open the back-door path, thereby *introducing* confounding.

For example, in Figure 1C we are interested in testing the causal association between shift work and obstructive sleep apnea. We might be tempted to control for sleepiness, since both shift work and obstructive sleep apnea cause sleepiness. However, sleepiness is a collider that naturally blocks the back-door path of shift work → sleepiness ← obstructive sleep apnea. Controlling for sleepiness would open this back-door path, introducing confounding.

To clarify, imagine that, in reality, shift work is not a cause of obstructive sleep apnea. If we encountered a sleepy person with obstructive sleep apnea, their sleep apnea would likely be the cause of their sleepiness, and therefore they would be less likely to be a shift worker. Conversely, if we encountered a sleepy shift worker, it is likely that shift work is the cause of their sleepiness rather than obstructive sleep apnea. We would therefore observe that sleep apnea occurs less commonly among shift workers, and thus report an inverse association. This confounded association results from conditioning on a collider (in this case, by only examining sleepy people). The same bias would occur if we were to adjust for sleepiness using a regression model.
Collider bias may also be present when neither the exposure nor the outcome is a direct cause of the collider variable. An example is “M-bias,” named after the shape of the DAG (Figure 1D) (19). In this example, we are testing the causal association between chronic beta-blocker use and the risk of developing ARDS. We might be tempted to adjust for the presence of auscultatory crackles at hospital admission, since: (a) heart failure leads to both chronic beta-blocker therapy and crackles; and (b) pneumonia causes both ARDS and crackles. These relationships may lead us to believe that “crackles” is a confounder, whereas in reality it is not. Instead, as Figure 1D shows, “crackles” is a collider on the back-door path of chronic beta-blocker therapy $\leftarrow$ heart failure $\rightarrow$ crackles $\leftarrow$ pneumonia $\rightarrow$ ARDS. Adjusting for the presence of crackles opens this back-door path, introducing confounding. Ignoring the presence of crackles would be the right thing to do.

We encourage investigators that wish to control for variables that do not close a back-door path to ensure that these additional variables are neither mediators nor colliders.

DAGs do come with limitations. They are non-parametric by nature. The directionalities of effects are not always known. DAGs are prone to misspecification when there is a lack of strong background information, and constructing a DAG can be challenging, with even small errors potentially leading to incorrect inferences. Despite these limitations, DAGs lay bare the assumptions made by the investigators, which can then be identified and corrected more readily during pre- and post-publication peer review than through more opaque methods.

This brief document cannot provide a detailed discussion of causal inference, but we hope that these examples encourage authors to consider using causal models in their research. We refer authors to a number of excellent resources on the topic (Table 2).
Variable Selection Methods That Do Not Adequately Control for Confounding

P-value-based and model-based variable selection methods (including forward, backward, and stepwise selection) should not be used for causal inference. These approaches ignore the causal structure underlying the hypothesis and therefore do not adequately control for confounding. Confounders and colliders are treated similarly. Methods relying on model fit or related constructs (such as $r^2$, Akaike information criterion, and Bayesian information criterion) also have no relevance to causal inference. These methods rely heavily on the available data, in which causal relationships may or may not have been captured and may or may not be evident. Specification of the model and the arbitrary variables included in any particular model will drive observed associations with the outcome.

Selection of variables that, when included in a model, change the magnitude of the effect estimate of the exposure of interest should not be used to identify confounders, for the reasons discussed above.

Identification of multiple “independent predictors” (“winners”) through purposeful or automated variable selection is an unacceptable approach for testing causal associations. If the authors have hypotheses about each variable, then a separate model for each variable should be generated using one of the above preferred approaches. Alternatively, a prediction model could be developed, if prediction, rather than causal inference, is the goal of the analysis.

“Table 2 Fallacy”

Causal models are typically designed to test an association between a single exposure and an outcome. The additional independent variables in a model (often called “covariates”) serve to
control for confounding. The observed associations between these covariates and the outcome have not been subject to the same approach to control of confounding as the exposure. Therefore, residual confounding and other biases often heavily influence these associations. This situation is known as “Table 2 Fallacy,” a term arising from the practice of presenting effect estimates for all independent variables in “Table 2” (20). We strongly caution authors to avoid presenting these effect estimates in the primary manuscript.

Causal Association, Causal Effect, and Claiming Causality

Readers may find it unusual that we are using the word “causal” to describe observed associations. When examining associations in observational causal inference studies, the intention is always to seek evidence to support (or refute) a true causal effect of the exposure on the outcome. Of course, we often cannot establish these causal effects from any single study. Yet, by acknowledging the intent, it is reasonable to use the label “causal association” (but not “causal effect”) to describe findings arising from an observational study.

We therefore caution authors that claims of causality should be avoided without substantial evidence of a true causal effect, as espoused by Bradford Hill and further developed by John Ioannidis (21, 22). It is reasonable to use the term “effect estimate” when referring to a causal association in an observational study, but assertions that an exposure has an “effect” or “impact” on the outcome, or that the exposure “protects against” or “promotes” the outcome should not be made.
A Note on Methods to Control for Confounding

Investigators may control for confounding either in the design or analysis of a study. Randomization to exposure, use of an instrumental variable, weighted regression via propensity-scores, adjustment using multivariable regression, stratification on a confounder, conditioning enrollment on a confounder (restriction), and matching on a confounder are common methods (4). We do not make recommendations for or against any of these methods.

Key Principle #2: Interpretation of Results Should Not Rely on the Magnitude of P-Values

In recent years, the merits of the p-value in causal inference have been questioned (23-26). P-values are frequently misinterpreted and misused (27). Although some disagree (28), they provide no information about the magnitude, direction, or clinical importance of an association. Accordingly, we recommend that P-values only rarely be presented in isolation (exceptions may include “omics” studies and tests for interaction). Effect estimates and measures of precision (e.g., confidence intervals or credible intervals) should be presented in addition to (or in place of) p-values.

We recommend interpreting the variability around an effect estimate when making conclusions about causal associations. For example, a rate ratio of 2.1 with a confidence interval of 0.97 to 4.2 and a corresponding p-value of 0.10 should not be reported as “no association,” since a rate ratio as large as 4.2 has not been plausibly excluded, and, at least within the study sample, an association was indeed observed. Instead, a statement such as
“The exposure was associated with a 2.1-fold increased rate of the outcome (95% confidence interval 0.97 to 4.2), but this estimate is imprecise” would be sufficient. In this example, the point- and interval-estimates are informative, yet (not surprisingly) the hypothesis test was inconclusive. Similarly, we recommend against using the vague labels “significant” and “non-significant,” which lead readers (and authors) to implicitly conclude that an association is present or absent. Use of the unqualified word “significant” tends to blur the important distinction between statistical significance and clinical significance. We favor simply reporting the quantitative findings as indicated above. The clinical, mechanistic, or biological interpretations of effect sizes provide greater value and should be used in place of these labels.

**Key Principle #3: Results Should Be Presented in a Granular and Transparent Fashion**

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, published in 2007, provides clear and valuable guidance on the reporting of results of human observational studies that test causal associations (29). We strongly recommend that authors adhere to the STROBE statement when reporting results, including the detailed guidance provided in the STROBE “Explanation and Elaboration” Document (30). In particular, when applicable, results should be presented in Tables modeled after those in Sections 15 and 16 of the STROBE “Explanation and Elaboration” Document (30), with the following in mind:
• In cohort studies, tabular presentation of results should include the number of events, person-time, incidence rates, and unadjusted and adjusted incidence rate ratios for each exposure level.

• In cross-sectional studies, tabular presentation of results should include the number of events, prevalences, and unadjusted and adjusted prevalence ratios for each exposure level.

• In case-control studies, tabular presentation of results should include the number and percent exposed for cases and controls separately, and unadjusted and adjusted odds ratios for each case group.

We encourage authors to take a thoughtful and careful approach to the visual presentation of quantitative results (31). When possible, presentation of individual data points should accompany measures of central tendency and variation. The “data-ink ratio” should be maximized by avoiding unnecessary lines, grids, and text (31). Abbreviations should be used sparingly. Continuous data should not be presented in bar charts with standard error bars (“plunger plots”) (32, 33). Authors should use color-blind friendly palettes.

Final Comment to Our Authors

This document is intended to provide firm guidance rather than absolute rules; to raise the rigor of the work reported in our journals; to improve the communication of research findings; to enhance the value and validity of the science in our field; to aid in replication; and, most
importantly, to improve the health of those living with respiratory disease, sleep disorders, and critical illness.
References


Figure Legends

**Figure 1:** Directed acyclic graphs illustrating (A) confounding, (B) mediation, (C) collider bias, and (D) M-bias. Each arrow represents a causal effect. In (A), the blue arrows represent an open back-door path: exercise $\leftarrow$ smoking $\rightarrow$ lung cancer. “Smoking” is a confounder that naturally leaves the back-door path open. Controlling for “smoking” will close the back-door path, eliminating confounding through this path. In (B), the black arrows all represent the direct and indirect causal paths of interest. “Immune function” partially mediates the association between exercise and lung cancer: exercise $\rightarrow$ immune function $\rightarrow$ lung cancer. Control of “immune function” would be inappropriate, since it would partially close the causal path, attenuating the observed association between exercise and lung cancer. In (C), the orange arrows represent a closed back-door path: shift work $\rightarrow$ sleepiness $\leftarrow$ obstructive sleep apnea. “Sleepiness” is a collider that naturally leaves the back-door path closed. Control of “sleepiness” would open the back-door path, introducing confounding through this path. In (D), the orange arrows represent a closed back-door path: chronic beta-blocker therapy $\leftarrow$ heart failure $\rightarrow$ crackles $\leftarrow$ pneumonia $\rightarrow$ acute respiratory distress syndrome. “Crackles” is a collider that naturally leaves the back-door path closed. Control of “crackles” would open the back-door path, introducing confounding through this path.
Table 1: Key Principles

**Key Principle #1: Causal inference requires careful consideration of confounding**
- Preferred variable selection methods
  1. Historical confounder definition with purposeful variable selection
  2. Causal models using directed acyclic graphs
- Variable selection methods that do not adequately control for confounding
  3. P-value or model-based methods
  4. Methods based on beta-coefficient changes
  5. Selection of variables to identify “independent predictors”
- Do not present all of the effect estimates from a model designed to test a single causal association ("Table 2 fallacy").

**Key Principle #2: Interpretation of results should not rely on the magnitude of p-values**
- P-values should rarely be presented in isolation.
- Present effect estimates and measures of variability with or without p-values.
- Variability around effect estimates should inform conclusions.
- A conclusion of “no association” should require exclusion of meaningful effect sizes.
- Avoid the word “significant” in favor of more specific language.

**Key Principle #3: Results should be presented in a granular and transparent fashion.**
- Use the STROBE statement and checklist.
- Model tables after the STROBE “Explanation and Elaboration” Document (Reference #31).
- Visual presentation of quantitative results
  - Present individual data points when possible.
  - Avoid excessive lines, text, grids, and abbreviations.
  - Continuous data should not be presented in bar charts with standard error bars ("plunger plots").
  - Use color-blind friendly palettes
### Table 2: Causal Inference Resources

**Books**


**Articles**


**Websites**
