Commentary
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by Markku Nurminen, DrPH, PhD

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In a recent commentary in this journal (1), Hernberg expressed an editor’s stance against the use of statistical significance testing in deciding whether confounding is present in an epidemiologic study of an exposure-effect relationship or not. He concluded that the selection of confounders to be controlled in the analysis of the data should instead be made according to the following rule: "Formally one can compare the crude relative risk and the relative risk resulting after adjustment for the potential confounder. A difference indicates confounding, and in that case one should use the adjusted risk estimate. If there is no or a negligible difference, confounding is not an issue and the crude estimate is to be preferred. Personal judgment comes into play when what is 'negligible' is decided" (p 316). Both Hernberg’s treatment of confounding and the prescription chosen to identify the problem invite an extended commentary for two main reasons. First, in causal inference the notion of confounding is more fundamental than any criterion of confounder control, despite the tacit assumption that the defining property of confounding is a difference between the crude and adjusted risk estimates resulting from the dissimilarities in the distribution of the covariate(s) between the exposed and unexposed groups. Second, the presence or absence of confounding depends on the parameter used to measure the effect of exposure on disease outcome. Because of their general interest, I would like to address both of these methodologic issues in some detail.

The distinction between the concepts of confounding and confounder is essential, but often ignored or obscured in epidemiologic literature. The definitions of confounding or confounder fall into two main classes. According to the first, based on the formal concept of collapsibility, confounding is a failure of the estimate for an adjusted (eg, stratified) effect parameter to equal the estimate for an unadjusted (crude) parameter obtained when a covariate is ignored as stratification is collapsed. Thus confounding is equated with noncollapsibility (or change-in-parameter estimate). The second, comparability-based definition views the effect of exposure as a comparison of the group’s outcome when exposed with what the same group’s outcome would have been if exposure had been absent. Consequently, the observed value of the outcome measure in the exposed group is compared with the expected value of the outcome measure that would have been observed in the exposed group if it had, hypothetically, not been exposed. The unexposed group’s actual outcome is used as a proxy for the exposed group’s unobserved value. When the two groups’ experiences differ, the groups are noncomparable, and confounding is said to result. Whittomore (2), Yanagawa (3), Boivin & Wacholder (4), and Becher (5) have defined confounding using the statistical concept of collapsibility, while Miettinen & Cook (6), Greenland & Robins (8) and Checkoway et al (9) have adopted the epidemiologic comparability definition. Some books present confounding in accordance with the comparability definition but then espouse the change-in-parameter-estimate criterion for deciding whether confounding is a problem or not in the estimation of the strength of the exposure effect, for example, Kleinbaum et al (10) and Hernberg (11, see the preceding quotation from Hernberg’s commentary).

As explicated by Greenland et al (12), the collapsibility approach requires that all the covariates assumed to be important predictors of the disease outcome be listed, and it specifies what is meant by their "control", before the problem of confounding can be defined. However, because residual confounding is always possible as a result of imperfect measurement of confounders with the use of imprecise covariates (see, eg, reference 13) or as a result of an unlimited number of undiscovered risk factors, a collapsibility-based definition cannot unambiguously estimate an unconfounded value for the causal

1 Finnish Institute of Occupational Health, Topeliuksenkatu 41 a A, FIN-002500 Helsinki, Finland.

Reprint requests to: Dr M Nurminen, Finnish Institute of Occupational Health, Topeliuksenkatu 41 a A, FIN-002500 Helsinki, Finland.
parameter. Moreover, the conditions for nonconfounding depend on the true (unknown) parametric form of the model that relates the disease outcome to exposure and is conditional on extraneous covariates. A relevant statistical point is that the collapsibility definition implicitly assumes the constancy (homogeneity) of effect measures across strata. This assumption, which is made by procedures such as the Mantel-Haenszel estimates of risk ratios and the logistic regression estimates of odds ratios, is frequently not tenable in epidemiologic applications and can therefore be regarded as a weakness of the definition (14). Another cogent objection is that stratum-specific measures can themselves be confounded by further unknown risk factors (12) or by random imbalance caused by small sizes of the strata (8).

In contrast, the comparability-based definition of confounding does not suffer from such drawbacks because the definition makes no reference to confounders or their control and because, according to this view, nonconfounding is invariant across models underlying the effect measures. The problem of confounding stems from the nonidentifiability of the essential causal parameters of the assumed statistical model that determined the observations. To put it another way, we are not able to estimate the effect because the observed outcomes can be predicted by different possibilities (parameter values) for exposure impact. But these parameters can be made identifiable if we assume the exposed and unexposed groups are comparable (6) or exchangeable (8). In other words, the causal contrasts would be unbiasedly estimable even if the exposure states of the two groups had been exchanged. For the derivation of the theory of epidemiologic confounding based on the assumption of exchangeability, see reference 8. With this approach, we can deduce that confounders must fulfill well-known necessary conditions, namely, that confounders (i) must be predictive of disease risk (even among the unexposed), (ii) must be associated with exposure in the population under study, and (iii) must not be a link in the causal chain from exposure to outcome or a consequence of the outcome. (Compare with reference 6.) Sometimes these properties are taken as defining a confounder and not just being derived properties (15, 16). However, these three conditions cannot be considered to identify a confounder because they are not sufficient to make a covariate a confounder (8). Nevertheless, they can be used in practice as operational criteria for screening out nonconfounders, since any confounder must meet all three criteria.

The comparability definition led Miettinen & Cook (6) inductively to conclude that the presence or absence of confounding should not be equated with the presence or absence of collapsibility and that the decision regarding the existence of confounding should not depend on the chosen parameter. Moreover, the degree of confounding — and hence the strength of an effect — cannot be directly measured from the observed data; it should always be evaluated against background disease risk, knowledge of subject matter, logical argument, evidence from previous studies, and the particulars of the empirical setting in which the study is being conducted. The dilemma posed by the conceptual identification of every important confounder is that, in addition to the factors brought forward by the study, one that, together with the included factors, constitutes a confounder may be omitted. There is a further problem in that, even if all the plausible confounders have suitably similar distributions between the compared groups, their joint effect may still cause bias. Criteria based singularly on associations within the data can also be misleading because the predictiveness of the potential confounders of the outcome can be a result of effect modification rather than a result of confounding (17). Therefore, the decision of whether a covariate requires control is both judgmental and subject to error.

However, the relative roles of prior information, as against data from the study population, involve subtleties that reach beyond the previous inductive examination of the problem (6). For example, given prior information that a covariate is a risk factor in a cohort study, inferences should be made conditional on appropriate measures (ancillary statistics) of discrepancies between this prior knowledge and the observed data (18). Conversely, if a covariate in a case-referent study is known a priori to be unassociated with either the exposure or the disease in the source population, then the crude estimate does not require adjustment irrespective of associations observed in the data (19). Statisticians have previously failed to recognize that epidemiologists have implicitly conditioned their causal analyses of exposure-effect relations with such ancillary statistics. This failure has probably prevented a coherent statistical definition of the epidemiologic concept of confounding (20).

Which definition of confounding should we adopt and which operational criteria for its detection should we select amid this conceptual discrepancy? The confusion can be explained by the use of statistical criteria for confounder control that are not coherent with the intuitive notions of confounding. Wichramaratne & Holford (21) offer a resolution by suggesting that (i) noncollapsibility of the chosen measure of effect and (ii) noncomparability of the exposed and unexposed groups are distinct phenomena. Exacerbating the problem is the fact that the criteria for a covariate to be a confounder according to the two definitions are not mathematically equivalent. However, Greenland et al (12) made the following important point: "If one elects to use a measure of effect for which comparability and collapsibility do not coincide, such as the incidence-odds ratio, then defining one of the two phenomena as
Table 1. Hypothetical data stratified by a covariate (C) that has the same distribution in exposed and unexposed cohorts, illustrating the inadequacy of odds-ratio collapsibility as a criterion for nonconfounding.

|                | Stratum 1: C present | Stratum 2: C absent | Pooled (ignoring C) |
|----------------|----------------------|---------------------|--------------------|
|                | Exposed | Unexposed | Exposed | Unexposed | Exposed | Unexposed |
| Diseased       | 50      | 10       | 90      | 50       | 140     | 60       |
| Nondiseased    | 50      | 90       | 10      | 50       | 80      | 140      |
| Size of subcohort (S) | 100     | 100      | 100     | 100      | 200     | 200      |
| Proportion with C | 0.5     | 0.1      | 0.9     | 0.5      | 0.7     | 0.3      |
| Incidence proportion |      |          |         |          |         |          |
| Incidence-proportion difference | 0.4   | 0.4      | 0.4     | 0.4      |         |          |
| Incidence-proportion ratio | 5.0   | 1.8      | 2.3     | 2.3      |         |          |
| Incidence-odds ratio | 9.0   | 9.0      | 9.0     | 9.0      |         |          |

* The stratified estimate for the incidence-proportion ratio is 2.3.
explained that the reason for the “discrepancy between nonconfounding and collapsibility in rate comparisons arises when person-time is a post-exposure variable whose distribution can be altered by the effects of exposure and other risk factors [p 498].” However, no conflict would result if incidence-proportion differences and ratios were used as the population measures of exposure effect on average risk and incidence-density rate comparisons were used only in situations in which they approximate survival-time (average hazard) comparisons.

Regarding Hernberg’s (1) chief point that “… confounding is bound to time and place and cannot be generalized. Therefore statistical significance testing is not the way to scrutinize potential confounding [p 315]”, not all statistician-epidemiologists see the matter categorically, even though the procedure has been strongly criticized for a long time. (See, for example, reference 30.) It is clear that the problems in selecting potential confounding factors are primarily substantive and not statistical, although there are some statistical guidelines that may prove useful. In the absence of prior knowledge about confounding in the exposure-effect relationship, investigators frequently rely on the data at hand to guide them in their decision of whether to adjust for a covariate or not. The data-based criteria for confounders always pertains to the particular population sample experience yielding the exposure-effect relation of the study. If the use of significance testing of potential confounders is rejected solely because it is a sample-to-population inference criterion (in frequentist statistics), then one is logically compelled to reject all similar criteria that can be used for such a purpose. There are several other statistical testing strategies besides the significance-test-of-the-covariate criterion, including the equivalence-test-of-the-difference and collapsibility test criteria (31). The equivalence test is preferable to the significance test on logical grounds, because it tests whether the amount of confounding present is worth worrying about, rather than testing a certainly false null hypothesis of nonconfounding (32). The impact of various confounder selection criteria on effect estimation was investigated in simulation studies for both case-referent data (33) and cohort data (34). The change-in-parameter-estimate criterion (with a specified percentage of difference between the crude and adjusted estimate) tended to perform best for both case-referent and cohort studies, even though significance testing methods can perform acceptably if their significance levels are set much higher than conventional levels (to values of 0.20 or more). Thus using statistical significance tests of potential confounders can be defended in some cases, but, as recommended by Robins & Greenland (35), if doing a frequentist test for confounding is insisted upon, such testing (i) should only be made in a preliminary style for deciding which of the strongest confounders to include in a multivariate adjustment and (ii) it should be reserved for situations in which there is little or no prior information about the investigated associations. In most cases, however, prior information exists that implies that the disease and the exposure are associated conditional on the covariate, or else that they have no such association. In such cases a preliminary test can be seriously misleading (31).

More advanced statistical methods that combine the favorable characteristics of stratification and multivariate modeling have been proposed for the multiconfounder situation (36, 37). Although criticized for exaggerating statistical significance (38), simulation findings (39) support the use of the multivariate confounder score and the propensity score analyses as valid methods for detecting and controlling confounders in most of the practical situations encountered in epidemiologic research.

Hernberg (1) also remarked that "The general rule is that confounders should be controlled, but that the nonconfounders should be left without control to enhance the sensitivity of the study [p 316]". The control of covariates, either by stratification or regression modeling, actually involves two goals (40). Primarily, bias (or statistical inconsistency) should be prevented. Secondarily, imprecision should be avoided. Miettinen (41, p 229) specified, according to the comparability definition, that, if a covariate is only a determinant of the outcome and has no association with the exposure, its control, though irrelevant for validity, nevertheless reduces the residual variance of the outcome variate and thus enhances the statistical efficiency of the analysis (ie., improves the precision of the estimates of exposure effect). But, if a nonconfounder is merely a correlate of exposure, its control reduces efficiency. However, proponents of the collapsibility approach maintain that ignoring a balanced covariate may have different implications for the validity and precision of both the estimates and the significance tests of exposure effect, depending on the scale of the outcome measurement (42).

In conclusion, the problem of confounding is a central, yet highly complicated issue in epidemiology, as in all nonexperimental causal research. Any attempt to clarify "confounding" in simple conceptual or statistical terms is destined to omit some important aspect of the topic. I hope that the commentary by Hernberg and my rejoinder will stimulate further discussion on the correct use of statistics in epidemiologic studies among the readers of this journal.

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