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Selection of Controls in Case-Control Studies

II. Types of Controls

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Types of control groups are evaluated using the principles described in paper 1 of the series, "Selection of Controls in Case-Control Studies" (S. Wacholder et al. *Am J Epidemiol* 1992;135:1019–28). Advantages and disadvantages of population controls, neighborhood controls, hospital or registry controls, medical practice controls, friend controls, and relative controls are considered. Problems with the use of deceased controls and proxy respondents are discussed. *Am J Epidemiol* 1992;135:1029–41.

bias (epidemiology); epidemiologic methods; retrospective studies

In this paper, we apply the comparability principles of study base, deconfounding, and comparable accuracy presented in our previous paper (1) to the practical problem of choosing a control group. A number of choices for sources of controls are discussed and evaluated within the framework of the principles. We also offer specific suggestions that we believe are useful in choosing controls.

POPULATION CONTROLS

In a study with a primary base, where the focus is the disease experience of a population during a specified time interval in a defined geographic area, randomly sampled controls from that population satisfy the study base principle. More complex sampling schemes, such as frequency matching or cluster sampling (2, 3), are also appropriate, as long as the analysis properly accounts for the sampling plan. When a roster identifying all members of the base is available, controls can be selected simply as a random sample from that roster as in a nested case-control study (2) or a case-cohort study (2).

When the probability of case identification among members of a primary base depends on a variable, the study base principle is violated and there can be selection bias, unless control selection depends proportionally on values of that variable. For example, when the probability of disease diagnosis depends on access to medical care, a hospital control series with similar dependence on access might be more appropriate than population controls (4). Or, in a case-control study of occupational risk factors using population controls, investigators might consider excluding cases diagnosed at smaller hospitals in the catchment region for logistic reasons. If these hospitals tend to serve rural communities, however, urban occupations may be overrepresented among the cases. An alternative type of control, such as hospital controls, or stratification by geographic factors in the design or analysis may alleviate this problem.

Advantages of population controls

There are a number of advantages of population controls.

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Abbreviation: RDD, random digit dialing.

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Same study base. Selection of population controls from a primary base ensures that the controls are drawn from the same source population as the case series (the study base principle (1)). The mechanisms for sampling from a population are similar to those commonly used in survey research.

Exclusions. The definition of the base can encompass the exclusions, e.g., not being in the catchment area at the appropriate time, being a previous case of the disease under study, or not being at risk of the disease under study, such as women who have had a hysterectomy in a uterine cancer study.

Extrapolation to base. The distribution of exposures in the controls can be readily extrapolated to the base for purposes such as calculations of absolute or attributable risk (5) or to learn about the distribution of exposures in the population; for example, a detailed diet questionnaire could be used to study differences in food consumption between blacks and whites. By contrast, a hospital control series that is appropriate for a study using cases drawn from the same hospital cannot be used for estimating attributable risk in a population without making assumptions about the representativeness of the case series in that population.

Disadvantages of population controls

Population controls can be inappropriate when there is incomplete case ascertainment or when even approximate random sampling of the study base is impossible because of nonresponse or inadequacies of the sampling frame (6). When case ascertainment is incomplete and probability of ascertainment depends on the factors being studied, hospital-based or other controls may be preferable (7).

Population controls have some other disadvantages.

Inconvenience. Sampling from the population instead of using a more readily available series, such as other hospitalized patients, can be less convenient and more expensive.

Recall bias. Differences between cases and healthy controls can lead to violation of the comparable accuracy principle. Despite an interviewer's best efforts to have the subject's response refer to the period before disease, the responses by a previously hospitalized case may reflect modifications in exposure due to the disease itself, such as drinking less coffee or alcohol after an ulcer, or due to changes in perception of past habits after becoming ill.

Less motivation. Population controls may be less motivated to cooperate than hospital controls.

Selection of population controls when a roster exists

Selection of population controls is simplest when there is a complete listing of the study base. It is useful if the roster has a telephone number or at least an address with which to make contact with the subject. Rosters that have been used include the following: annual residence lists, compiled by law in some areas such as Massachusetts (8) and several European and Asian countries (9); birth certificate records for studies of disease in children (10); Health Care Financing Administration files for Medicare recipients, with coverage of about 98 percent of the United States population aged 65 years and over (11); and electoral lists prepared for each election by a door-to-door survey in such countries as Great Britain and Canada. It is important to remember that, when the cases are identified by a method other than follow-up of subjects on the roster, such as through a disease registry, cases who are not included on the roster, such as those who are not citizens when using electoral lists, should be excluded from the study.

Selection of population controls when no roster exists

When no roster exists, it can be difficult to ensure that every eligible subject in the study base has the same chance of selection. Bias can be induced when methods rely on contacts with a household, either by telephone (12) or in person, and only one eligible control per household is selected. Con-

sider a study of a disease in children where controls must be within 2 years of age of the case to which they are matched and only one control per household will be selected. A child with a sibling of similar age is less likely to be selected as a control than one with no siblings. This violates the study base principle and, since cases are selected regardless of the ages of other family members, can lead to bias in estimating the effects of variables related to family size (12). Independent determination of whether to select each subject would eliminate this problem, or more than one control can be selected from the same home, and the possible dependence in their responses can be accounted for in the analysis (3).

Random digit dialing. Random digit dialing (RDD) can be used to select population controls when no roster exists. RDD and its variants generate sets of telephone numbers without relying on a directory that would not have new or unpublished numbers (13). The aim of RDD is to ensure that each residential number has an equal chance of selection, while minimizing the number of phone calls to nonresidential or inappropriate numbers (13).

Investigators have flexibility in the details of RDD (13, 14). In the standard method (13), a random sample is drawn from working sets of telephone exchanges provided by the telephone company, i.e., the first several numbers of the complete telephone number, typically eight of ten (including area code) in the United States. The number is then completed with two random numbers. The complete number is dialed to determine whether it is a working residential phone. If it is, a predetermined number of calls are made to that exchange; if not, the exchange is discarded. The extra steps are included in order to reduce the numbers of calls to exchanges that have relatively few residential numbers.

Does RDD satisfy the study base principle or can it generate a selection bias? It is easy to show that each phone number in the area has the same chance of being reached. The probability that an exchange is selected is proportional to the number of working numbers in the exchange, but the probability that a particular number is chosen from that exchange is inversely proportional to the number of working numbers in the exchange. However, the goal in control selection is a random sample of eligible subjects, not of telephone numbers. Incomplete phone coverage, residences that can be reached by more than one phone number, more than one person in the household who is eligible to be a control, and nonresponse can all lead to possible selection bias, unless accommodation is made in the design or analysis. Stratification on numbers of telephone lines and eligible residents in the household can alleviate some of the problems. Advances in technology, such as answering machines and call forwarding, have added complications to this method.

The first contact with a household is most often used for screening and to obtain a census of the household. Information on the address of the house and on the name, age, sex, and race of each household member is obtained. Based on the responses, a sampling frame is generated, and a random sample of identified eligible subjects is selected to be controls. These individuals can then be contacted by letter, by telephone, or in person for interview. When the sampling scheme is simple, such as when it is based simply on age and sex, the census and the interview itself can be done in a one-step process (14, 15), thereby reducing the overall percentage of refusal.

When telephone coverage is low, RDD will miss a substantial proportion of subjects and can result in biased estimates of the effects of exposures related to telephone coverage, such as socioeconomic status. While telephone coverage in the United States is 93 percent, it is lower for residents of the South, for blacks, and for the poor; in 1986, only 56 percent of Southern blacks living in households with yearly income below $5,000 had telephones (16). In the United States, the difference in the proportion of smokers in households with phones and in those without phones is 1 percent, though this difference is 4 percent among those with income below $5,000 (16). Incomplete tele-

phone coverage is often, therefore, a smaller problem than nonresponse and refusal.

The clustering of exchanges in RDD results in a sample that is not random, since not every possible subset of the population can be chosen. This clustering does not bias estimates of effects but can lead to overly optimistic estimates of the precision of point estimates unless addressed in the analysis (3).

Sometimes a variation of RDD is used with controls selected using the exchange of the case in order to generate subjects matched on factors that are difficult to measure but are believed to be related to geographic area (17, 18). It is not clear, however, whether "neighborhood matching" would satisfy the study base criterion. Would controls selected to have similar phone numbers actually become cases (e.g., be admitted to the study hospital, if the cases were a hospital series) had they been diagnosed with disease? Moreover, the extent to which such a procedure matches on area or region has not been empirically demonstrated. Matching on primary care practice, discussed below, may be a better approach in some situations.

RDD can be expensive and time-consuming when targeting subgroups of the population. For example, an average of almost 35 households must be screened to identify one black male, 64 households to identify one Hispanic male between 20 and 29 years of age (19), and almost 70 to identify one male aged 75 or older (13). Hence, some studies in the United States use Health Care Financing Administration rosters as a substitute to identify controls over age 65.

RDD is an option for identifying controls from a particular ethnic group who tend to be clustered in certain neighborhoods because less effort is expended in nonproductive exchanges (13). The Donnelley data base (Donnelley Marketing Information Services, Stanford, Connecticut), which classifies exchanges by race and income, can also be used for stratification to identify blacks and Hispanics more cost effectively (19); it is not so helpful, however, for identifying groups such as Asian Americans whose residential patterns are less concentrated geographically (19). However, this technique may violate the study base principle and lead to bias when the exposures are related to cultural factors associated with the diversity of the subject's neighborhood, since eligible subjects living in heterogeneous areas may be underrepresented in the control group. For example, Asian Americans living in so-called Chinatowns are likely to have life-styles and diets different from those living in an ethnically heterogeneous neighborhood.

Neighborhood controls. Population controls can also be selected using residences, rather than telephone numbers, as the sampling unit. This strategy can be particularly useful when telephone coverage is low. In area probability sampling, controls are selected randomly from a roster of residences, perhaps obtained from a recent census. However, creating a roster when one is not available can be extremely expensive.

Instead of using a random sample from a roster of residences, "neighborhood controls" are typically selected from residences in the same city block or other geographic area as the case, in an attempt to reduce the variability of factors such as access to medical care and socioeconomic status. For neighborhood controls to satisfy the study base principle, one must consider the base as divided into geographically defined strata. Use of neighborhood controls in a study with a secondary base may not satisfy the principle; for example, a neighbor who would not be admitted to the same hospital under the circumstances that led to admission of the case would be outside the base. Thus, bias could result if the source of cases is a religiously affiliated hospital and the neighborhood is religiously heterogeneous.

Neighborhood controls are usually chosen deterministically (nonrandomly) within a stratum defined geographically. If the selection is not random, one must rely on an assumption that the selection process is independent of the exposure, which is equivalent to the exposure distribution being the same as that in the study base (1, 20, 21). To protect that independence, the interviewer should not be given the flexibility to

choose which house to select. Instead, a particular algorithm, such as the one depicted in reference 22 or perhaps based on a reverse directory (sorted by address), should be used in order to avoid bias arising from interviewer selection of residences that appear more likely to cooperate.

Ideally, the neighborhood control should have been a resident of the house when the index case was diagnosed. Controls who recently moved into a neighborhood and are chosen to match cases from the neighborhood 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 study base problem but does not solve it, since people who moved out of the neighborhood will still be missed (1). Whenever cases are diagnosed several years before control selection, use of current residents (or any other current roster) raises the possibility of distortion of the distributions of factors associated with mortality and migration, particularly if socioeconomic or ethnic characteristics of the neighborhood have changed. Old reverse directories, visits to long-term residents, property tax records, old plat maps, and registers of deeds can be used to historically reconstruct neighborhoods (23) in order to find neighborhood controls contemporaneous with the case.

Neighborhood controls have two main advantages. 1) Control selection does not require the existence of a roster or use of a telephone, *and* 2) confounding factors associated with neighborhood may be balanced between cases and controls.

Thus, neighborhood controls can be an attractive alternative for studies with a primary base when no roster of the population is available or, possibly, for studies where the cases are obtained from hospital lists. The disadvantages of neighborhood controls include the potential for not satisfying the study base principle, particularly in studies with a secondary base; the high cost associated with contacting each potential control (24); the use of the household as the sampling unit, as in selection of controls by telephone; and the difficulty in documenting nonresponse, since one does not know the number of eligible subjects in homes for which there is no response. In addition, there may be overmatching on the study exposure because of similarities between cases and controls from the same neighborhood on exposures related to residence, particularly in buildings with more than one household unit. These multiunit dwellings, especially apartment buildings, present additional problems because of the difficulty of enumerating all household units within the building for sampling. Moreover, access to the buildings themselves can be a problem in many large cities.

HOSPITAL OR DISEASE REGISTRY CONTROLS

When a list of admissions or discharges from a hospital or clinic is the source of the cases, the same list can be used as the source of controls, too. The points below regarding hospital controls also apply to disease registry controls, drawn, for example, from a tumor or malformation registry. One attraction of hospital controls is that one can reasonably assume that patients admitted to the same hospital as the cases are members of the same (secondary) base (1, 20). The most serious danger with hospital controls is that choosing subjects with other diseases may jeopardize the assumption of representativeness of exposure (1, 20, 21), namely, that the distribution of the exposures under study in the controls is the same as that in a random sample from the base that produced the cases. This is equivalent to assuming that there is no relation between exposure and the diagnoses used to determine inclusion of controls. For example, use of other women who undergo dilatation and curettage as controls for a study of endometrial cancer (25) probably meets the assumption regarding membership in the secondary base but fails the representativeness of exposure assumption when estrogen use is related to conditions indicating dilatation and curettage (26–28).

The representativeness of exposure assumption is not quite as difficult to meet as

it may seem because it must hold only within strata used in the analysis or conditionally on factors for which adjustment will be made in the analysis (1, 20). Thus, for example, stratification by sex eliminates bias for an exposure even if the exposure is associated with a control disease unconditionally, as long as it is unassociated with the control disease separately for males and females.

Hospital or registry controls are usually more appropriate than are population controls if a sizable fraction of diseased subjects in the base will not become cases in the study and if the ones who do have different exposures from those who do not. For example, multiple sclerosis patients referred to an academic center about 60 miles (about 100 km) away were found to have demographic and severity characteristics different from those of other multiple sclerosis patients at the center from the same area who were not referred (29). It would be difficult to reflect this heterogeneous referral pattern using population controls. Use of hospital controls from another disease with a similar referral pattern might provide more assurance that all subjects share the same study base; alternatively, stratifying by geography or by referral status might be effective.

Use of a hospital control series consisting of subjects with a disease the outward manifestations of which are identical to those of the disease of interest can eliminate one source of selection bias. When differential diagnosis is made on these subjects, the ones with the index disease become cases and the ones with the "imitation" disease become controls. If the imitation disease is unrelated to the exposure of interest, these controls would be appropriate; Miettinen (20, p. 79) describes them as "ideal."

Hospital controls have other advantages.

Comparable quality of information. A major advantage is that generally hospital controls are more comparable to cases with respect to quality of information, since they too have been ill and hospitalized. However, careful consideration of the environment where information is gathered, the content and phrasing of the questions, and the diseases to be included in the control series is needed, since simply being sick does not necessarily entail comparable accuracy and avoidance of recall bias. Selecting hospital controls with conditions that are believed to lead to similar errors in recall may alleviate some of the problems that cause this form of information bias. For example, in a study of birth-related risk factors for testicular cancer in men treated at a military or tertiary care hospital, controls were age-matched men with other cancers, presumed to be unrelated to the study exposures, at the same hospitals (30). Since subjects' mothers provided information on the key exposures, which occurred during early childhood, the use of hospital controls was particularly appropriate because it ensured that the sons of all the mothers interviewed for the study had had malignancies (30). Further, the study hospitals drew patients from across the United States, so these controls were likely to have referral patterns similar to those of the cases (30).

Convenience. Hospital controls may be the most convenient choice when controls will be asked to provide bodily fluids or to undergo a physical examination, as when looking for dysplastic nevi in a study of skin melanoma.

In addition to the need to satisfy the representativeness of exposure assumptions noted above, hospital controls have other difficulties.

Different catchments. Even when controls are identified from the same registry or hospital as the cases, the catchments for different diseases within the same hospital may be different (31), violating the study base principle. For example, an urban teaching hospital associated with a medical center may provide primary medical care to poor people in the neighborhood and also serve as a tertiary referral center providing sophisticated services for certain medical conditions. Restricting the study base to people living in the vicinity of the hospital can alleviate the problem (20, 21) but may reduce the number of cases substantially.

Stratification by distance between hospital and residence or by referral status might be an effective alternative.

Berkson's bias. If the study exposure is related to the risk of being hospitalized for the control disease, the exposure distribution in the series may not reflect the base. For example, diabetics are more likely to be admitted to the hospital with heart disease than are nondiabetics, which could bias studies focusing on diet. This is an example of Berkson's bias, which is caused by selection of subjects into a study differentially on factors related to exposure (32).

Composition of a hospital control series

We believe that the best strategy regarding the selection of diseases to form a hospital- or disease registry-based control group is to exclude from the control series all conditions likely to be related to exposure (20, 33). The payoff for the extra effort in the study design will be more confidence in the validity of the results. If there is an association, subjects admitted to the hospital for the disease need to be excluded from the control series (34); however, a previous history of the disease should not be grounds for exclusion, unless the exclusion is also applied to cases (35). These exclusion rules apply regardless of whether the association is positive or negative, causal or not.

In theory, a possible association of exposure with a control disease should be assessed after controlling for confounders included in the analysis. If adjustment for a confounder eliminates a crude association between exposure and a potential control disease, adjustment for that same confounder in the analysis of the study will eliminate the bias caused by using that disease as a source of controls.

Similarly, an association between the control disease and a confounder is acceptable, if the effect of the confounder is controlled in the analysis. Also, patients with any disease that cannot be clearly distinguished from the study disease should be excluded from the control series to reduce bias due to misclassification of disease.

If there is complete confidence that a single disease is unrelated to the exposure of interest, the entire control series may be selected from among patients with that disease. However, only rarely is there convincing evidence that the assumption of independence of the study exposure and a control disease is satisfied. Therefore, inclusion of patients with several diseases minimizes potential bias if any one disease turns out to be related to exposure (36, 37). When related diseases, such as other cancers for a study of a particular cancer or other perinatal outcomes for a study of birth defects, are used, the possibility of information bias may be reduced (38, 39). Again, however, any of the diseases that are related to the exposure (based on a priori knowledge) should be excluded (33). Overall, we recommend using more diseases rather than fewer; this protects the investigators if later evidence links one or more of the control diseases positively or negatively to an exposure.

CONTROLS FROM A MEDICAL PRACTICE

Choosing controls from the primary medical practice of the cases can be a useful strategy when it is otherwise difficult to find controls who are comparable to cases on access to medical care or referral to specialized clinics. For example, medical practice controls may be more appropriate than hospital controls when cases are drawn from an urban teaching hospital, because potential subjects admitted to this hospital may be mixtures of poor clinic patients and high-socioeconomic-status private patients in far different ratios from those of the case series.

Controls selected from the same medical practices as the cases are drawn from the appropriate secondary base (1, 20), if one can make the assumption that two patients in the same primary care practice with the same presentation would follow the same pathway through the medical care system. A disadvantage of medical practice controls is

the extra complexity entailed by a random selection process for controls within several different practices.

The study base principle can be jeopardized with medical practice controls, since the exposure distribution for controls may not be the same as that in the study base, as when patients choose a physician for reasons relating to particular conditions that are themselves related to exposure. Similarly, if those conditions lead to modification of exposure subsequent to symptoms or treatment, the study base principle can be violated, unless the timing of the changes can be ascertained. For example, medical practice controls were used in a study that reported a positive association between coffee drinking and pancreatic cancer risk (40). Because the controls were patients with gastrointestinal disorders, some of them had conditions that were either caused by coffee drinking or treated by removing coffee from the diet, and thus the level of coffee drinking was not representative of the study base. The magnitude of the bias introduced by inclusion of such controls is dependent on the proportion of controls with diet-altering conditions and the relations of these diseases to coffee consumption (41). Control conditions associated with a confounder do not need to be excluded, if there will be adjustment for the confounder in the analysis. Thus, smoking-related conditions not related to coffee drinking might be included in the control series (34).

FRIEND CONTROLS

Friends of cases may be a more convenient and inexpensive source of controls than are other alternatives. Controls can be selected from a list of friends or associates obtained from the case at little extra effort while the case is being interviewed. Friends may be likely to use the medical system in similar ways. Moreover, biases due to social class are reduced since usually the case and friend control will be of a similar socioeconomic background.

Nonetheless, we have strong reservations about the use of friend controls. A possible theoretical justification of friend controls is that the base is divided into mutually exclusive "friendship strata" and that the exposure of a friend control is representative of that of the friendship stratum. Alternative justifications for friend controls are as a nonrandom sample from the base, if friends will all be in the same study base, or, if not, as an indirect way to probe the base (1, 20). None of these rationales is very persuasive. It is unrealistic to believe that the study base is divided into mutually exclusive friendship strata and that the controls are selected from only within the case's stratum (42). Even if this were true, the control selection within the stratum is deterministic and possibly related to exposure (1, 42). The credibility of representativeness of exposure is low for factors related to sociability, such as gregariousness or, possibly, smoking, diet, or alcohol consumption, because sociable people are more likely to be selected as controls than are loners (42).

"Friendly control" bias was suspected in a case-control study of patients with insulin-dependent diabetes mellitus, where friend controls were designated by the parents of cases (43). Insulin-dependent diabetes mellitus cases were found to be more likely to have learning problems, to have few friends, to dislike school, and to have recent illness in the family. While these findings could be due to true risk factors or to recall bias, they are more likely to be due to selection bias, since children perceived to have problems may be less likely to be identified as friends and, therefore, as controls (44). Further, there was some evidence suggesting that parents gave names of children from families with "mainstream" social characteristics (44).

A less serious problem is that the use of friend controls can lead to overmatching, since friends tend to be similar with regard to life-style and occupational exposures of interest, as in a study of head trauma and seizures (45); the loss of efficiency due to overmatching depends on how strongly head trauma is correlated among friends (e.g.,

motorcycle racers and boxers) and how closely it is related to gregariousness.

These problems can be alleviated to some extent by asking cases for the names of several friends and choosing controls randomly from the list or by asking for names of associates rather than friends (31, 46) so that the control will not be the case's closest, and perhaps most sociable, friend. However, those on the list will still tend to be more sociable than is a loner who is not on anyone's list (but can become a case), and there is no reason to believe that the extra friends named will have different characteristics from those who would be named on a shorter list (47). In addition, some cases may not be willing to provide names of friends (48), increasing nonresponse.

Despite serious shortcomings, friend controls may be useful in some exceptional circumstances, such as in a study of exposures unrelated to friendship characteristics, as is likely in a study of a genetically determined metabolic disorder (48, 49).

RELATIVE CONTROLS

The choice of relative controls is motivated by the deconfounding principle, not the study-base principle (1). When genetic factors confound the effect of exposure, blood relatives of the case have been used as a source of controls (50) in an attempt to match on genetic background. Spousal and sibship relationships form strata and meet the reciprocity requirement (1, 42), but the theoretical justification for other relatives is more tenuous. Spouses might be a suitable control group if matching on adult environmental risk factors is sought. When sibling controls are used in studies of the association between genetic markers and the risk of cancer, confounding by factors related to ethnicity is minimized (51); however, cases and controls may be overmatched on a variety of genetic and environmental factors that are not risk factors but are related to the exposure under study. For example, effects of risk factors associated with family size cannot be assessed in a study using sibling controls because of overmatching (31).

Trade-offs in using relative controls are illustrated in a study of the association between tonsillectomy and Hodgkin's disease (52) that used two control groups, siblings and spouses, to control for socioeconomic status in childhood and adulthood, respectively. A higher risk for tonsillectomy was found with spousal controls than with sibling controls, suggesting either positive confounding by childhood socioeconomic status or negative confounding by adult socioeconomic status.

THE CASE SERIES AS THE SOURCE OF CONTROLS

An individual can serve as his own control for a study of an acute event when the effect of an exposure is transient (53), such as the effect of a possible triggering activity on myocardial infarction. The impact of the exposure is evaluated by comparing the proportions of events occurring during the putative period of elevated risk and the proportions of time each individual has been at elevated risk. This "case-crossover" design (53) can be thought of as a case-control design where each stratum consists of a single individual (or as a cohort study with many noninformative strata). The study base principle is clearly satisfied. Although there is no possibility of between-subject confounding, a second exposure that tends to occur at the same time or at different times from the study exposure can cause confounding (53). This design has the advantages that only patients need to be studied (53) and that recurrences can be handled easily.

However, for studies of chronic diseases where the main focus is on more stable time-dependent covariates, the use of a study series of cases only, as might be found in a disease registry, requires a complete and accurate exposure history and the strong assumption that the exposure of interest is unrelated to overall mortality (54). This

study design may also have lower power than more conventional studies (54).

PROXY RESPONDENTS AND DECEASED CONTROLS

Interviews with proxy respondents are often used when subjects are deceased or too sick to answer questions or for persons with perceptual or cognitive disorders (55). Because proxy respondents will tend to be used more often for cases than for healthy controls, violation of the comparable accuracy principle is likely. Surrogates, particularly spouses and children, generally provide accurate responses for broad categories of exposure information, although more detailed information is usually less reliable (56–60). For some variables, such as cigarette smoking, and consumption of coffee and alcohol, spouses and children are remarkably accurate, even when compared with reinterviewed living subjects (61, 62). Proxies may even provide better information than the index subjects, such as in nutritional studies among older subjects, where a subject's wife may have prepared much of her husband's food (63).

When feasible, reducing the time interval between diagnosis and interview of cases can reduce the number of proxy interviews required. When information is obtained from a surrogate because the case is dead, using a living control sampled properly from the base can violate the comparable accuracy principle. However, insisting on a dead control (64) violates the study base principle, since the base consists of living subjects and subjects who die represent a special sample from that base. In order to use dead controls, one needs to assume representativeness of exposure (1), that the dead controls have the same distribution of exposure variables as does the base. This assumption has been demonstrated to be incorrect for a number of personal behavior variables, including use of tobacco and alcohol (65), even after deaths from causes believed to be associated with the study exposure are excluded (66).

Interviews with surrogates of appropriately selected living controls do not make accuracy fully comparable since the controls are still alive while the cases are deceased, and responses by their surrogates may be influenced by factors associated with the subject's death (67). Nonetheless, validation studies (68, 69), in which the responses of a proportion of the living subjects and their proxies are obtained, can be used to reduce the bias due to errors from proxy responses.

In studies with deceased cases, the use of proxy interviews for appropriately selected live controls is usually preferable to the use of dead controls, particularly if the study exposure is likely to be associated with overall mortality. The advisability of insisting on a proxy interview for a live control depends on what information will be obtained from the interview. When exposure is assessed directly, comparable accuracy for cases and controls in an interview designed primarily to elicit information on confounders does not necessarily reduce the bias in the estimate of the effect of exposure (1, 67, 70); therefore, a proxy interview for the control may not help. Using proxy interviews for live controls should be considered only when 1) information about a key study exposure is to be obtained by interview *and* 2) a proxy report for the case is likely to be substantially less accurate than the control's self-report about the key study exposure.

Controls in proportionate mortality studies

A proportionate mortality study can be viewed as a case-control study with controls obtained from a registry consisting of deaths (71). The underlying assumption is that the distribution of the exposure under study among subjects who died from other causes is the same as that in the base, which consists of living persons only. Just as in other registry-based studies, deaths from causes related to the study exposure must be excluded from the control series (21). Thus, this kind of study may not be suitable for investigating exposures such as smoking that are risk factors for causes of death repre-

senting a high proportion of mortality. One advantage of the approach is that a roster for the eligible controls can be established conveniently; any absences from the base typically will not lead to selection bias, since the efficiency of the system for registering deaths from most causes is unlikely to vary substantially with cause of death. However, errors in attribution of cause of death do occur, for example for AIDS, suicide, or cirrhosis of the liver, resulting in misclassification bias and over- or underexclusion of subjects.

NUMBER OF CONTROL GROUPS

Some researchers have suggested choosing more than one control group (72, 73). It certainly is reassuring when the results are concordant across control series. However, when the results are discordant (25, 27, 52), the investigators must decide which result is "correct" and essentially discard the other. We therefore believe that doubt is not a good basis for choosing an additional control group. Rather, the best strategy usually is to decide which series is preferable at the design stage.

Multiple control groups might be helpful when each serves a different purpose, as when each control group provides the ability to control for a particular confounder. In this situation, the second control group can act as a form of replication.

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