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A typology of four notions of confounding in epidemiology

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ABSTRACT

Confounding is a major concern in epidemiology. Despite its significance, the different notions of confounding have not been fully appreciated in the literature, leading to confusion of causal concepts in epidemiology. In this article, we aim to highlight the importance of differentiating between the subtly different notions of confounding from the perspective of counterfactual reasoning. By using a simple example, we illustrate the significance of considering the distribution of response types to distinguish causation from association, highlighting that confounding depends not only on the population chosen as the target of inference, but also on the notions of *confounding in distribution* and *confounding in measure*. This point has been relatively underappreciated, partly because some literature on the concept of confounding has only used the exposed and unexposed groups as the target populations, while it would be helpful to use the total population as the target population. Moreover, to clarify a further distinction between *confounding "in expectation"* and *"realized" confounding*, we illustrate the usefulness of examining the distribution of exposure status in the target population. To grasp the explicit distinction between *confounding in expectation* and *realized confounding*, we need to understand the mechanism that generates exposure events, not the product of that mechanism. Finally, we graphically illustrate this point, highlighting the usefulness of directed acyclic graphs in examining the presence of *confounding in distribution*, in the notion of *confounding in expectation*.

1. Introduction

Confounding is a major concern in epidemiology. Since the publication of the seminal paper by Greenland and Robins,[1] many epidemiologists have explained the concept of confounding by examining risk measures under a simple potential-outcome (or counterfactual) model for a cohort of individuals.[2–8] Exchangeability of potential outcomes between the exposed and unexposed groups is one of the most fundamental assumptions in making causal inference, and confounding is a common source of lack of exchangeability.[9] Despite its significance, the different notions of confounding have not been fully appreciated in the literature, leading to confusion of causal concepts in epidemiology.

This article aims to highlight the importance of differentiating between the subtly different notions of confounding from the perspective of counterfactual reasoning. We also show that directed acyclic graphs (DAGs) provide a simple algorithm to identify a sufficient set of confounders if the underlying causal structure is properly reflected. To achieve these goals, we use the concept of response types in a simple example. The concept of response type is an essential foundation of causal inference because the causal effect of exposure on disease frequency in a population depends on the distribution of the response types of individuals in that population, not necessarily on the population distribution of the covariates.[1] This point, however, has been relatively underappreciated because, despite its sophistication and usefulness, the response type of each individual is unobservable.

2. Overview of a simple example

To consider the effect of smoking cessation on lung cancer during a defined time period, we use an example of four subjects (Table 1). In an epidemiologic study of these subjects, let us suppose that subjects #1 (male) and #3 (female) were actually exposed

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Table 1
Characteristics of the four smoking subjects during the target time period.[a]

Subject ID	Sex	History of asbestos exposure	Smoking	Lung cancer	Lung cancer if male/female[b]		Response type
					Quit smoking (i.e., exposure)	Did not quit (i.e., non-exposure)	
Subject #1	Male	Yes	Quit	Diseased	Diseased	(Diseased)	Doomed
Subject #2	Male	No	Did not quit	Diseased	(Non-diseased)	Diseased	Preventive
Subject #3	Female	No	Quit	Non-diseased	Non-diseased	(Non-diseased)	Immune
Subject #4	Female	No	Did not quit	Diseased	(Non-diseased)	Diseased	Preventive

[a] Effect of smoking cessation on lung cancer.
[b] Parentheses indicate that these particular outcomes are counterfactual.

(i.e., quit smoking) and subjects #2 (male) and #4 (female) were actually unexposed (i.e., did not quit smoking). During the follow-up, one of the exposed and both of the unexposed subjects suffered from lung cancer. Consequently, the observed risk difference (RD) estimate for the effect of smoking cessation on lung cancer can be calculated as: $1/2 - 2/2 = -1/2$. Likewise, the observed risk ratio (RR) estimate can be calculated as: $(1/2)/(2/2) = 1/2$. These results suggest that smoking cessation can prevent lung cancer.

When we consider a binary exposure and a binary outcome, individuals can be classified into the following four different response types.[1]

- Type 1 or "doomed" persons: Exposure is irrelevant because outcome occurs with or without exposure
- Type 2 or "causal" persons: Outcome occurs if and only if they are exposed
- Type 3 or "preventive" persons: Outcome occurs if and only if they are unexposed
- Type 4 or "immune" persons: Exposure is irrelevant because outcome does not occur with or without exposure

Response types of the four subjects are shown in Table 1. No subjects are classified as a "causal" response type, implying that the effect of smoking cessation is in the same direction for all four subjects. This assumption has been referred to as negative monotonicity.[10,11] Although monotonicity assumptions may be biologically plausible in some situations, they can never be empirically verified with data because they make reference to all individuals in the population. Here, we use such an assumption to simplify the discussion. The conditions presented in our paper can be used even when the monotonicity assumption is violated.

In the following sections, we illustrate a typology of four notions of confounding by exploring and extending this simple example (Box 1 and Fig. 1). For simplicity, we use deterministic counterfactuals for each subject and assume that no random error attributable to sampling variability exists.[6]

Box 1
Four notions of confounding

- **Confounding in distribution**: We say that there is no *confounding in distribution* of the effect of exposure on outcome if the group that actually had a particular exposure is representative of what would have occurred had the entire target population been exposed to the same level of exposure.
- **Confounding in measure**: We say that there is no *confounding in measure* of the effect of exposure on outcome if a particular measure of interest is equivalent to the corresponding causal measure in the target population.
- **Confounding in expectation**: We say that there is no *confounding in expectation* of the effect of exposure on outcome if the exposure assignment mechanism results in balance.
- **Realized confounding:** We say that there is no *realized confounding* of the effect of exposure on outcome if a particular exposure assignment results in balance, irrespective of the exposure assignment mechanism.

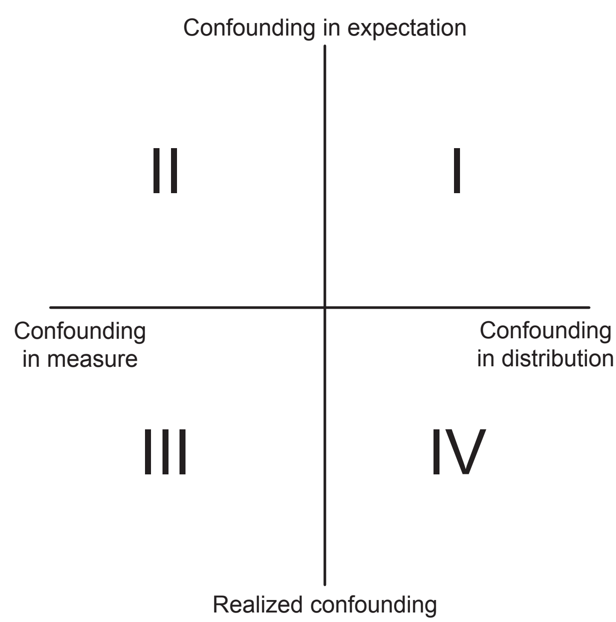

Fig. 1. Typology of four notions of confounding. DAGs are primarily useful to examine the presence of confounding in the first quadrant. DAG, directed acyclic graph.

3. Significance of differentiating between the notions of *confounding in distribution* and *confounding in measure*

The causal effect of exposure on disease frequency in a population depends on the distribution of response types of individuals in that population. Table 2 shows the distribution of response types in the exposed and unexposed groups of the abovementioned example. We also show the distribution in the total population; let p_i, q_i, and r_i, $i = 1$–4, be proportions of response type i in the exposed group, the unexposed group, and the total population, respectively. Note that r_i can be calculated as $p_i/2 + q_i/2$ because the numbers of the exposed and unexposed groups are balanced (Table 1). Among the exposed group, only type 1 and type 2 persons will develop the outcome, and the risk, or incidence proportion, of lung cancer in the exposed group is $p_1 + p_2$. Among the unexposed group, only type 1 and type 3 persons will develop the outcome, and the corresponding risk is $q_1 + q_3$. Therefore, the associational RD can be obtained using the proportions of response types as: $(p_1 + p_2) - (q_1 + q_3) = 1/2 - 2/2 = -1/2$, which is equivalent to the