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Selection of Controls in Case-Control Studies

I. Principles

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A synthesis of classical and recent thinking on the issues involved in selecting controls for case-control studies is presented in this and two companion papers (S. Wacholder et al. *Am J Epidemiol* 1992;135:1029–50). In this paper, a theoretical framework for selecting controls in case-control studies is developed. Three principles of comparability are described: 1) *study base,* that all comparisons be made within the study base; 2) *deconfounding,* that comparisons of the effects of the levels of exposure on disease risk not be distorted by the effects of other factors; and 3) *comparable accuracy,* that any errors in measurement of exposure be nondifferential between cases and controls. These principles, if adhered to in a study, can reduce selection, confounding, and information bias, respectively. The principles, however, are constrained by an additional efficiency principle regarding resources and time. Most problems and controversies in control selection reflect trade-offs among these four principles. *Am J Epidemiol* 1992;135:1019–28.

bias (epidemiology); epidemiologic methods; prospective studies; retrospective studies

The purpose of this series of papers is to present a theoretical framework for control selection in case-control studies and show how practical issues can be addressed within this framework. We discuss controversial areas of control selection using the framework and attempt to offer advice when there is relevant empiric information or experience to guide us. For the most part, issues of analysis will not be addressed in the review.

In this paper, the first of three, the principles underlying control selection are developed. These principles also apply to the design of cohort studies, as would be expected since the case-control design is simply an efficient sampling technique to measure exposure-disease associations in a cohort or study base. In theory, every case-control study takes place within a cohort, although in practice it can be difficult to characterize the cohort or study base. The identification of the appropriate study base from which to select controls is the primary challenge in the design of case-control studies.

In our second paper (1), we apply the principles presented in this paper to the selection of control groups used in case-control studies, including population controls, hospital controls, medical practice controls, friend controls, and relative controls. We also discuss the use of proxy respondents and deceased controls.

In the third paper of the series (2), we focus on issues encountered after a particular control group has been selected. Some of

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Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

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the areas discussed are matching, ratio of controls to cases, number of control groups, nested case-control studies, two-stage sampling designs, and issues relating to information bias such as contemporaneity of cases and controls.

We do not intend the principles described and illustrated in these papers to be used for determining whether a study is up to standard. Perfect adherence to a principle can be as difficult to achieve as perfect experimental conditions in a laboratory. Sometimes, one principle can conflict with another. Indeed, tolerating a minor violation of a principle is often the only way to study a particular exposure-disease association. Such a study can still provide valuable information, particularly when the impact of the violation can be evaluated or bounded.

COMPARABILITY PRINCIPLES

Three basic tenets of comparability underlie attempts to minimize bias in control selection. These are the principles of *study base, deconfounding,* and *comparable accuracy.*

Study base principle. Cases and controls should be "representative of the same base experience" (3, p. 545). The base is the set of persons or person-time, depending on the context, in which diseased subjects become cases. The base can also be thought of as the members of the underlying cohort or source population for the cases during the time periods when they are eligible to become cases (4). Typically in chronic disease epidemiology, membership in the base is dynamic in the sense that a subject may be in the base at certain times and out of it at other times. The simplest way to satisfy this principle is to choose a random sample of individuals from the same source as the cases; if comparability of time, e.g., age or calendar time, is essential, the sampling should be from the members of the base at risk at the same time as the case's diagnosis. Immigration and emigration from the catchment area affect whether someone is in the study base at a particular time; a subject is in the base only when he or she would be enrolled as a case if diagnosed with disease at the time. A useful paradigm with an explicitly defined study base is the "nested case-control study" (2, 5–7) where controls are selected randomly from the "risk set," the subjects in the cohort who are at risk at the time of diagnosis of each case.

Deconfounding principle. Confounding should not be allowed to distort the estimation of effect. Confounders that are measured can be controlled in the analysis. Unknown or unmeasured confounders should have as *little variability* as possible. Since this variability is measured conditionally on the levels of other variables being studied, the use of stratification or matching can, in effect, reduce or eliminate the variability of the confounder. For example, using siblings as matched controls in a study of environmental risk factors may result in less variability for genetic risk factors within the matched set and, hence, less confounding than using controls who are not siblings. The extent of bias from an unmeasured or uncontrolled confounder depends on the strengths of the associations between it and the study exposure and disease risk.

Comparable accuracy principle. The degree of accuracy in measuring the exposure of interest for the cases should be equivalent to the degree of accuracy for the controls, unless the effect of the inaccuracy can be controlled in the analysis.

We believe that the results of a case-control study become more credible to the extent that these three principles are met. Strict adherence to the principles of comparability outlined here ensures that an apparent effect is not due to 1) differences in the way cases and controls are selected from the base; 2) distortion of the effect by other, unmeasured, risk factors related to exposure; or 3) differences in the accuracy of the information obtained from cases and controls. The aim of the principles is to reduce or eliminate, respectively, selection bias, confounding bias, and information bias.

However, there is an additional practical principle that constrains attempts at comparability.

Efficiency principle. The study should be

implemented so as to learn as much as possible about the questions being investigated for a fixed expenditure of time and resources.

Study base principle

The importance of defining the study base in epidemiologic investigations has been recognized for a long time (8). Miettinen (3, 9, 10) distinguishes between a primary base and a secondary base. In a study with a primary base, the base is defined by the population experience that the investigator wishes to target, with the cases being subjects within the base who develop the disease. A population-based case-control study is an example of a study that uses a primary base, where population experience is defined geographically and temporally. However, particularly when ascertainment of all cases in a primary base is difficult or impractical, it may be preferable to use a secondary base, where the cases are defined before the base is identified. In this approach, the base is defined as the source of the cases, and controls are individuals who would have become study cases if they had developed disease during the time of the investigation (9). For example, in a hospital-based study, the cases might be all patients diagnosed with the study disease at one hospital; the individuals contributing to the (secondary) base would be all subjects who would be diagnosed at that hospital had they developed the study disease.

Thus, while the major challenge with a primary base is complete case identification in the base, the major challenge with a secondary base is definition of the study base. Sometimes it may not be possible to resolve definitively whether and when a particular person is in the secondary base. Whether the base is primary or secondary, the critical point is that the *base* and the *cases* need to be defined so that the cases consist, exclusively, of all (or a random sample of) subjects experiencing the study outcome in the base, and that the controls are derived from the base and can be used to estimate the exposure distribution in that base.

The fundamental trade-off between a primary base and a secondary base is that it is easier to sample for controls from a well-defined primary base than from a secondary base, where it may not be obvious whether or not an individual is a member of the base; on the other hand, case ascertainment is complete by definition in a secondary base but can be problematic with a primary base. Selection factors affecting which cases are ascertained and included in the study or the accuracy of identification of the base can cause bias in either a primary or secondary base setting. Identification of a setting where no selection factor operates on the cases or on the sample of the base is often a major challenge in case-control studies, as in the three following examples.

Referral hospital. In a study where the cases are subjects who were treated at a referral hospital, the (secondary) base consists of those individuals who would have been treated at that hospital had they been diagnosed with the study disease. The difficulty, of course, is in identifying exactly who would have been referred to that hospital had they developed the study disease.

Underascertainment of cases. Incomplete case identification can be substantial for diseases with mild symptoms and for those that do not require medical attention; hence, there could be a spurious association with variables related to utilization of medical services in a study using self-identified cases. A primary base would be unworkable in a study of male infertility, since infertile men will not become cases unless they are attempting to have children *and* seek medical help (11). A secondary base approach would restrict controls to men who, if they were infertile, would seek help, just as all the cases have. Failure to restrict the secondary base accordingly, and thereby failure to exclude controls who would not seek medical advice, could result in a misleading association with correlates of seeking medical attention.

Temporal differences. When cases are diagnosed long before controls are selected, it can be difficult to reconstruct the base that was contemporaneous with disease incidence.

Problems in identifying the base sometimes make it very difficult to choose the study base that would be the most scientifically informative. This is particularly true when becoming a case is contingent on a previous condition, as in the following examples.

Screening. A simple and powerful approach to evaluate the efficacy of screening for breast cancer would compare mortality in screened and unscreened women in a base of women who had developed early stage breast cancer (12, 13). However, it would be difficult for a case-control study to use this approach because of the problem in identifying members of the base for the denominator of the mortality rate, particularly in unscreened women. Thus, the standard but less efficient approach for case-control studies is to choose controls from a broader base consisting of women at risk for breast cancer (14, 15).

Prenatal survival. Exposure to human teratogens may affect prenatal survival and, thus, the opportunity to observe a congenital malformation. This can lead to misleading estimates of effects in case-control studies using livebirths as controls (16).

Spontaneous abortion. The ideal base for a case-control study of previous therapeutic abortion on risk of ectopic (tubal) pregnancy would be women who conceive. However, identification of women with intrauterine pregnancies who spontaneously abort would be incomplete, since the women themselves may never become aware of the conception (17). If women who had a previous therapeutic abortion are at extra risk for unnoticed spontaneous abortions, the proportion of missed intrauterine conceptions will differ by exposure, and use of this base could be prone to bias. If the base is women who are trying to conceive, it would be difficult to separate the effects of factors related to conception itself, such as contraceptive use, from those leading to ectopic pregnancy in women who do conceive.

Acquired immunodeficiency syndrome (AIDS) after human immunodeficiency virus (HIV) infection. In studies of progression to AIDS after HIV infection, the time of seroconversion is typically unknown. Thus, defining a base of HIV-positive subjects is difficult (18).

Sampling from the study base. In simple random sampling, controls are selected randomly from the base. Therefore, each eligible individual has the same probability of selection as a control, and the sampling is independent; i.e., the presence of a specific subject in the sample does not make the presence of any other more or less likely. In stratified sampling and frequency matching, the base is subdivided into strata determined by factors such as age and sex, and the sampling fraction is allowed to vary across strata. More complex sampling schemes, such as two-stage (19–21) and cluster sampling plans (22), can be used as long as the joint distribution of the exposures of interest in the base can be estimated without bias; generally these require knowledge of the relative sampling fractions and a nonstandard analysis.

Selection bias can be introduced when the sampling fractions for individuals in the base depend on an exposure variable in an unknown way. This dependence is typically indirect and inadvertent, such as when control selection by telephone tends to exclude poor people without phones. However, an analysis of the effects of *other* variables will be unbiased when the source of the dependence can be identified and handled in the analysis as if it were a confounder (23, 24). Unfortunately, recognizing the presence of selection bias can be quite difficult, and this solution requires identification of the selection factor. As with confounding, there is no bias when the selection probability depends on a factor that is unrelated to the exposure.

The study base principle entails the requirement of representativeness of the base but not necessarily of the general population. Representativeness of the general population is crucial in estimating the prevalence of disease, the attributable risk, or the distribution of a variable in a population based on a sample (25). But representativeness, per se, is not needed in analytical studies of the relation between an exposure and disease (9, 25). An association found in any

subpopulation may be of interest in itself; in a representative population, an association that is limited to one group may be obscured because the effect is weaker in other groups or because of differences in the distribution of the exposure. On the other hand, detection of variability of the strength of association (effect modification) can be missed if the study base is narrowly defined. If there is reason to believe that an effect is strongest in one particular subgroup, exclusion of other subgroups might be the best strategy for demonstrating that effect; thus, a study of the effect of a possible risk factor for myocardial infarction might restrict the base to subjects who had a previous one. The power of a study targeted at a subgroup can even be greater than the power of a study of the entire population, despite the reduced number of subjects, when the effect is larger in the subgroup (26). Other grounds for exclusions that may increase statistical or economic efficiency include 1) inconvenience (e.g., subjects likely to be too hard to reach); 2) anticipated low or inaccurate responses (e.g., exclusion of subjects who do not speak the language of the interview); 3) lack of variability in the exposure (27, 28) (e.g., a study of the effects of oral contraceptives on subsequent risk of breast cancer should probably exclude women who were past reproductive age when oral contraceptives were introduced into common use); or 4) subjects at increased risk of disease due to other causes (e.g., subjects at high risk for leukemia as a result of chemotherapy for Hodgkin's disease), because cases from the treated group are likely to be attributable to the treatment and therefore may not contribute much to the understanding of other risk factors.

An exclusion rule that applies equally to cases and controls is valid (29) because it simply refines the scope of the study base. One that applies to one but not the other violates the study base principle. For example, a study design that excludes potential controls who had changed their residence between the time of diagnosis of the matched case and the time of selection but places no analogous restriction on the residential mobility of the cases (30) violates the study base principle, and the estimate of effect for an exposure associated with such residential mobility could be biased (30).

Nonrandom selection from the study base. In theory, choosing the controls to be a random sample from the base ensures that the controls are representative of the base. When random selection is not practical, as when identification of the base is difficult, a nonrandom subset can be selected if a representativeness assumption regarding the study exposure is met: that the distributions of the exposures of interest are the same in the control series as in a random sample of the (secondary) base (3, 9).

For example, hospital controls are a nonrandom subset of the study base rather than a random sample from the study base; the validity of a hospital-based study rests on the (perhaps tenuous) assumption that the distribution of exposure among the chosen hospital controls is the same as in the base itself or differs because of measurable factors (1, 9). This assumption is reasonable when the following two conditions apply.

Identical catchment populations. Subjects who are admitted to the hospital for the case disease would have been admitted to the same hospital for the control disease, and, conversely, subjects who are admitted for the control disease would have been admitted for the case disease. Thus, determinants of hospitalization and the choice of hospital must be considered carefully in studies with hospital controls.

Exposure independent of admission. The exposure is unrelated to the reason for admission of the control.

In the male infertility example considered above, a control series consisting of men whose wives have been identified as infertile at an infertility clinic (11) would be a nonrandom sample of the appropriate secondary base that would have the same determinants of seeking medical attention as the cases. However, it could introduce selection bias for male correlates of causes of female infertility, such as sexually transmitted disease in the husbands of women with pelvic inflammatory disease (11).

Use of deterministic (nonrandom) schemes for control selection, such as choosing the case's best friend or neighbors, can avoid the need for a representativeness assumption for exposure if 1) the base is divided into nonoverlapping strata and 2) all members of the base in the stratum that includes the case are selected as controls (31). Thus, instead of random selection, a 100 percent sample (31) from a (typically very small) stratum of the study base is chosen. (Strictly speaking, this would not be a case-control study, since no sampling is involved; it is a cohort study where all the strata with no cases can be ignored.) Together, these two requirements imply reciprocity (31). If A is included as a control for B, then B would have to have been included as a control for A, if A had become the case; this is exactly what is done in a cohort study. In practice, selection of a subset of the stratum deterministically would not produce bias, unless the selection were related to exposure (31). But the possibility of bias does exist with any scheme that allows control selection to be determined by the case or the case's physician.

Controls from outside the study base. A proxy control series from outside the base can be used as an "indirect way to probe the base" (9, p. 82), if the representativeness of exposure assumption is met. For example, in a study where blood group is the exposure of interest, use of females as controls when the actual base consists only of males would be theoretically acceptable, under the assumption that blood group distribution does not vary by sex (32). (Of course, published rates on the distribution of blood group might obviate the need for any controls.) In more common situations, it may not be known whether the representativeness assumption actually holds for a given exposure. The validity of the assumption for each exposure studied needs to be assessed individually.

Controls currently living in a neighborhood who are chosen to match cases diagnosed several years earlier should be excluded since they are outside the study base. Excluding controls who have moved into the neighborhood since diagnosis of the case reduces the problem but does not solve it, since people who moved out of the neighborhood will still be missed.

Deconfounding principle

While the study base principle clarifies who can be entered into the study, the deconfounding principle addresses the problem created when the study exposure is associated with other risk factors. The principle applies to control selection with respect to unmeasured confounders, since measured confounders can be handled in the analysis.

Confounding can bias the results of any epidemiologic study. Complete assurance of control of confounding is achieved (in theory) by eliminating the variability in the confounding factor. Thus, if the study base consists entirely of males, there can be no confounding by sex. Some control for confounding by genotype might be achieved by the use of relatives of the cases as matched controls. Similarly, controls are sometimes selected to match the neighborhood of the case in order to control for unknown risk factors relating to socioeconomic and ethnic variables or, particularly, access to medical care, which is difficult to control for otherwise. However, controlling for the confounding effects of a risk or selection factor by matching on its correlate or proxy does not eliminate confounding bias (33).

This principle, however, can conflict with the efficiency principle. Selecting controls to have the same values of confounders as cases results in controls who are likely to be more similar to cases with respect to exposure (34); i.e., restricting the variability of the confounding variable will also reduce the conditional variability of the exposure of interest when the exposure and confounder are highly correlated. Studying a population that is almost uniform with respect to unmeasured confounders but also nearly uniform on the exposures of interest is not an effective strategy (35); it is a form of overmatching (in the sense that subjects are effectively, if not deliberately, "matched" on the exposure) that can reduce the precision of esti-

mates of effect without affecting validity (2, 35, 36). Generally, matching on variables that are not risk factors is also overmatching, since the matching may reduce the variability in the exposure of interest without controlling for any confounding (2, 36, 37). On the other hand, reduced precision might be inevitable in the presence of confounding, since it can be a consequence of control for confounding in the design and analysis.

Comparable accuracy principle

Error in the measurement of variables is unavoidable in epidemiologic studies, particularly when information is obtained retrospectively. When the bias due to measurement error can be removed in the analysis, as when the relations between the observed and true exposure measurements are known for cases and controls or an appropriate validation study can be used (38, 39), this principle need not influence control selection. For example, measurements made using both "gold standard" and error-prone methods on some study subjects can allow unbiased estimation of the effects of a poorly measured exposure (38–40). Even when cases' information was obtained from one clinic and that of controls from another, subjects for whom information from both clinics was available can be used as a validation study and can yield unbiased estimates under the assumption that being interviewed in both clinics is unrelated to the responses given (41).

When no correction is possible in the analysis, the comparable accuracy principle calls for all measurement errors that result in distortion of the estimates of effect to be nondifferential; i.e., the error distributions should be the same for cases and controls, as seems reasonable when the mechanisms generating the errors for both groups are the same and are not influenced by disease status. In control selection, one needs to consider the accuracy of information that can be obtained from the controls, e.g., whether recollection of past exposures is better if hospital controls are used rather than healthy population controls.

With nondifferential errors, the bias is typically (but not always) in a predictable direction (toward lack of association) and, unless the measurement is so bad as to be *negatively* correlated with the truth, seldom reverses the direction of the association (42, 43). On the other hand, the effect of differential measurement error on estimates of association is usually unpredictable.

Thus, adherence to the comparable accuracy principle does not eliminate its corresponding bias—information bias. Only elimination of errors (or correction for bias in the analysis using additional information or assumptions (39)) can remove bias entirely. Adherence to this principle may not even reduce bias, as in the hypothetical example presented in table 1. The true odds ratio is 6. When the exposure of the cases is misclassified with specificity and sensitivity both equal to 80 percent, the observed odds ratio from controls with 100 percent specificity and sensitivity will be 3.2 (table 2), which is *less* biased than the 2.7 that would be observed from controls with 80 percent sensitivity and specificity (table 3). So why make this a principle if adhering to it can increase bias? The rationale is to ensure that a positive finding cannot be induced simply by differences in the accuracy of information about cases and controls. While recent work (42, 44) indicates that equal accuracy does not guarantee bias toward the null, a reversal of the *direction* of the association seems unlikely.

Differential errors can be hard to avoid in case-control studies in which exposure information is obtained from interviews with the subjects. Even when interviewers can be blinded to the disease status of a subject, the case generally knows the diagnosis at the time of interview. The disease itself and hospitalization and treatment of the disease may change actual habits as well as perception of current and past habits.

The comparable accuracy principle should not be taken to mean that creating strata within which the errors are equal will be helpful. In fact, stratification designed to achieve nondifferential error within strata can increase bias (45). Thus, creating a stra-

TABLE 1. Hypothetical example: exposure classified correctly

Measured exposure	No. of cases	No. of controls	Observed odds ratio
Present	800	400	6.00
Absent	200	600	1.00
Total	1,000	1,000	

TABLE 2. Hypothetical example: exposure misclassified for cases only*

Measured exposure	No. of cases	No. of controls	Observed odds ratio
Present	680	400	3.19
Absent	320	600	1.00
Total	1,000	1,000	

* Specificity and sensitivity are 80% for cases and 100% for controls.

TABLE 3. Hypothetical example: exposure misclassified for cases and controls*

Measured exposure	No of cases	No. of controls	Observed odds ratio
Present	680	440	2.70
Absent	320	560	1.00
Total	1,000	1,000	

* Specificity and sensitivity are 80% for both cases and controls.

tum of direct-interview cases and controls and another for proxy-interview cases and controls does not necessarily reduce bias. Examining the interaction, however, may be helpful since the bias will be greatest in the strata with poorest classification (46).

Comparable opportunity for exposure?

Since the focus of a study should be on whether the risk of disease is related to the level of exposure actually received, cases and controls do not need to have equal *opportunity* to be exposed (3, 25, 47). Thus, in a study of cancer treatment on subsequent risk of leukemia, a case who received a treatment could be matched to a control whose physician never prescribed that treatment. Of course, when it is easy to identify subsets of subjects without exposure opportunity, they can be excluded on efficiency grounds. For example, in a study of oral contraceptive use and risk of myocardial infarction, it would be foolish to include males since sex is a confounder and since there is no variability in exposure in the male stratum.

Comment

The use of the term "comparability" in the principles delineated above does not necessarily entail equality. Instead, it means that the study results should be as valid as those that would be obtained under equality. Therefore, our framework of comparability principles, under certain assumptions, allows controls to be selected from outside the study base (1, 9); allows external information to be used to correct for an unmeasured confounder (48); and allows for the use of separate validation studies of the exposure for cases and controls to correct for unequal accuracy (49, 50). Thus, violations of "equality" do not always violate the comparability principles.

EFFICIENCY PRINCIPLE

Savings in money and time are two motivations for choosing a case-control design. These factors also affect decisions about other aspects of design, such as the ratio of controls to cases, whether and on which variables to match (3), the source of controls (2), and how they will be recruited. The efficiency principle calls for consideration of costs as well as validity in selection of controls. Statistical efficiency refers to the amount of information obtained per subject; more broadly, efficiency encompasses the time and energy needed to complete the study. For example, even when matching can improve statistical efficiency, the payoff may not be worth the extra effort needed to recruit subjects (51).

We have already seen how the efficiency principle can conflict with the deconfounding principle. When control of confounding is essential for bias reduction, the efficiency principle must be subordinated. However, the principle is important in choosing

among control selection strategies, for example, whether to match or to control in the analysis for each potential confounder (3, 52). Precision of the estimates of effect of a given exposure depends on the variance of the exposure, conditional on the matching factors and the other variables that are adjusted for in the model, regardless of whether or not they are confounders. When a second risk factor is strongly related to exposure and there is a need to control for its confounding effect, any strategy for controlling the effects of the confounder will reduce the conditional variance of the exposure and can reduce efficiency substantially. In a matched-pairs study, this phenomenon is manifested as a reduction in the number of discordant pairs.

SUMMARY

In this paper, we have presented and described what we believe are the major principles underlying control selection in case-control studies. The principles of study base, deconfounding, and comparable accuracy all address the issue of comparability between cases and controls. Perhaps the key concept is that of the study base. If the study base is identified correctly and if controls are chosen from it properly, the exposure experience of the controls should be representative of the individuals who compose the base. At times, however, the pragmatic principle of efficiency limits the investigator's ability to achieve comparability, reflecting the tension between efficiency and comparability inherent in epidemiologic research.

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