JAMA Guide to Statistics and Methods

Confounding by Indication in Clinical Research

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In the assessment of the effect of a treatment or potential risk factor—termed an exposure—on a patient outcome, the possibility of confounding by other factors must be considered.[1] For example, if researchers studied the effect of coffee drinking on the development of lung cancer, they might observe an apparent association between these 2 variables. However, because drinking coffee is also related to smoking, the observed association between coffee drinking and lung cancer does not represent a true causal relationship but is rather the result of the association of coffee drinking with smoking—the confounder—which is the true cause of lung cancer.

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This illustration is a simple example of the very complicated and multifaceted phenomenon of confounding. Distortion from a confounder can appear to strengthen, weaken, or completely reverse the true effect of an exposure. In addition, multiple factors can interact to cause confounding in both epidemiologic and clinical research. Notwithstanding these complexities, a confounding variable can be readily identified if it meets 3 important criteria.[1] First, a confounder must be an independent risk factor for the outcome, either a causal factor or a surrogate for a casual factor (eg, smoking for lung cancer). Second, a confounder must be associated with the exposure (eg, smoking and coffee drinking). Third, a confounder cannot be an intermediate variable between the exposure and the outcome (eg, smoking is not caused by drinking coffee).

A particularly important type of confounding in clinical research is "confounding by indication," which occurs when the clinical indication for selecting a particular treatment (eg, severity of the illness) also affects the outcome. For example, patients with more severe illness are likely to receive more intensive treatments and, when comparing the interventions, the more intensive intervention will appear to result in poorer outcomes. This is called "confounding by severity" to emphasize that the degree of illness is the confounder. Because the degree of severity affects both treatment selection and patient outcome and is not an intermediate between the treatment and outcome, it fulfills the criteria for confounding.

The nonrandomized assessment of tracheal intubation vs bag-valve-mask ventilation for pediatric cardiopulmonary arrest reported by Andersen et al[2] in the November 1, 2016, issue of *JAMA* is likely to be complicated by confounding by indication. Clinical conditions (eg, asthma, cystic fibrosis, and upper airway obstruction) existing before and during a patient's cardiopulmonary resuscitation will both affect the patient's outcome and influence the type of airway management.[2] In other words, it is likely that children with more severe disease and worse overall prognosis for survival had a greater probability to be intubated.[2] This possibility is especially great because severity of illness is both a strong predictor of mortality and a strong predictor of the clinical decision to intubate.

Not all confounding by indication is related to severity of illness. Other factors that affect both the type of intervention and the outcome can result in this form of confounding. For example, patients with health insurance may receive different interventions for their illness compared with patients without insurance. Furthermore, patients with insurance also tend to be healthier and have access to better overall medical care, thus improving their overall measured outcomes. In this case, having health insurance may act as a confounder when estimating the effect of the treatment on the outcome.

Addressing Confounding in Clinical Research

The primary goal of clinical research, whether observational or interventional, is to obtain valid measures of the effects of treatments or potential risk factors on patient outcomes. Because confounding distorts the true relationship between the exposure of interest and the outcome, investigators attempt to control confounding to provide valid measures of the observed associations or treatment effects.[3] In particular, randomized clinical trials (RCTs) use randomized treatment assignment to balance potential confounding factors—whether measured, unmeasured, or unknown—that might affect the outcome to ensure that those factors are unrelated to the assigned intervention. Thus, RCTs do not typically require use of statistical methods to adjust for confounding, as the randomization process is meant to limit all forms of confounding.

In some settings, RCTs may be inappropriate, impossible, or not feasible.[4] In these situations, observational studies are often used to investigate causal relationships in which the treatment assignment for each patient is not randomized but instead is determined by clinical indications. These types of observational studies are generally more difficult to interpret than RCTs. Without an opportunity to randomize the exposure, potential confounding frequently exists. Failing to adjust for confounding during the statistical analysis could result in inaccurate estimates of the relationship between the exposure and the outcome.

Use of Methods to Control Confounding

To control confounding, clinical researchers implement study design procedures to prevent confounding (eg, randomization, restriction, and matching) and conduct statistical procedures in the analysis to remove confounding (eg, stratified analyses, regression modeling, and propensity scoring) for both clinical trials and observational studies. Previous JAMA Guide to Statistics and Methods articles have summarized the use of logistic regression models and propensity score methods.[5,6]

Andersen et al used propensity score matching to statistically adjust for confounding.[6] The propensity score is the probability that a patient receives a specific treatment based on his or her characteristics and the clinical indications determined by the treating physician. This probability is used to match patients receiving

the treatment of interest with those receiving the comparison treatment to control confounding by balancing potential confounding factors between these groups.

What Are the Limitations of Methods to Control for Confounding?

Incompletely controlled "residual" confounding may persist in clinical investigations despite study design and statistical procedures aimed at eliminating this form of bias.[1,7,8] This can occur in RCTs when the randomization process fails (typically in smaller trials) to completely balance confounders between the treatment groups. More likely, residual confounding occurs in observational studies of interventions when statistical analyses do not adequately adjust for confounding. Reasons for failure of statistical adjustments include the following: (1) failure to measure the confounding variable so that it cannot be included in the statistical analysis (ie, "unmeasured confounding"); (2) use of a measure for the confounding variable that does not accurately reflect or capture the characteristic it is supposed to represent (eg, the variable used to describe the confounder is an imperfect or misclassified measure of the characteristic); and (3) use of overly broad categories for the confounder (ie, even for patients with the same value for the confounding variable there is important variability in the likelihood of receiving each treatment and in experiencing the outcome).

How Should the Results Be Interpreted?

In the study by Andersen et al, some degree of confounding by indication exists in the comparison between tracheal intubation and bag-valve-mask ventilation. Confounding by indication is evident because inclusion in the propensity score–matched statistical analysis of certain clinical conditions that might influence a clinician's decision to intubate a patient (eg, illness category, preexisting conditions, whether the arrest was witnessed; see Supplement in Andersen et al[2]) reduced the strength of the estimated deleterious effect of tracheal intubation. For example, in the unadjusted statistical analysis, tracheal intubation during pediatric cardiopulmonary resuscitation was associated with decreased survival to hospital discharge, with a risk ratio of 0.64 (95% CI, 0.59-0.69; $P < .001$). However, in the propensity score–matched adjusted statistical analysis, the risk ratio effect estimate was only 0.89 (95% CI, 0.81-0.99; $P = .03$). This change in estimate with statistical adjustment is evidence of confounding by 1 or more clinical conditions that were included in the multivariable analyses.[9] Furthermore, if all of the important confounding variables were not included in the adjusted analyses, then residual confounding could still persist. Although Andersen et al implemented sophisticated statistical methods to specifically limit confounding by indication, their observational cohort study may not have included measures of all potential confounding, such as factors concerned with the resuscitation phase that influenced the decision to intubate the patients.

Caveats to Consider When Interpreting an Analysis Intended to Adjust for Confounding by Indication

When assessing an observational study of treatment effects for confounding by indication, the reader should consider why clinicians select specific interventions and how those decisions might be influenced by factors that also directly affect outcomes. Conversely, investigators must know and understand the causal and noncausal relationships among the intervention, potential confounders, and the outcome to ensure potential confounding is controlled. Underlying pathophysiologic processes must also be considered when determining what variables should be measured and included in any statistical analysis. Any assessment of a clinical intervention should include an evaluation of confounding by indication that is best accomplished by the following: (1) understanding the underlying pathophysiologic mechanisms leading to specific outcomes; (2) understanding the criteria for confounding and describing the relationships between potential confounders and both intervention and outcome variables; and (3) understanding effective study designs and statistical methods that reduce or eliminate confounding by indication.

ARTICLE INFORMATION

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REFERENCES

1. Rothman KJ, Greenland S, Lash T, eds. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
2. Andersen LW, Raymond TT, Berg RA, et al. The association between tracheal intubation during pediatric in-hospital cardiac arrest and survival. *JAMA*. doi:10.1001/jama.2016.14486
3. Greenland S, Morgenstern H. Confounding in health research. *Annu Rev Public Health*. 2001;22:189-212.
4. Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ*. 1996;312(7040):1215-1218.
5. Tolles J, Meurer WJ. Logistic regression: relating patient characteristics to outcomes. *JAMA*. 2016;316(5):533-534.
6. Haukoos JS, Lewis RJ. The propensity score. *JAMA*. 2015;314(15):1637-1638.
7. Szklo M, Nieto FJ, eds. *Epidemiology: Beyond the Basics*. 3rd ed. Burlington, MA: Jones & Bartlett; 2014.
8. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *Am J Epidemiol*. 2007;166(6):646-655.
9. McNamee R. Confounding and confounders. *Occup Environ Med*. 2003;60(3):227-234.