



## Selection of Controls in Case-Control Studies

### III. Design Options

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Several design options available in the planning stage of case-control studies are examined. Topics covered include matching, control/case ratio, choice of nested case-control or case-cohort design, two-stage sampling, and other methods that can be used for control selection. The effect of potential problems in obtaining comparable accuracy of exposure is also examined. A discussion of the difficulty in meeting the principles of study base, deconfounding, and comparable accuracy (S. Wacholder et al. *Am J Epidemiol* 1992;135:1019-28) in a single study completes this series of papers. *Am J Epidemiol* 1992;135:1042-50.

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In our previous papers, we presented basic principles of control selection (1) and discussed different kinds of control groups (2). This paper addresses some of the other decisions involved in control selection, of which the major themes are issues of stratification and efficiency and the effects of time. The principles of deconfounding and efficiency are the main concerns in considering some special sampling techniques, including matching, cluster sampling, and two-stage sampling. Efficiency is paramount in our discussion of the control/case ratio, replacement of controls, and using a single control group for multiple case series. Consideration of the time of membership in the study base is crucial in the discussion of nested case-control, case-cohort, and case-base designs.

### MATCHING

Random sampling from the study base, where controls are chosen independently of characteristics of the cases, is the simplest strategy for control selection. Matching is an option that sometimes can improve efficiency in the estimation of the effect of exposure by protecting against the situation where the distributions of a confounder are substantially different in cases and controls (3). However, the improvement is typically small (3), except for strong confounders. There are several other reasons to match.

*Control of unmeasured confounders.* Identifiable but not quantifiable variables with many categories, such as neighborhood or telephone exchange, can serve as proxies for environmental or socioeconomic confounding factors that are difficult to measure (4). Matching on such a variable may balance cases and controls with respect to unknown confounders. Use of the cases' identical twins as controls is an extreme form of this kind of matching.

*Power.* Matching can ensure that there are sufficient controls to estimate an effect in a particular subgroup or to identify an interaction (5). For example, matching on smoking instead of choosing controls indepen-

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dently of smoking could make it easier to find an interaction between the exposure and smoking if smoking had a large effect on risk and was rare in the population, by ensuring a sufficient number of smoking controls. The two-stage design, a generalization of matching discussed below, can also be used to achieve this goal.

**Time comparability.** In unmatched studies, it can be difficult to achieve time comparability between cases and controls for exposures that vary over time. Matching on time-related variables provides a simple reference point for variables based on these exposures.

**Feasibility.** Matching may be the most feasible method of obtaining controls. For example, when a case is defined as a perinatal death, the next live birth can be chosen as a control (6). Use of a random sample of live births from a computer tape of births would delay the interview of controls, leading to possible violation of the comparable accuracy principle as well as possibly increasing nonresponse.

**Completeness of control for confounding.** Perfect matching, followed by a matched analysis, results in complete control for a continuous confounder under a multiplicative model of the joint effects. Alternative strategies, such as regression adjustment for the confounder, can result in bias if its effect is misspecified, e.g., if linearity is wrongly assumed. Categorization may leave some residual confounding, but this is of little importance unless there is a substantial gradient in risk within strata (7).

On the other hand, matching has several disadvantages.

**Cost.** Matching can add cost and complexity to a sampling scheme by requiring extra effort to recruit controls (5).

**Exclusion of cases.** Matching can result in the exclusion of cases when no matched control can be found (8, 9), particularly when matching on several variables.

**Longer study duration.** Matching will slow down a study when control selection must wait for cases to be identified and for complex matching variables to be obtained for cases and potential controls.

**Reduced flexibility in analysis.** Stratified or matched analyses can be considered, even when there was no matching or stratification in the design. But matching at the design stage reduces the investigator's flexibility during the analysis. For example, overmatching that occurs in the design cannot be corrected in the analysis. Furthermore, matching usually precludes the ability to directly estimate or test the effect of the matching variable as a risk factor and the fitting of a nonmultiplicative risk model involving the matching variable and the exposure (5). However, in the multiplicative model, it is possible to fit interactions with the matching variables. Below, we discuss a method that can be used to estimate the effect of matching variables and to fit nonmultiplicative models, as long as the values of the matching variables are retained for subjects who are identified for the study but excluded because of the matching criteria.

### Variables on which to match

Matching reduces the possibility of severe loss of efficiency due to a major discrepancy in the empiric distributions of a strong risk factor between cases and controls. Matching should be considered only for risk factors whose confounding effects need to be controlled for but that are not of scientific interest as independent risk factors in the study. Matching on variables that are unrelated to risk of disease is pointless; it can only reduce a study's efficiency (4). Age, sex, and race are often used as matching variables because they are usually strong confounders and because their effects are usually well-known from descriptive epidemiology (10).

### Forms of matching and stratification

One form of matching is individual matching where a selected control must have exactly or approximately the same value of the matching factor as the corresponding case. Frequency matching or quota matching results in equal distributions of the matching factors in the cases and the selected controls. For these forms of matching, the control cannot be recruited until the case

is identified. Approximate frequency matching can begin immediately; it uses the anticipated, rather than the actual, case distribution and thereby allows the control selection process to operate independently of the case selection process. However, if some of the matching strata are extremely small, approximate frequency matching can be wasteful (11), since the control/case ratio will vary. Probability matching (12) defines strata based on the matching variables. A random mechanism is used to select eligible subjects, with the probabilities of inclusion for each subject determined by the investigators based on the odds ratios for disease associated with the subject's stratum. This approach does not require knowledge of the exposure distribution in the cases and allows for a more informative analysis (13), as discussed below.

### Overmatching

We use the term "overmatching" to refer to matching that is counterproductive, by either causing bias or reducing efficiency (14). Matching on an intermediate variable in a causal pathway between exposure and disease can bias a point estimate downward (7), since the exposure's effect on disease, adjusting for (conditional on) intermediate variable, is less than the unadjusted effect. For example, matching on presence of endometrial hyperplasia in a study of the relation between estrogen and endometrial cancer is overmatching leading to bias (14, 15). Why? The parameter we seek to estimate is a measure of the impact on disease risk of a change in the level of exposure. Matching on endometrial hyperplasia effectively restricts the comparisons of exposure to subjects concordant on presence of hyperplasia; this does not allow the full impact of estrogen on cancer risk to be assessed, since presence of hyperplasia itself is strongly influenced by estrogen use. Matching on a factor that is a surrogate for or a consequence of disease or matching on a correlate of an imperfectly measured exposure (15) can also lead to overmatching and bias.

The other main form of overmatching can reduce the efficiency of a study by restricting the variability of an exposure that is correlated with the exposure under study (16). This form of "overmatching" can occur even when matching per se was not used in the selection of controls, as when an overly homogeneous base is used for the study. Miettinen and Cook (17) note that the use of a variable indicating the presence of yellow fingers, presumed to be related to smoking but unrelated to risk of lung cancer (after controlling for smoking), would be an example of overmatching. There is much less variability in smoking, conditional on presence of yellow finger, than unconditionally; since having yellow fingers is not a risk factor, it does not affect the point estimate but does reduce efficiency.

### RATIO OF CONTROLS TO CASES

Determination of the number of controls to be selected is another important design decision. It is useful to consider the ratio of controls to cases. There is usually little marginal increase in precision from increasing the ratio of controls to cases beyond four (18), except when the effect of exposure is large (19). In general, the best way to increase precision in a case-control study is to increase the number of cases by widening the base geographically or temporally rather than by increasing the number of controls, because the marginal increase in precision from an additional case is greater than from an additional control (assuming there are already more controls than cases in the study). In matched and stratified studies, the most efficient allocation of a fixed number of controls into strata is usually one that sets the ratio of controls to cases to be approximately equal (4).

### REPLACEMENT OF CONTROLS

Controls who refuse to participate in a study should sometimes be replaced on efficiency grounds, as when replacement can prevent wasting a case who otherwise would have no matched control. However, subjects who refuse to participate in case-control

studies may have a different exposure distribution from those who do participate. Replacing refusers will not increase the validity of a study, since refusers will still be excluded.

The situation is different when information on the primary exposure, perhaps obtained from medical records, is available, but some information on a confounder (perhaps obtained by interview) is not. Then, the impact of excluding the control is probably more serious than that of the missing information regarding the confounder, and the control should not be replaced. When controls are replaced, reported response rates should reflect the actual percentage of eligible subjects who refuse to participate.

### ONE CONTROL GROUP FOR SEVERAL DISEASES

Use of a single control group for more than one case series can lead to savings of money and effort (20–22). Systematic errors in assembling the control series would presumably affect each individual series equally, but the availability of a larger number of controls would increase the precision of point estimates. While the use of the same controls for different diseases induces some dependence in the estimates of effect for different diseases (23), no special analysis is required, except when *comparing* the risk factors for the various diseases (24). In fact, this strategy can have another advantage; i.e., it can help to calibrate the control series by identifying exposures having stronger (or weaker) than expected associations with several diseases, resulting from special characteristics of the control group. The fact that the same control series was used for several diseases should be discussed in the reports from the studies, so that readers can judge whether findings resulted from the unique characteristics of the control series.

### NESTED CASE-CONTROL AND CASE-COHORT STUDIES

#### Controls in nested case-control studies

A particular form of case-control study that, in fact, does have a roster of subjects available for control selection is the nested

case-control study or case-control within a cohort study (19, 25, 26). This design paradigmatically satisfies the study base principle since the base is the cohort as it moves through time. Typically, for each case, a set of controls is selected from subjects at risk at the time of disease occurrence of the case. The matching in the design allows for tight control of the confounding effects of time in the analysis. Thus, this design is useful when close matching on time is required, as in studies of the incidence of a rare disease, such as cancer.

Just as in the calculation of person-years in a cohort study, membership in the base depends on time (1, 4). A subject is in the base while under follow-up, i.e., when the subject would be enrolled as a case in the study upon development of disease. So a subject cannot be selected before entry to the cohort, after loss to follow-up, after death, or after becoming a case (unless subsequent occurrences of disease would make the subject a case again, as, perhaps, in a case-control study of ear infection in young children). In nested case-control studies with age matching, a subject chosen to be a control for a case at a given age should not be excluded from the set of controls because of subsequent development of disease. Thus, a control who subsequently develops disease can also serve as a case (27).

If the times when a subject is actually in the base are available with the roster, selection of controls from the base is simply a matter of sampling. Sampling can be stratified according to factors available for all members of the roster at the time of entry to the cohort. Control selections at the various times of diagnosis of the cases should be mutually independent and should not be influenced by future disease status of the subject or by use as a control for another case (27–29); thus, the same individual can serve as a control for more than one case (27, 28). These rules mirror the approach in the analysis of the proportional hazards model with time-to-event data, where virtually all cases served previously as “controls” and virtually all controls are used more than once (30).

## Controls in case-cohort studies

The case-cohort design is an alternative to the nested case-control design with a simpler sampling scheme but a more complex analysis (24, 31, 32). In its simplest form, a subcohort or random sample from all members of the cohort is selected to be the source of all controls. Adjustment for the confounding effects of time is achieved in the analysis, by comparing the exposures of each case to those of a set of controls consisting of all members of the subcohort who were at risk at the time of diagnosis of the case. We think of a case-cohort study as a variant of a nested case-control study where controls are selected without matching on time (24, 32). The following several advantages of the case-cohort study are due to the use of "unmatched" controls.

**External comparisons.** It is easy to obtain estimates comparing the risk in the cohort with that of an external population (32). For example, the case-cohort design has been used to compare the risk of breast cancer in a cohort of women who received noncontraceptive estrogen treatment with the risk for other women living in the same region (33).

**Ease of selection.** Sampling of controls can begin before the roster of subjects and the list of cases have been completely identified. As soon as each member of the roster is identified, randomization can be used immediately to determine inclusion in the subcohort (24).

**Multiple diseases.** Since there is no time matching of cases to controls, a single subcohort can serve as a source of controls for multiple disease types (20, 24, 31).

**Primary time scale.** Unlike the nested case-control design, the case-cohort design does not require a decision about the primary time scale until the analysis stage (24). Thus, for example, all analyses of a nested case-control design with age matching control for age in a study of a treatment-related second cancer, while controlling for age alone or time since first cancer alone is possible in a case-cohort design (24).

It is worth noting that for either design, there is a possibility of differential misclas-

sification if information about cases is obtained before that about controls (24, 34). Other practical considerations have recently been discussed (24). The statistical efficiency of the nested case-control design is often slightly higher than that for the case-cohort design when a single disease is being studied (34), except when there are small amounts of censoring and late entry (31). More refined approximations of the efficiency of nested case-control, case-cohort, and related designs can be obtained when the cohort has been assembled, i.e., when the cases and their event times, as well as the interval at risk for all subjects, are known, but exposure information is not yet available (29).

## CASE-BASE STUDIES

Controls are sampled for the case-base design (20, 35) in the same way as the subcohort is selected in the case-cohort design; it differs from the standard case-control design only in that control subjects are sampled from the base, regardless of their disease status. The case-base design can be thought of as a variant of the case-control design that allows estimation of the risk ratio, because the exposure odds in the base (not just in the cases and noncases as in the case-control study) can be estimated.

## ARE CASES ELIGIBLE TO BE CONTROLS?

We have noted several situations, including the nested case-control, case-cohort, and case-base designs, where subjects who qualify as cases can be included as controls. In general, a future case is in the base until his or her disease is diagnosed and, therefore, should not be excluded from the sampling of controls for a case diagnosed at an earlier time.

## TWO-STAGE SAMPLING

Recently, some two-stage sampling designs have been proposed as economical alternatives to standard case-control studies (13, 36–38). The savings accrue from not

requiring all exposure and confounder measurements for all subjects; sometimes a substantial reduction in expense can be achieved with little loss in statistical efficiency compared with the study with information on all subjects. In these designs, first-stage variables, i.e., exposure or confounder measurements that are relatively easy to obtain, are gathered for all subjects. The remaining, second-stage variables are obtained on only a subset of subjects, with the sampling fractions depending on disease status and the first-stage variables. The first-stage variable might be an exposure that would be obtained from a record, while the second-stage variable might be a confounder, such as smoking, which required a personal interview. Alternatively, the first-stage variable might be a confounder and the second-stage variable might be the exposure (13). This approach could be helpful, for example, in a study of the effect of residential radon exposure on lung cancer risk (12, 13). First-stage variables might include age and smoking. Nonsmoking cases and smoking controls will have higher probabilities of selection for the part of the study requiring expensive fieldwork for residential radon measurements. The power for assessing a radon-smoking interaction will be enhanced, compared with a matched or an unmatched design, by forcing the proportions of cases and controls in the smoking and nonsmoking strata to be near 0.5 (13, 37). A two-stage design can also be considered where the second-stage variable is a more refined version of the first-stage variable. For example, the probability of obtaining a detailed occupational history can be allowed to vary, depending on the subject's current job title.

The two-stage design proposed originally uses random samples of the subjects in each cell of the cross-classification of the first-stage variable and disease to determine which subjects to include for second-stage measurements (36–38). An alternative randomized recruitment approach uses randomization, with the probabilities, which are dependent on the approximate odds ratios (determined a priori) associated with the

subject's level of the first-stage variable (12, 13).

A two-stage approach can be more efficient than matching for estimating the main effects of exposures and interactions (37) and allows for estimation of the effects of first-stage variables, in contrast to standard matched studies (13). However, any matched study can be viewed and analyzed as a special case of the two-stage study, if information on the matching factor is retained for all eligible subjects, including those excluded because they did not satisfy the matching criteria. This allows estimation of the main effect of the matching variable as well as the fitting of nonmultiplicative models.

### CLUSTER SAMPLING

In cluster sampling, controls are selected in groups, to reduce expense, rather than independently (39). Choosing several controls who live in the same household or near one another can be economical when less effort is needed to include an additional member of the cluster than to include an independent control. Thus, cluster sampling might be appropriate for population control groups when blood samples are needed. The clusters themselves must be selected so that each member of the base population has an equal chance of being selected (1), and an analysis taking clustering into account must be used (39).

### AVOIDING INFORMATION BIAS

A widespread concern about interview-based case-control studies is that cases recall previous exposures differently than do controls. Cases may spend time thinking about possible reasons for their illness, may search their memories for past exposure or even exaggerate or fabricate exposure, or may try to deny any responsibility for the disease. Therefore, some suggest using control groups of diseased subjects in the name of equal accuracy (40). While accuracy of information and how that accuracy differs between cases and controls are considerations

in the choice of control group, one must also be concerned about choosing controls with conditions possibly related to exposure (2, 41, 42).

Unfortunately, the literature on the question of differential recall for cases and controls is sparse, and the interpretation of the published studies is difficult (43). Most recent empiric research suggests that differential accuracy does not cause serious distortion (40, 44–48). Empiric work on the accuracy of recall for a broader range of variables would help in the decision of what is the appropriate source of controls in situations when there is a suspicion of differential accuracy.

In many studies, information about time-dependent exposures (variables whose values can vary over time), such as consumption of food items or cigarette smoking, should be obtained in such a way that the entire history will be available. This is typically not practical, and, instead, questions usually refer to a particular period of time. Unless the periods of time correspond for cases and controls, the comparable accuracy principle may be violated. If controls are matched to cases on age, questions about exposures should refer to exposures at the same age for cases and controls. In a diet and cancer study, if a case is asked about usual diet 5 years prior to the diagnosis of cancer at age 60, the questions to a perfectly age-matched control should refer to usual diet at age 55, regardless of the control's age at interview. For frequency-matched or unmatched studies, some sort of average might be attempted, such as starting exposure questions for all subjects with, "Before 1985, . . ." This should be the practice even if a control, who was selected from among those free of disease at age 60, is not interviewed until age 63. (Of course, one has to assume that the respondents are answering the questions the way they are asked.) The time intervals between interviews of cases and of controls should be similar (and as short as possible), so the elapsed times from the period to which the questions refer in the interview will be similar in cases and controls; also, any secular trends in exposure

prevalence would be less likely to cause bias (49, 50). Similarly, matching on calendar time should be considered, if it can ensure that exposure measurements are comparable with respect to time, as in case-control studies performed in an occupational setting, where industrial hygiene data from different years may be affected by changes in the quality of the measuring instruments.

## DISCUSSION

In the first paper of this series (1), we presented four basic principles—study base, deconfounding, comparable accuracy, and efficiency—that we believe provide a theoretical framework for the evaluation of issues in control selection. Various practical problems have been addressed, and possible solutions have been examined using these principles.

It may be difficult or impossible to satisfy all principles in a study. Sometimes an attempt that is feasible turns out to be harmful. Just as unnecessary matching can reduce efficiency and even cause bias, avoiding violations of principles that are purely theoretical and have no effect on inference is not advisable. It is important to remember that the validity of a study can be undermined more by an equivocal violation of principle than by a clear violation of principle that results in only minor bias. Since all biases are not created equal, quantification of the extent of bias is important (51, 52); otherwise, an attempt to avoid a violation of one principle may induce a more serious violation of another. Therefore, the implications of alternative approaches need to be considered carefully. For example, allowing concerns about the theoretical possibility of recall bias to determine the type of controls to choose, when in fact little or no recall bias may exist, could lead to a more biased study, if controls were drawn from a diseased group related to the study exposure.

It is important to recognize that development of a protocol that deals with the theoretical considerations discussed here is not enough; careful fieldwork is needed to make sure the study is properly executed. Thus, a

low response rate, particularly when nonresponse might depend on exposure level, may violate the study-base principle and threaten a study's validity.

The "ideal" (53) control group rarely exists in epidemiologic studies. Besides additional theoretical work, empiric studies are needed to measure the impact of violations of the principles so intelligent trade-offs can be made when planning a study. We believe, however, that although proper control selection will continue to be problematic, the most serious mistakes in control selection can be avoided by keeping a few basic principles in mind.

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