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Commentary

Can Cross-Sectional Studies Contribute to Causal Inference? It Depends

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Cross-sectional studies—often defined as those in which exposure and outcome are assessed at the same point in time—are frequently viewed as minimally informative for causal inference. While cross-sectional studies may be susceptible to reverse causality, may be limited to assessment of disease prevalence rather than incidence, or may only provide estimates of current rather than past exposures, not all cross-sectional studies suffer these limitations. Moreover, none of these concerns are unique to or inherent in the structure of a cross-sectional study. Regardless of when exposure and disease were ascertained relative to one another, a cross-sectional study may provide insights into the causal effects of exposure on disease incidence. Simply labeling a study as "cross-sectional" and assuming that 1 or more of these limitations exist and are materially important fails to recognize the need for a more nuanced assessment and risks discarding evidence that may be useful in assessing causal relationships.

cross-sectional studies; study design

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Use of shorthand terminology to describe epidemiologic study designs is convenient but has predictable risks. One of the primary benefits is to provide a tool for succinct communication of complex ideas, taking advantage of shared background knowledge. For example, labeling a study as using a nested case-control or case-crossover design succinctly conveys some key features of the way participants were selected or how information was obtained. Similarly, the term "cross-sectional study" is used as shorthand to indicate that information on disease and information on exposure were obtained at the same point in time. The term is frequently used in a pejorative sense and to denote that a given study cannot contribute useful information towards causal inferences. For example, the National Toxicology Program's Office of Health Assessment and Translation handbook assigns cross-sectional studies a low confidence rating (1), and a World Health Organization publication on water quality and infectious disease states simply that "a cross-sectional study can only provide information on the association between an exposure and disease, and the temporal relationship between exposure and disease cannot be established" (2, p. 143). Despite the inherent inability of most cross-sectional studies to reconstruct the cohort from which the available population originated, results of such studies can nonetheless contribute to causal inference. Dismissing findings from such studies solely on the basis of their design risks discarding valuable information that would result from a more nuanced examination of the strengths and limitations of individual studies that takes into account the substantive issues and details of the study methods, as is necessary for any study design (3). Asserting that such studies are not intended for assessing etiology seems disingenuous. Regardless of the original intent of the developers of the data resource, generating confounder-adjusted measures of association almost always indicates an interest in causal effects, as routinely reflected in cross-sectional studies based on survey data (4, 5) or baseline enrollment data in longitudinal studies (6, 7).

Leading epidemiology textbooks define a cross-sectional study in different ways: Szklo and Nieto (8) use the term *cross-sectional* as synonymous with studies of disease prevalence rather than incidence and note that such studies may be susceptible to reverse causality. Even within one of the leading methods texts (9), there are a variety of views expressed or implied: Cross-sectional studies are discussed as a fundamental study type for estimating disease

prevalence (p. 88), as a method of sampling populations (p. 497), and as a descriptive tool that "cannot distinguish between incidence and natural history for the purpose of causal inference" (p. 569). In Pearce's (10) succinct approach to classifying epidemiologic study designs, the term *cross-sectional* is not mentioned directly, but Pearce suggests that the only structural features that need to be taken into account are whether the study examines disease incidence or prevalence and whether there is outcome-dependent sampling. Where neither exposure nor disease status is known at the time of sampling, it is obviously not possible to be selective on either attribute. The specific study features that are variably reflected by the term "cross-sectional study" need to be examined to assess susceptibility to bias. Studying disease prevalence rather than incidence, assessing exposure in an inappropriate time period, and the potential for reverse causation are all potentially important limitations regardless of the design, but assuming that 1 or more of these limitations inevitably result in cross-sectional studies forgoes the need for a more thorough examination, potentially undervaluing informative research.

The implication of simultaneously assessing exposure and disease is that we have only a snapshot of instantaneous disease status (i.e., an estimate of the point prevalence of disease) and contemporaneous exposure status. However, data collected at a given point in time can sometimes be used to estimate exposure histories and thus address the relevant time window for etiology (11). Similarly, it may be possible to obtain information needed for the identification of timing of disease onset in relation to exposure history: Is it still a cross-sectional study if we ascertain and make use of this information to appropriately sequence exposure history and disease incidence and are able to account for attrition over time? What if reverse causality is impossible—for example, when the exposure is a germline genetic characteristic? In isolation, knowing that exposure and disease were assessed simultaneously is of limited value in assessing the degree to which a given set of results is susceptible to bias. All study designs need to account for the temporal course of disease etiology, and the label "cross-sectional" does not automatically mean that this has been done improperly.

PRIMARY METHODOLOGICAL CONCERNS IN CROSS-SECTIONAL STUDIES

There are a series of biases that may be associated with the simultaneous measurement of exposure and disease. While none are unique to this mode of data collection and they are not always present, simultaneous measurement of exposure and disease raises specific concerns: First, contemporaneous exposure may not be etiologically relevant; second, disease prevalence may be a poor proxy for disease incidence; and third, the association between exposure and disease may be susceptible to reverse causality.

Contemporaneous exposure may not be etiologically relevant

In the hypothesized etiological process linking a specific exposure to disease, there are time windows in which exposure is influential and other windows in which it is not (12). The key in any study is to assess exposure during the etiologically relevant time period. For example, for many chronic diseases, the etiologically relevant time windows are not known with precision or certainty but tend to be lengthy, potentially years or decades in duration. If we only measure a time-varying exposure at the point in time when the data are being collected, after the etiological period has ended (i.e., the disease already is or is not present), we are measuring irrelevant exposure and failing to measure the potentially consequential exposure which occurred in the past—a form of exposure misclassification (13). Sometimes this is obvious: In a study of smoking and bronchitis, we know that a participant's smoking status on the day, week, or month of diagnosis is not etiologically relevant to bronchitis. In contrast, if we are trying to determine whether texting while walking leads to increased risk of being struck by a motor vehicle, the ideal time to assess exposure is the moment before the accident occurs (or does not occur), and we would not be primarily concerned with behaviors over an extended period in the past. Even when exposure and disease status are ascertained at the same time, there are often ways to determine historical exposures of etiological interest based on recall or archival records (11) or biomarkers of past exposures (e.g., using deciduous teeth to assess lead exposure (14)). Thus, rather than automatically downgrading a study on the basis of the timing of exposure ascertainment in relation to the presence of disease, there is a need for a thoughtful judgment as to whether the exposure estimate reflects the etiologically relevant period in the past.

Disease prevalence may be a poor proxy for disease incidence

The sources of uncertainty in using disease prevalence as a proxy for incidence are well-known, with disease prevalence reflecting a combination of disease incidence, persistence, and survival (8). For example, studies in which participants are selected on the basis of prevalent disease are vulnerable to length-biased sampling in which individuals with the longest-lasting disease (due to any combination of extended survival or failure to recover) are more likely to be selected as prevalent cases in the study. To the extent that exposure is associated with average disease duration, the association between exposure and disease prevalence will not accurately reflect the association between exposure and disease incidence (10). However, exposure is not necessarily associated with disease duration; and even when it is, studies that sample participants when disease is already present may be able to obtain accurate historical information on timing and duration of disease onset for estimation of historical incidence (11). In other cases, disease may be of sufficiently short duration that the point prevalence may approximate the instantaneous risk in a given population (e.g., pediatric ear infections). A one-time assessment of exposure and disease reflects the point prevalence at that moment, and the pertinent question is whether we can use information on exposure and prevalent disease to draw meaningful inferences about the causal effect of exposure on disease incidence.

The exposure-disease association may be susceptible to reverse causality

There are multiple pathways by which the presence of disease or its precursors may affect the actual or measured exposure. With fallible, self-reported exposures, recall bias is a consequence of reverse causality in which the presence of disease influences either the actual exposure or the measured/reported exposure. For biomarkers of exposure, when disease is already present at the time of ascertainment, there is potential for reverse causality in which the disease process alters the exposure indicator (15, 16). Not only is the exposure status measured at the time of disease ascertainment not the etiologically relevant exposure, the measure itself may be altered by the presence of the disease. This is the biological counterpart of recall bias, in which the presence of disease distorts the self-reported exposure. With some biomarkers, depending on the pharmacokinetics and extent of variation in exposure over time, even a contemporaneous exposure measure may be informative regarding the historical etiological period. Inferences regarding susceptibility to reverse causality require scrutiny of the specific exposures and diseases of interest and how they may relate to one another.

RECOMMENDATIONS AND CONCLUSIONS

In evaluating the validity of epidemiologic studies for inferring causality, it is essential to consider specific biases that may cause deviation between measures of association and causal effects, rather than assume that they are automatically present and understate the study's value. The temporal relationship between exposure and disease, the accuracy of exposure assignment (including the potential for recall bias and reverse causation), and the adequacy of prevalence as a proxy for incidence should always be considered. At best, the label "cross-sectional study" flags these issues as worthy of examination. Just as it is incorrect to assume that cross-sectional studies are automatically guilty of specific biases, it is a mistake to assume that longitudinal studies are automatically free of these biases, that randomized clinical trials are superior to observational studies, or that case-control studies are less informative than cohort studies. Knowing the study design raises specific questions but does not provide answers, and the presumption of a universal hierarchy of validity for causal inference should be avoided (3).

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