# Chapter 5. Selection bias and other miscellaneous biases

CHAPTER 5.

# Selection bias and other miscellaneous biases

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## 5.1 Introduction

Epidemiological studies are intended to obtain valid exposure effect estimates for a target population (e.g. all women aged 20 years or older). In practice, specific epidemiological studies are, or at least should be, based on a clearly defined source population (e.g. all women in France aged 20 years or older), followed up over a clearly defined risk period (e.g. 2010–2020). However, it is rare for a study to include all of the source population over the entire risk period. In cohort studies, there could be incomplete recruitment at baseline, and some participants may be lost to follow-up. Case–control studies, by design, involve recruiting a sample of control participants from the source population, and there may also be incomplete recruitment of case or control participants; this may create selection bias if, as a result, the two groups are different from the full source population with respect to exposure status or level.

Selection bias is present when the effect estimate (e.g. the odds ratio [OR]) of the association between the exposure and the outcome in the study population is different from that in the source population, because of selective recruitment into the study or selective loss to follow-up. Thus, the defining characteristic of selection bias is that it occurs as a result of differences between the study population and the source population from which it is selected. Selection bias can occur for a variety of reasons, either during initial recruitment from the source population (e.g. differential recruitment with respect to both the exposure and the outcome) or during follow-up (e.g. differential retention in the study). In a published paper, selection bias can be particularly difficult to assess, for example by *IARC Monographs* Working Groups, because few papers report the information required to assess and quantify it.

Selection bias is distinct from issues of generalizability (or transportability) (Richiardi et al., 2013). The terms *representativeness*, *generalizability*, and *transportability* refer to comparisons between the target population and the source population. In most studies, the concept of the target population is left undefined, and there is no need to invoke some hypothetical target population to validly design and analyse a study. Moreover, if an exposure has a non-null effect in a defined source population, or even in a specific study population, this is of concern in

itself, irrespective of issues of transportability. Thus, in theory, issues of transportability are usually not central to *IARC Monographs* reviewers, because the focus is generally on whether there is a non-null effect in any population, rather than the size of the effect in a specific population. In contrast, evidence synthesis often does involve an assessment of consistency of results across studies, at least in qualitative rather than quantitative terms, and any major inconsistencies will require further consideration and explanation.

Selection bias is often confused with issues of representativeness (Munafò et al., 2018) but these are very different concepts (see Chapter 2). In fact, many important causal associations (e.g. smoking and lung cancer) have been discovered or confirmed in studies involving particular subgroups of the general population, such as the classic study of smoking and lung cancer in British doctors (Hill and Doll, 1956). Thus, a study should not be assumed to suffer from selection bias simply because it is not based on a random sample of the general population.

According to this definition of selection bias, if information is obtained for all of the source population over the entire risk period, then the study population is the same as the source population; therefore, selection bias does not occur. Defined in this way, selection bias closely aligns with collider bias (see Chapter 2; Hernán et al., 2004; Pearce and Richiardi, 2014), arising because it is only possible to analyse data for those who have been included in the study, and therefore the analysis is conditioned on selection into the study. Selection bias is not only the result of collider stratification. It can also occur when selection is associated with effect modifiers. Without stratification by, or standardization over, those modifiers, the effect estimated in such a study may be very different from the effect that would have been estimated in the source population. This type of selection bias may be less relevant in the context of cancer hazard identification. Example 5.1 examines selection bias in a case–control study.

## Key message

In general, important selection bias will occur if the selection (through either recruitment or loss to follow-up) is associated with both exposure and disease status together (e.g. if exposed case participants are more likely or less likely than other groups to be recruited) (Richiardi et al., 2013). Therefore, this chapter focuses on the situation in which selection is associated with both exposure and disease.

A primary question posed to expert reviewers, such as *IARC Monographs* Working Groups, in the context of hazard identification is, "Can we reasonably rule out selection bias as an explanation for an observed exposure–cancer association?" This can be particularly difficult to assess, because most published studies provide little or no discussion of the potential for selection bias, in contrast to the usually more extensive discussions of the potential for confounding (Chapter 3) or misclassification (Chapter 4).

## Key message

Although selection bias is often the most mathematically simple bias for which estimates of effect (see Chapter 7) can be bias-adjusted, the information needed for such bias adjustments is rarely available or reported in published papers.

One exception to the typical lack of available information is the literature on the Interphone study (Cardis et al., 2010); this example is used frequently in this chapter, although it is recognized that this level and detail of information is usually not available to *IARC Monographs* Working Groups or other expert reviewers.

This chapter starts by discussing selection bias in cohort studies and then considers the additional forms of selection bias that can occur in case–control studies. Methods are then presented for assessing selection bias in a published paper.

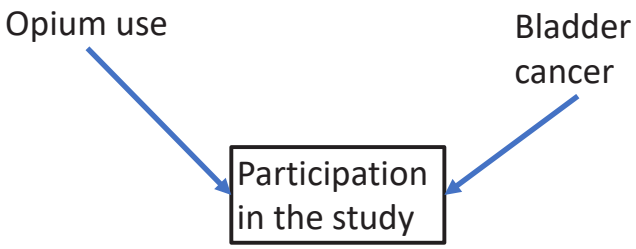
## 5.2 Identifying selection bias in cohort studies

Many cohort studies of cancer rely on the willingness of people to participate, both at baseline and during follow-up. Furthermore, the researchers may choose different inclusion and restriction strategies in specific analyses that may also affect the composition of the study population. When reviewing such studies, it is important to consider whether such selection may have biased the results. The relation of selection bias to other types of bias is defined in Chapter 2.

**Example 5.1.** Selection bias in a case–control study

Fig. 5.1 illustrates the occurrence of selection bias in a case–control study of opium use and bladder cancer, an example discussed in more detail later in this chapter. Chapter 2 introduced the use of directed acyclic graphs (DAGs) to ascertain the possible presence of selection bias. In this DAG, participation in the study is affected by both opium use and bladder cancer. Opium users may be more hesitant than non-opium users to participate in a study. People with bladder cancer (potential case participants) may be more likely than control subjects to participate in the study (e.g. because of their interest in the subject) or less likely to participate because of their illness status. A box is drawn around "Participation in the study" to indicate that all analyses condition on this factor (i.e. analyses are limited to this group). In this example, an opium use–bladder cancer association could be found in a study, even if one did not truly exist. Alternatively, if this were not a case–control study but, rather, included the entire source population, then selection bias could not occur, because everyone would be enrolled in the study and nothing could affect participation. Thus, whether someone had used opium or had bladder cancer would not affect participation in the study, and there would be no arrow from "Opium use" or " "Bladder cancer" to "Participation in the study". (text continues on page 125)

**Fig. 5.1.** Illustrative example of possible selection bias in a case–control study of opium use and bladder cancer.




### *5.2.1 Non-response at baseline*

The first stage at which selection bias may occur in a cohort study is in the initial recruitment into a study. As discussed in the previous section, if the entire source population is recruited, which may be the situation in a register-based study that does not rely on consent to participate, then selection bias cannot occur (at least at baseline). However, even if there is incomplete recruitment or participation, the study population can still provide unbiased effect estimates (or, at least, estimates that are unbiased by selection issues). For example, a study with a 40% response rate at baseline may nevertheless be almost completely unbiased if non-response is not associated with either exposure or disease. Selection at baseline that is related to a particular exposure (e.g. socioeconomic status [SES]) should not bias future results, as long as participation is not also associated with future disease status (e.g. if affluent people are more likely to participate than non-affluent people, but their participation is not related to whether they will or will not develop the disease being studied). However, if exposure and outcome jointly determine selection (e.g. affluent people who will eventually develop the disease are more likely to participate in the study, or non-affluent people who will stay healthy are more likely to participate than others), this will result in a selection bias arising because the analysis includes only those who participated in the study (i.e. the analysis conditions on participation in the study) (see Chapter 2 and Section 5.1). There is also the possibility of selection bias if, instead of the outcome itself, it is an outcome risk factor that determines selection at initial recruitment, because that risk factor could alter the causal effect estimate in the study population, acting in the same way as a confounder (see Chapter 2).

However, such bias will usually be small, as shown in Example 5.2.

Side Box 5.1 outlines the key information that should be reported to facilitate assessment of bias due to non-response at baseline.

Traditionally, in cohort studies, the assumption has been that because potential participants are not aware of their risk of future disease at baseline, this will not influence their decision to participate, and selection at baseline has been considered a minor problem compared with loss to follow-up, which may be jointly determined by exposure and outcome. However, this has been questioned in the UK Biobank study, for which the initial response rate was only 5.5%, and in which it was shown that participation in the study was related to some particular exposures and outcomes (Fry et al., 2017; Munafò et al., 2018). However, this bias would apply only to the cross-sectional analyses of the baseline data, and will usually be small (see Example 5.2).

Moreover, Richiardi et al. (2013) have argued that this type of selection bias will not occur in a cohort study if people with prevalent disease at baseline (or who are diagnosed soon after baseline) are excluded, assuming that other factors that influence participation do not also affect disease (see Example 5.3). This is possible in cohorts for which electronic health record-linked data are available; this would enable the identification of cases of disease that occur after recruitment. Therefore, for *IARC Monographs* Working Groups it is important to consider the probable latency period (usually assumed to be about 5 years for cancer) during which disease may be present but not yet diagnosed.

### *5.2.2 Loss to follow-up*

Selection bias may also occur when loss to follow-up differs between exposed and unexposed people, because this is related to the ability to observe disease outcomes.

## Key message

Selection bias occurring from loss to follow-up is perhaps of more concern than selection bias from recruitment in cohort studies (and in case–control studies based on them), because exposure, predictors of the outcome, and the outcome itself may now jointly determine participation.

**Example 5.2.** Magnitude of selection bias

Pizzi et al. (2011) demonstrated that when both the exposure and another risk factor that is independent from the exposure double the probability of selection into the study and the other risk factor also doubles the risk of the outcome, this selection bias will result in an observed relative risk of only 1.02 for the exposure–outcome association when the true relative risk is 1.0. Moreover, this bias can be corrected if the analyses are adjusted for the risk factors that determine the selection. In this example, it is assumed that the exposure is not associated with the other risk factor in the source population; if they were associated, the bias would be larger. (text continues above)

**Side Box 5.1.** Information that should be reported to enable the assessment of bias due to non-response at baseline

The key parameters that should be reported to enable the post-publication assessment of selection bias are the probability of participation in the study stratified on exposure and disease status. Unfortunately, these are rarely, if ever, available. In particular, for studies involving consent from the participants, this information will rarely be available for those who do not consent, although some information may be available from the sampling frame (e.g. some population registers include information on age and sex). Authors should report not only the overall response rate but also the response rates in key subgroups of interest by baseline exposure status. In addition, descriptive tables of participants and non-participants (with sex, SES, age, ethnic group, and major risk factors if possible) should be provided. (text continues above)

**Example 5.3.** Assessing bias due to non-response at baseline in an occupational cohort study of flight attendants

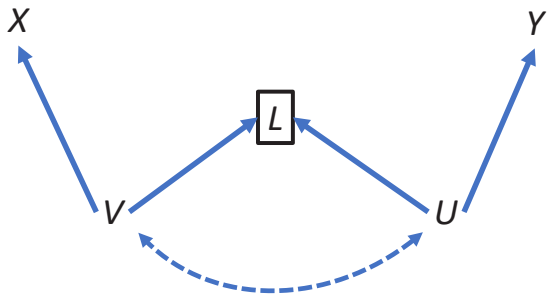
A study was conducted to evaluate the association of exposure to cosmic radiation and circadian disruptors with breast cancer risk in former flight attendants (Schubauer-Berigan et al., 2015). The response rate for inclusion in this study was 64.4%. Selection bias could have occurred if participation was related to employment characteristics as a flight attendant and also to the disease. The breast cancer incidence cohort of flight attendants was a subset of a cohort (the mortality cohort) of former flight attendants employed by Pan American World Airways (Pan Am) for at least 1 year, for which the main outcome considered was breast cancer mortality. The incidence cohort was assembled from the personnel records of Pan Am. Women ($n$ = 9461) in the mortality cohort were invited to participate in the incidence cohort by completing a detailed telephone interview or mailed questionnaire (2002–2005), which contained questions about their demographic information, work history, and non-occupational risk factors for breast cancer (e.g. reproductive history and use of alcohol, tobacco, and hormone replacement therapy [HRT]). The next of kin of deceased flight attendants were also contacted and were each invited to complete the questionnaire about the decedent. Duration of employment was closely correlated with estimated cumulative exposure to cosmic radiation.

After some minor exclusions, the incidence cohort included all the respondents to the telephone interview and mailed questionnaire ($n$ = 6093 women, 64.4% of the 9461 eligible women in the mortality cohort); 2% of the cohort overall and 8% of those with breast cancer were deceased. The response rate for proxies of decedents ($n$ = 134) was lower (41%) than among living cohort members (65%). For women who died after a breast cancer diagnosis, the response rate was similarly low (46%). The median duration of Pan Am employment based on workplace records among the respondents was 5.8 years and was slightly longer than for the mortality cohort (5.0 years), suggesting that long-term employees of Pan Am were more likely to respond to the questionnaire. Other major sociodemographic differences between participants and non-participants were very small (Pinkerton et al., 2016). Although there were some small differences in response rates between deceased and living cohort members, the overall potential selection with regard to breast cancer could be expected to be minimal, given the small number of decedents and the lack of major differences in major socioeconomic and exposure factors between participants and non-participants. The fact that the participants had worked slightly longer than the non-participants, and therefore had more shift work (which is a potential circadian disruptor and thus a possible risk factor for breast cancer), is unlikely to have resulted in large selection bias, unless breast cancer risk also affected participation in the study. (text continues on page 127)

Selection bias from loss to follow-up can also occur in randomized trials, even when the exposure (which in a randomized trial would be the intervention) has been randomized at baseline. In particular, if there is loss to follow-up and this is jointly associated with both exposure status and outcome status, then selection bias can result, because all analyses will include only those participants for whom there are follow-up data. When both the exposure and the outcome affect participation in follow-up, the structure of the bias is analogous to the DAG illustrated in Fig. 5.2. In this DAG, a predictor ($V$) of the exposure ($X$) causes loss to follow-up ($L$), and a separate predictor ($U$) of the outcome ($Y$) also causes loss to follow-up. An analysis that is restricted to those who are not lost to follow-up ($L$ = 0) will suffer from selection bias, as illustrated by the fact that the backdoor pathway $X$–$V$–$U$–$Y$ is unblocked in the DAG (as explained in Chapter 2). Without further analytical adjustments for loss to follow-up (such as analytical adjustment for $V$), the analysis of the effect of $X$ on $Y$ among $L$ = 0 will be biased.

Such biases are usually difficult to assess in published studies, because the relevant information is often not available or not reported (Example 5.4 and Side Box 5.2). However, reviewers can draw a DAG, such as the DAG illustrated in Fig. 5.2, and determine whether the authors

**Fig. 5.2.** DAG showing bias due to loss to follow-up in a cohort study: *L*, indicator for loss to follow-up; *U*, unmeasured covariate; *V*, measured covariate; *X*, exposure of interest; *Y*, outcome.




**Example 5.4.** Bias due to loss to follow-up in an occupational cohort study of flight attendants

Cancer follow-up is frequently based on existing cancer incidence or mortality records. However, national cancer incidence registries are available in only a small number of countries. When cancer incidence is not available through linkage to records, other follow-up methods are needed. An example is a study in the USA of breast cancer among Pan Am flight attendants (Schubauer-Berigan et al., 2015).

Breast cancer incidence in the flight attendant cohort was compared with that in the general population. The incidence cohort included 6093 women who responded to a questionnaire, of whom 134 were proxy respondents in the survey, mostly for deceased cohort members (see Example 5.3).

Information on incident breast cancers was first obtained through self-report of a cancer in the questionnaire. A medical record follow-back of each reported case of cancer was conducted by contacting the physician's office, hospital, or other health-care organization in which the cancer diagnosis was made and obtaining supporting documentation of the diagnosis. Self-reported breast cancers that were refuted by a review of the medical records were not included, but reported cancers that were neither confirmed nor refuted were included. The incidence cohort was also linked to cancer registries in six states, based on the locations of the domiciles for the airline and on common states of residence for the cohort; 82% of the cases of breast cancer in the cohort were verified using medical record follow-back, cancer registry linkage, or both. Loss to follow-up could have occurred if a substantial proportion of the cohort lived in areas without a cancer registry. However, this did not seem to be the situation for this study. (text continues on page 128)

**Side Box 5.2.** Information that should be reported to enable the assessment of bias due to loss to follow-up

The ideal information that would be reported to enable investigators to determine the presence of bias due to loss to follow-up would be the distribution of exposure, outcome, and confounders, stratified by whether participants were lost to follow-up. Unfortunately, this information will not generally be available, and it will be impossible to know whether the outcome distribution differs by loss to follow-up, because such data are not collected from those who are lost to follow-up. Instead, investigators are limited to examining the distribution of exposures and confounders collected earlier in the study and evaluating whether there are differences in distributions between those who were and were not lost to follow-up. Any differences in loss to follow-up by the exposure or other key variables should be reported and treated as possible sources of selection bias. (text continues on page 128)

adjusted for a sufficient set of variables to reduce selection bias due to loss to follow-up. In the absence of such information, reviewers can conduct a sensitivity analysis for the probable extent and direction of selection bias (due to loss to follow-up) using the methods presented in Section 5.4.4.

### 5.2.3 Time-zero specification

In the previous section, it is assumed that the source population is followed up for the entire risk period, and that this risk period is properly defined. To explore this concept further, it is necessary to first define the concept of *time zero*. In a randomized controlled trial, this is the time at which a potential study participant meets all of the criteria for inclusion. The inclusion criteria have been applied and treatment has been randomized; at this point, follow-up time (outcome recording) has begun (Hernán et al., 2016). In a cohort study, one should attempt, as much as possible, to align these components, to define a time zero. Time-zero misalignment can sometimes create selection biases (Example 5.5).

### 5.2.4 Left truncation (prevalent exposures)

Left truncation can result when the effects of exposure occur fairly rapidly after first exposure but study participants are not studied from first exposure. This situation is also known as prevalent exposures, i.e. when follow-up of participants begins after exposure has begun, so cumulative (prevalent) exposure at enrolment is the starting point.

As shown in Example 5.6, hazardous effects have often been missed in cohort studies in which most study participants were only followed up from 10 or more years after first exposure. This type of bias can often lead to paradoxical results, as with HRT use: the people at highest risk die early, leaving the healthiest exposed people to be studied at later time points and suggesting an apparent beneficial effect of the exposure when the study is limited to that group (Flanders and Klein, 2007). The direction and magnitude of the bias are highly context-specific. For example, in a cancer cohort study of an exposure with a long latency period (i.e. the time between exposure and disease induction), there may be little or no bias from left truncation (e.g. if the 5–10 years after first exposure are not included). In contrast, as

**Example 5.5.** Identifying time zero in an occupational cohort study of flight attendants

In an occupational cohort study, if there is a requirement that eligible participants have worked in the industry for at least 1 month, then time zero will usually be a specified period (1 month) after the start of employment, and follow-up will start from that date. Bias will occur if follow-up time is counted from the start of employment, because person-time will then be counted for the eligibility period, but anyone who dies during that year will be excluded from the study. In the study of the Pan Am flight attendants described in Examples 5.3 and 5.4 (Schubauer-Berigan et al., 2015), participants were eligible for inclusion if they had been employed by the airline for at least 1 year. In the statistical analyses of the association between circadian disruption metrics and breast cancer, follow-up began no earlier than 1 year after the start of employment (other criteria for the start of follow-up were also applied). (text continues above)

**Example 5.6.** Left truncation as a source of selection bias in studies of hormone replacement therapy

Hernán (2015) has identified left truncation as a source of selection bias in studies of the effects of HRT use in women, where cohort studies and randomized controlled trials initially yielded different findings, with the former showing protective effects and the latter showing increased risks from HRT use. Hernán (2015) showed that this was because the hazardous effects of exposure on cardiovascular disease occurred in the first 5–10 years after first exposure. (text continues above)

shown in Example 5.6, for HRT use, left truncation would produce serious bias because the hazardous effects occurring 5–10 years after first exposure would not be identified.

## Key message

In cancer studies, left truncation is of concern mainly when the induction or latency period is likely to be short, for example for most childhood cancers and for some adult cancers, such as leukaemia, or when follow-up begins decades after the start of exposure.

Cohort studies (and corresponding nested case–control studies) that involve left truncation (prevalent exposures) may suffer from selection bias (Danaei et al., 2012). However, Vandenbroucke and Pearce (2015a, b) have argued that although this form of selection bias can occur, the resulting effect is often trivial. This is particularly true for studies of outcomes, such as occupational cancer, where the induction time for the exposure to have an effect can be long (Example 5.7). Moreover, Vandenbroucke and Pearce (2015a, b) have shown that, provided the relevant information is available for each period of time since first exposure, any such left truncation bias can be removed or minimized by stratifying on (and adjusting for) time since first exposure in the analysis (Side Box 5.3).

### 5.2.5 Insufficient follow-up

The corresponding problem of right truncation occurs when study participants are not followed up for a sufficiently long period after first exposure. For example, if a study involves a risk period of 10 years but is restricted to incident exposures (i.e. participants exposed for the first time during the risk period), then the maximum follow-up time after the first exposure for any study participant will be 10 years, which will be insufficient for most studies of cancer, particularly cancers with long latency, such as many solid tumours. This depends on the research question, but if, for example, the hypothesis is that the exposure can cause cancer 10–25 years after first exposure and

**Example 5.7.** Left truncation in a population-based cohort study of breast cancer

In a cohort study of night shift work and breast cancer that was based on the Generations Study, middle-aged women were asked at baseline about their exposure to night shift work during the previous 10 years (Jones et al., 2019). The study found no association between being a night shift worker within the previous 10 years and invasive breast cancer (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.85–1.14). Because of the left truncation in exposure assessment, long-duration night shift workers were included in the exposed group only if they had survived long enough to enter the 10-year recording period and if they were still working night shifts at that time. Furthermore, because night shift work is most common at young ages, the unexposed group could have included an unknown number of women who had worked night shifts at earlier periods in their lives. (text continues above)

**Side Box 5.3.** Information that should be reported to enable the assessment of bias due to left truncation

The key parameters that should be reported to enable the post-publication assessment of selection bias due to left truncation are the proportions of study participants who were affected by prevalent exposures at baseline and, ideally, for how long these participants had been exposed (minimum, median, and maximum) before follow-up started. Ideally, the reported findings should also be stratified by time since first exposure. For cancer, because of the relatively long induction or latency period, one would expect the exposure–disease association to vary over time since first exposure. In this situation, heterogeneity by time since first exposure is expected and may also account for differences between studies (e.g. if there were different distributions of time since first exposure in different studies). (text continues above)

follow-up has been for only 10 years from first exposure, this represents a selection bias. Thus, Vandenbroucke and Pearce (2015a, b) argue for the inclusion of both incident and prevalent exposures, but with stratification on, and adjustment for, time since first exposure, if appropriate (Example 5.8 and Side Box 5.4).

## 5.3 Identifying selection bias in case–control studies

The case–control design is a particularly efficient approach for studying rare diseases that can be difficult to study prospectively because a large cohort size, a long follow-up period, or both would be required to accrue enough case participants and attain adequate statistical power. Population-based case–control studies can also be advantageous (Side Box 5.5), because they enable the study of exposures across the whole range of occupations and industries, whereas industry-based cohort studies tend to be focused on a restricted group of agents within a specific setting.

As noted earlier, if a cohort study is based on a particular population over a certain period, selection bias can occur from selection into the study, loss to follow-up, left truncation, or right truncation. All of these biases can occur in a corresponding case–control study based on the same source population followed up over the same period. For example, if the source population for a cohort study is restricted to incident exposures (e.g. the newly employed inception cohort in a particular factory or industry) and the follow-up period is too short, bias due to right truncation can occur. A case–control study based on this source population and risk period will be affected by exactly the same bias.

Additional selection issues can arise in case–control studies, particularly because control participants are selected from the source population and bias may occur as a result of this selection process. Bias may also occur if not all of the case participants in the source population and risk period are selected for recruitment into the study. The focus here is on the inappropriate selection of case or control participants, and on non-participation of case and control subjects. It should be reiterated that it is important to distinguish selection bias from generalizability, as discussed in Section 5.1.

When evaluating the literature with regard to the potential for bias due to the selection of case or control participants, the ultimate focus will often be not only on whether there is bias but also on the potential direction and magnitude of the bias. This chapter first discusses the mechanisms of potential bias, with some examples, before turning to the

**Example 5.8.** Right truncation in the cohort of atomic bomb survivors in Japan

A classic example to examine the effects of latency and right truncation draws on the studies conducted among survivors of the atomic bombs in Hiroshima and Nagasaki, Japan. Because the radiation occurred at a known time point, this provides a useful example. In an analysis with follow-up from 1950 through 2000, Richardson et al. (2009) showed that there was no evidence of an association between radiation and lymphoma mortality during periods up to 35 years after irradiation. It was only during follow-up periods of 36–45 years and 46–55 years after irradiation that positive associations were observed, pointing to the need for long follow-up to avoid right truncation. (text continues above)

**Side Box 5.4.** Information that should be reported to enable the assessment of bias due to right truncation

The key parameters that should be reported to enable the post-publication assessment of selection bias due to right truncation are the minimum, median, and maximum lengths of follow-up for the study participants from baseline, as well as the corresponding times since first exposure. As with left truncation (see Side Box 5.3), to enable the assessment of possible bias due to right truncation, the findings should also be stratified by time since first exposure. Once again, heterogeneity by time since first exposure is to be expected for many cancer outcomes. (text continues above)

**Side Box 5.5.** The population-based case–control study Interphone

Within the four main themes considered in this book to illustrate the concepts of interest (red meat consumption, opium consumption, radiofrequency electromagnetic field (RF-EMF) radiation, and night shift work), examples are often drawn from the Interphone study of RF-EMF radiation exposures (Cardis et al., 2010). This carefully conducted multicentre study included several ancillary and detailed analyses to rule out potential biases. While the study is cited here for illustrative purposes, this should not be considered as a judgement on the quality of the study but, rather, reflects the extensive attention given to methodological issues in the study. Therefore, the study represents a model of careful consideration and discussion of such issues. Most published studies do not report this level of information relevant to selection bias. In this situation, one is usually left with other tools for assessing selection bias, for example through the use of negative control exposures or negative control outcomes (see Section 5.4.2) or hypothetical sensitivity analyses (see Section 5.4.4). (text continues on page 132)

question of direction and magnitude of bias in Section 5.4.4. The initial focus is on relatively simple selection mechanisms that enable the reader to intuit the implied direction of the bias. Section 5.4.4 gives more formal tools to determine the direction and magnitude of bias. Elsewhere in this book, biases are discussed in terms of being towards or away from the null. However, selection bias results in biases that are either upwards or downwards, and in this chapter the result of selection bias is referred to in those terms. For instance, an upward bias (which may result if exposed cases are more likely than unexposed cases to be enrolled in the study) could result in a true odds ratio of 1.5 being estimated as an odds ratio of 2.0, which is both upwards and away from the null. However, the same mechanism could bias a true odds ratio of 0.5 to an estimated odds ratio of 0.8, which is both upwards and towards the null.

### *5.3.1 Selection of case participants*

#### *(a) Source of case ascertainment*

Ascertainment of all eligible case participants within a source population can be achieved in several ways, such as using central registry information that is continually updated to include incident cases, or conducting comprehensive active ascertainment of case participants across medical facilities (pathology departments, hospital registries, etc.). Referral by medical sources (treating physicians, clinics, etc.) alone may result in incomplete ascertainment of case participants. To avoid incomplete selection of case participants, information from several sources can be used for cross-validation (Example 5.9).

Depending on the approach being used, cases of more-aggressive or less-aggressive cancers may be missed (Example 5.10). Population-based ascertainment of benign tumours, which are not necessarily included in central tumour registries, can pose a particular challenge. Ascertainment across a very large number of treating institutions may be necessary but is logistically difficult (Example 5.11).

**Example 5.9.** Cross-validation to improve ascertainment of case participants

To improve the accuracy of case ascertainment of brain tumours in the Interphone study, most study centres used one or more secondary information sources, including medical archives, hospital discharge and billing files, and hospital or regional cancer registries (Cardis et al., 2007). (text continues above)

**Example 5.10.** Potential bias resulting from differential selection of case participants

In a case–control study of opium consumption and urinary bladder cancer, conducted in the Islamic Republic of Iran (Shakhssalim et al., 2010), an *IARC Monographs* Working Group noted that there appeared to be a selection of case participants with less-aggressive bladder cancer (Table 2.2 in IARC, 2021). Such differential selection of less-severe cases of cancer could introduce bias if, for example, case participants were ascertained from a screening programme in which opium users were less likely to participate. This could occur because of differences in access to health services or in willingness to access them. In such a situation, exposed case participants would be underrepresented in the case–control study, compared with unexposed case participants, and this would bias the observed effect towards the null. (text continues on page 133)

**Example 5.11.** Potential bias from incomplete case ascertainment of benign tumours

In the Interphone study, many participating centres did not have access to centralized registries of benign parotid gland tumours, and complete case ascertainment would have been problematic (Cardis et al., 2007). As a result, only malignant parotid gland tumours were included in the study. This would not necessarily introduce a selection bias, but it would mean that the findings applied only to malignant tumours and may not be generalizable to benign tumours. (text continues below)

### *(b) Type of diagnosis confirmation*

Studies of cancer usually rely on cases of cancer that have been verified histologically. Rapid access to pathological findings is especially important for cancers with a poor prognosis, and this can preclude the use of central registries. Alternative approaches, which can vary in sensitivity, are sometimes used, depending on the disease and the study setting (Example 5.12).

### *(c) Exclusion of case participants based on previous history of cancer*

In some studies of cancer, patients with previous histories of other cancers are excluded as case participants; this can result in the incomplete inclusion of eligible case participants in the source population and risk period (Example 5.13).

### *(d) Disease detection issues*

Some cancers (e.g. prostate, breast, colon) may be more likely to go undetected in countries where detection is associated with higher SES. The ascertained cases may thus underrepresent subpopulations with lower SES, who in turn may have greater or lesser exposure. An example of this could be lower breast cancer detection among women with lower SES, who may be more often exposed to night shift work. With this selection mechanism, exposed cases would be less likely to enrol than unexposed cases; the observed effect estimate (e.g. the odds ratio) would be biased downwards, and any observed positive effect estimate would be smaller than the true effect estimate due to this selection bias.

### *(e) Inclusion of prevalent cases of cancer*

Cancer case–control studies are usually based on newly diagnosed incident cases (Vandenbroucke and Pearce, 2012). In general, prevalent cases of cancer (i.e. those that were diagnosed at some previous time point) should not be included. However, for some rare tumours with a very prolonged onset, such as chronic lymphocytic leukaemia, it may be difficult to conduct a sufficiently large study without also including prevalent cases. It is sometimes not reported clearly whether a study was

**Example 5.12.** Potential selection bias arising from different sources of case ascertainment

In most participating countries in the Interphone study, diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging (Cardis et al., 2007). However, in a few countries, only histologically confirmed tumours were included. This could introduce selection bias if a particular exposure were associated with diagnostic imaging. For example, if diagnostic imaging were available only through private hospitals, the case group (identified through histology) might underrepresent cases of cancer in more-affluent patients compared with less-affluent ones, and would also underrepresent exposures associated with affluence, although biasing the odds ratio downwards for these exposures. (text continues on page 134)

**Example 5.13.** Potential bias from excluding people with previous cancer from the study

In the Interphone study, patients in Denmark who had been found to have had any previous cancer (excluding non-melanocytic skin cancer) were excluded from the study (Cardis et al., 2007). If mobile phone use was associated with other cancers, this exclusion could lead to fewer exposed cases being eligible for the study. If this were the only source of bias, it would bias the observed effect estimate downwards. More probably, such a source of bias would affect the selection of control participants to a lesser extent. Interested reviewers can use the simple methods outlined in Section 5.4.4 to determine the direction of bias. (text continues on page 134)

restricted to incident cases of cancer or also included prevalent cases (Example 5.14).

Selection of case participants in case–control studies can be accomplished by selecting either all eligible cases or a representative sample of those cases. The most common approach is for an investigator to try to enrol all eligible cases (in the source population, over the risk period) in a case–control study. However, it is also possible to conduct a case–control study by selecting a fraction of the eligible cases. In this study design, investigators should sample cases using the same sampling frame used for controls, namely that selection of case participants should be independent of their exposure status. This point is examined in greater detail in Section 5.3.2.

### *5.3.2 Selection of control participants*

#### *(a) Population control participants*

Ideally, in case–control studies, case and control participants should represent the same underlying source population over the same risk period. Appropriate selection and recruitment of control participants in a study can be a significant challenge logistically and may pose a threat to study validity. Population-based control participants are usually preferred, and several approaches can be taken to attempt a full population coverage; for example, electoral lists, telephone directories, or lists of general practitioners, where available, could be consulted (any restrictions in availability would apply to the source population and should therefore also be applied to the case participants). Exhaustive recruitment of eligible population control participants is difficult, and response rates in case–control studies of cancer have been shown to decrease over the years. For instance, the median response rate among population control participants in this type of study conducted in 1971–1980 was 75.6%, compared with 53.0% in 2001–2010 (Xu et al., 2018). Although a lower response rate does not necessarily produce selection bias, there is a higher potential for such bias to occur. The most important point to emphasize in selection of control participants is that for an unbiased estimate, control participants should represent the exposure distribution in the source population. A sufficient approach to solving this problem is to sample control participants from the

**Example 5.14.** Potential bias arising from inclusion of prevalent cases

When reviewing a case–control study of opium consumption and urinary bladder cancer conducted in the Islamic Republic of Iran (Shakhssalim et al., 2010), the *IARC Monographs* Working Group noted that it was unclear whether newly registered cases of cancer might include prevalent cases (IARC, 2021). If prevalent cases were included, this would mean that the overall case group would be weighted towards patients with less-aggressive tumours, because those previously diagnosed with more-aggressive tumours were more likely to have died. If opium consumption caused less-aggressive tumours and these were overrepresented in the study because of the inclusion of prevalent cases, this in turn would produce an increase in the estimated odds ratio compared with that which would have been obtained if the case group had been restricted to patients with only incident tumours. (text continues on page 135)

source population without regard to their exposure status.

Study participants have repeatedly been shown to have a higher education level or higher SES than non-participants (e.g. Fry et al., 2017). Large differences in SES between case and control participants could reflect selection bias if exposure is associated with SES. This may apply particularly to the selection of control participants, for which there are often larger problems of non-response than in the selection of case participants (Example 5.15).

### *(b) Hospital control participants*

In some instances, it is logistically difficult or impossible to enumerate the source population and therefore impossible to recruit control participants at random from the same source population as the case participants. A common alternative strategy is to recruit as the control group patients (in the same source population and risk period) who have other diseases but attend the same health services as the case participants. In recruiting such control participants, it is important to draw on other diseases unrelated to the exposure of interest (so that selection of control participants does not depend on the exposure), because otherwise there is a risk of introducing selection bias. Although it is not possible to remove such selection bias through analysis, the direction of the bias can be predicted based on knowledge of the exposure and relation to the disease in the control group.

## Key message

If the exposure of interest is a risk factor for the control disease or the prevalence of the exposure is lower in the source population than among the control participants (for some other reason), then the odds ratio estimate is biased downwards. Conversely, if the exposure of interest is a preventive factor for the control disease or the prevalence of the exposure is higher in the source population than among the control participants (for some other reason), then the odds ratio estimate is biased upwards.

**Example 5.15.** Indirect evaluation of potential selection bias from differential participation rates in a case–control study

In a case–control study of night shift work and prostate cancer, the sociodemographic characteristics of participants and non-participants, stratified by case–control status, were compared using census-based SES indicators for participants' residential addresses (Barul et al., 2019). The small differences in SES observed between participants and non-participants provided reassurance that there was not major selection bias based on exposure. If such information were not available, one could still attempt to estimate the probable magnitude and direction of any such bias using the quantitative methods outlined in Section 5.4.4. (text continues above)

Control diseases should be selected with caution after the research question and the exposure of interest have been clearly defined. Furthermore, several diseases can be chosen to dilute potential bias introduced by using one particular disease for the control participants, as well as to provide a sufficient sample size to enable sensitivity analyses with various disease control series.

### *(c) Berkson bias*

Berkson bias is a special type of selection bias that may arise when case participants are selected from hospitalized patients and the exposure of interest affects the probability of hospitalization if some case participants are more likely to be hospitalized if they also have another disease (Snoep et al., 2014). Under this scenario, Berkson bias may occur both in studies with population control participants and in studies with hospital control participants. Fortunately, in cancer studies based on incident cases of cancer, the impact of Berkson bias is likely to be reduced, because most (if not all) case participants selected in the hospital will have been hospitalized because of the case disease (Pearce and Richiardi, 2014). Thus, among those case participants, the exposure is not an independent cause of hospitalization; in other words, it is unlikely that a case participant was incidentally discovered among people admitted to the hospital for a different reason. The same logic applies to selection of control participants when control participants are recruited from within a hospital; the control disease should be the cause of hospitalization, rather than being merely present in patients hospitalized for other reasons (see Examples 5.16 and 5.17).

**Example 5.16.** Evaluating potential Berkson bias in a case–control study

Mohebbi et al. (2021) conducted a case–control study of opium use and head and neck squamous cell carcinoma in 10 provinces in the Islamic Republic of Iran. Included case participants had an incident head and neck cancer and were actively identified through review of admission and treatment information of patients admitted at the cancer care centres of the provinces involved in the study. Control participants were "hospital visitors who were relatives or friends of hospitalized patients in either nononcology wards or who visited the hospital for any reason other than receiving treatment concurrently" (Mohebbi et al., 2021). Berkson bias is unlikely in this study, because all case participants had an incident disease and control participants were not hospitalized. Although Berkson bias may not be a concern in this study, it should be noted that the recruitment of friends as control participants could cause substantial bias, for other reasons. If opium use does, in fact, cause head and neck cancer, we would expect a higher prevalence of opium use among case participants than among the general population. However, friends of hospitalized patients who are opium users may also be more likely to use opium and, as a result, the control series could overestimate the prevalence of opium use in the general population, biasing the observed effect estimate downwards. (text continues above)

**Example 5.17.** Evaluating potential selection bias from recruitment of hospital-based control participants

The Working Group for *IARC Monographs* Volume 126, on opium consumption (IARC, 2021), evaluated several hospital-based case–control studies, all conducted in the Islamic Republic of Iran. For some of these studies, the Working Group raised concerns about the possibility of selection bias arising as a result of the choice of the control diseases. To avoid this source of selection bias, the disease (or diseases) used to identify hospital-based control participants should be unrelated to the exposure of interest (opium consumption in this example), while it can be affected by other risk factors for the case disease that are unrelated to the exposure of interest. (text continues on page 138)

The direction of Berkson bias can be predicted, theoretically, if the direction of the association between the exposure and the control disease is known or, empirically, if there is information on the prevalence of the exposure in the source population (e.g. the catchment area of the hospital). If the exposure of interest is a risk factor for the control disease or the prevalence of the exposure is lower in the source population than among the control participants (who have the control disease), then the odds ratio estimate is biased downwards; if the exposure of interest is a preventive factor for the control disease or the prevalence of the exposure is higher in the source population than among the control participants, then the odds ratio estimate is biased upwards.

Another source of non-population control participants includes visitors to hospitals (see Example 5.16). In some instances, this is less likely to result in selection bias because the visitor control participants are perhaps more likely than hospitalized control participants to be representative of the general (source) population (Example 5.18); however, great caution should be exercised because hospital visitors could share similar exposure patterns to the case patients being visited.

#### *(d) Using more than one control group*

The inclusion of more than one control group allows for a triangulation approach in which the extent and direction of bias is likely to vary across the control groups, and the findings obtained for the different groups can be compared (see Chapter 6). This approach is often used in hospital-based case–control studies in which people with different diseases are recruited to form different control groups (Example 5.19). This topic is discussed further in Section 5.4.4.

### *5.3.3 Participation of case and control participants*

There is a potential for selection bias when both the disease and the exposure status affect participation in the study. This is common in case–control studies, because potential participants typically know their disease and exposure status. In addition, case and control participants may be approached in different settings (e.g. hospitalized case participants and population control participants), and case participants with a poor prognosis might be excluded if they die before recruitment is possible. Furthermore, a person's interest in the study topic may depend on the outcome status (in general, case participants are expected to be more motivated to participate than control participants) as well as on the exposure (some people may believe, for example, that their participation in a study is not essential if they have had no or low exposure); see Example 5.20a.

**Example 5.18.** Recruiting hospital visitors as control participants

In a case–control study of opium use and oesophageal cancer in the Islamic Republic of Iran, hospital visitors were recruited as control participants (Shakeri et al., 2012). In this study, as noted in Examples 5.22 and 4.14, this control group had an exposure prevalence similar to that observed in the general population of the region, whereas hospital-based control participants in a related study had a higher prevalence of opium use compared with the general population. (text continues above)

**Example 5.19.** Triangulation across control groups in a study of titanium dioxide exposure

In a study of occupational exposure to titanium dioxide and lung cancer, an analytical control group was recruited that combined a random selection of an equal number of control participants from the general population and from patients with other cancers, to balance the advantages and disadvantages of recruiting population and hospital-based control participants (Boffetta et al., 2001). (text continues above)

## Key message

Often, participation does not depend directly on the exposure but is related to factors, such as age, sex, or SES (e.g. if young, working-class men are less likely to participate), that are frequently related to exposure (e.g. occupational exposure to pesticides) (Xu et al., 2018). If those determinants of participation were identified and adjusted for, this selection bias could be controlled as if it were a confounder (from a DAG perspective, this is equivalent to blocking a backdoor pathway that was opened due to conditioning on a collider).

For example, if the outcome was not related to SES in the source population but there was differential participation (between case and control participants) by SES in the study population, then SES would be associated with the outcome in the study population; one can then control for this selection bias, by controlling for SES, just as one would control for confounding (Example 5.20b).

At the time of recruitment, and depending on the method of recruitment, it is sometimes possible to ask people, typically control subjects, who decline to participate a few quick questions about their exposure status in general terms and use this information to identify or model potential bias based on exposure (Example 5.20c).

To mitigate the impact of non-response due to death or severe illness, case–control studies may incorporate proxy interviews with the next of kin of the index participants. Although this approach reduces the potential for selection bias and increases the study power, it may introduce bias through non-differential or differential misclassification (see Section 4.2.3). For this reason, studies involving proxy interviews often include a sensitivity analysis restricted to index interviews (Example 5.20d).

## 5.4 Tools for assessing and adjusting for selection bias

When a published paper is considered, selection bias can be particularly difficult to assess, because most published studies provide little or no discussion of the potential for selection bias, in contrast to the usually more extensive discussions of the potential for confounding or misclassification. Furthermore, even if the authors of a paper discuss selection bias, the information needed to determine the extent of selection bias (participation rates of cases or controls, with data for exposure or disease status) is generally unavailable. Therefore, one can be left with the impression that selection bias is possible in the study being considered (e.g. because of a low response rate) but have little information to assess whether such bias is likely or its probable magnitude and direction.

**Example 5.20a.** Potential bias from non-participation in a population-based case–control study

In the Interphone study, a multicentre case–control study of mobile phone use and risk of specific cancer types, the overall participation was 53% for population control subjects, 64% for case subjects with glioma, 78% for case subjects with meningioma, and 82% for case subjects with acoustic neuroma (Cardis et al., 2007; Vrijheid et al., 2009). Of the eligible control subjects identified, 30% refused to participate and 13% could not be traced; the refusal proportion was 11% for all three case participant subtypes, but patients with glioma were more commonly deceased or too ill to participate (15%) than patients with meningioma (2%), patients with acoustic neuroma (0%), or control participants (0%). Because both the proportions of participation and the reasons for non-participation differed between case and control subjects, it is likely that the study was affected by selection bias; however, for this bias to occur, mobile phone use should be associated with participation in case participants, control participants, or both. For example, if people with brain tumours who used mobile phones more often were concerned about the consequences of their phone use and enrolled in the study more often than people with brain tumours who used mobile phones less often, then an upward bias (away from the null if the true OR > 1 and towards the null if the true OR < 1) in the estimated odds ratio would result. (text continues above)

**Example 5.20b.** Demographic variables as surrogates for examining selection bias

In the Interphone study, the proportions of participation by sex and age group were reported separately for case and control participants (Cardis et al., 2007). In general, these two variables were unrelated to participation, except for a much lower participation among older women with glioma and a slightly higher participation in women than in men among control participants. The study estimates were adjusted for age and sex, which were matching variables. The fact that demographic variables were not related to participation may argue against the presence of selection bias, but this is only indirect evidence, because the exposure, namely the use of mobile phones, might still be a determinant of participation. (text continues on page 139)

**Example 5.20c.** Use of short questionnaires among non-respondents in a case–control study

Some centres in the Interphone study asked people who declined to participate (30% of the eligible control participants and 11% of the potential case participants) to complete a short non-response questionnaire (NRQ) (Vrijheid et al., 2009). At the 12 centres that asked eligible control subjects to complete an NRQ, 57% ($n$ = 1678) of control group refusers and 2% ($n$ = 26) of other non-participants who were eligible for the control group completed the NRQ. At the nine centres that used the NRQ for potential case participants, 215 potential case participants completed the NRQ, representing 41% of case group refusers and 4% of other non-participants who were eligible for the case group. In both case and control subjects, regular mobile phone use was more common among study participants than among non-participants who completed the NRQ. The differences were large (69% vs 56% among control participants and 66% vs 50% among case participants). The data collected using the NRQ also indicated an association between refusal and lower education level. This variable had already been selected as a potential confounder for inclusion in all multivariable analyses (Cardis et al., 2007). (text continues on page 139)

**Example 5.20d.** Examining the potential for bias from use of proxy interviews

In the Interphone study, proxy interviews were used for 13% of the case participants (mainly those with gliomas) and 1% of the control participants (Cardis et al., 2007). The exclusion of these participants would have reduced the response proportion among case participants to 59%, not very different from the response proportion observed among control participants. Results of the sensitivity analyses excluding proxy interviews were consistent with the results of the main analyses (INTERPHONE Study Group, 2010). (text continues on page 139)

In this section, tools are discussed that can be used to assess selection bias in published papers when the relevant information is available. Three general types of assessment are considered: (i) substantive knowledge and the use of DAGs; (ii) assessment of selection bias within a single study; and (iii) assessment of selection bias through comparisons across studies. Quantitative sensitivity analysis for selection bias is addressed in Section 5.4.4.

### 5.4.1 Tool S-1: substantive knowledge and DAGs

Assessing the potential for selection bias requires expert knowledge, usually from previously published studies, and mechanistic knowledge. Ideally, this can be summarized in a DAG (see Chapter 2). For example, in a cohort study, if loss to follow-up is systematically associated with both exposure history and disease status (e.g. as in the healthy worker survivor effect; Checkoway et al., 2004), then there is the potential for selection bias, which can be represented in a DAG, in which conditioning on selection (inclusion in the follow-up) produces an open pathway from exposure to outcome, i.e. collider stratification bias. The DAG will not identify whether such a bias is likely to occur (this depends specifically on the recruitment and retention processes of the particular study) or its probable magnitude and direction (although this can be estimated using signed DAGs; see Section 2.6), but it does provide a framework for considering whether such a bias is possible and evaluating any strategies that the authors may have adopted to minimize, control for, or assess it.

Similarly, in a case–control study, if the response rate is particularly low among control participants, it is possible that selection bias may have occurred if recruitment was related to exposure status (Example 5.21). Again, this bias arises through conditioning on inclusion in the study (it is usually only possible to analyse the data for those who were recruited) and introduces an open pathway from exposure to outcome, i.e. collider bias.

Assessing whether the recruitment of hospital control participants has generated a bias, and, if so, its probable magnitude and direction, requires substantive knowledge from previously published studies, or mechanistic information (Example 5.22).

**Example 5.21.** Potential selection bias from differential participation in a case–control study

In the Interphone study, almost all exposed groups were found to have lower risks of brain tumours than the unexposed groups. It has been hypothesized (Cardis et al., 2007) that potential control participants who did not own a mobile phone were less likely to participate. If this were the situation, mobile phone use would be overestimated in the control participants, thus producing a downward bias in the estimated odds ratio. (text continues above)

**Example 5.22.** Potential bias from recruitment of hospital-based control groups

As noted in Example 5.18, Shakeri et al. (2012) conducted a case–control study of opium use and oesophageal cancer in the Islamic Republic of Iran, which involved the recruitment of inpatients in hospitals as control participants. The prevalence of opium use was found to be significantly higher in the hospital control participants than would have been expected on the basis of general population data. One potential explanation for this is that opium use may cause other health problems that result in hospitalization or may be associated with other lifestyle factors that increase the risk of these other health problems. In this situation, the prevalence of opium use in the hospital control participants would be higher than that in the source (general) population, thus producing selection bias. (text continues on page 142)

### 5.4.2 Tools S-2 to S-6: assessment of selection bias within a study

#### (a) Tool S-2: negative control exposures

A negative control exposure approach (see also Chapters 2, 3, and 4) involves assessing the association with another exposure that is believed to not be plausibly associated with the outcome under study but is likely to be subject to a similar selection bias (Example 5.23).

#### (b) Tool S-3: negative control outcomes

A similar approach can be taken with regard to negative control outcomes (Example 5.24). This approach is usually most applicable to cohort studies, because case–control studies are usually based on a single outcome.

#### (c) Tool S-4: ad hoc reanalysis of published data

In some circumstances, if the necessary information is available, it is possible to reanalyse published results in a manner that potentially reduces selection bias. For instance, if it is thought that there has been selective recruitment with regard to exposure status – for example, if unexposed people are less (or more) likely than exposed people to enrol as control participants – it may still be possible to conduct a dose–response analysis that is restricted to exposed participants (Example 5.25). This relies on the assumption that even if unexposed people were less (or more) likely than exposed people to participate, the level of exposure among those who are exposed does not affect the probability of recruitment. This approach has often been used in occupational epidemiology when risk is compared between people with various levels of exposure rather than between exposed and unexposed people; unexposed people are regarded as an entirely different group (Saracci and Samet, 2010). For example, more valid estimates may be obtained by comparing manual workers across different levels of exposure, rather than by comparing the exposed workers with the general population.

#### (d) Tool S-5: comparisons with external data

A further approach for assessing selection bias involves making comparisons with external data on the exposure prevalence in the source population (Examples 5.26 and 5.27). This can involve information either on the exposure itself (e.g. pesticide exposure in the general population) or on a surrogate of exposure (e.g. being a farmer).

**Example 5.23.** Using negative control exposures to examine potential selection bias in a case–control study

In a case–control study of night shift work and breast cancer, any selection pressures (e.g. control participants being less likely to participate if they have never worked night shift) are likely to apply to other non-standard work shifts (e.g. afternoon shift), rather than only to night shift work. If it is well established that afternoon shift work is not associated with breast cancer, then afternoon shift work could serve as a negative control exposure. If a strong association were found between afternoon shift work and breast cancer in the case–control study, this would provide evidence of selection bias, as well as its probable magnitude and direction. (text continues above)

**Example 5.24.** Using negative control outcomes to examine potential selection bias in a case–control study

If it is well established that the main exposure is not associated with a particular outcome (outcome B) that is different from the main outcome under study (outcome A), then this information can be used to assess selection bias (e.g. due to selective recruitment or loss to follow-up). In particular, if the effect estimate (e.g. odds ratio) is elevated to a similar extent in both the main study outcome and the negative control outcome, this may indicate that the increase in risk for the main study outcome is due to bias. (text continues above)

**Example 5.25.** Using dose–response analysis to examine potential selection bias in a case–control study

In the Interphone study, almost all exposed groups were found to have lower risks of brain tumours than the unexposed groups. For example, the odds ratio for the lowest exposure group (< 5 hours of cumulative call time) was 0.8, compared with the unexposed group (INTERPHONE Study Group, 2010). It has been hypothesized (Saracci and Pearce, 2008) that potential control participants who did not own a mobile phone were less likely to participate. If this were the situation, mobile phone use would be overestimated in the control participants, thus producing a downward bias (towards the null if the true OR > 1 and away from the null if the true OR < 1) in the estimated odds ratio. One way to investigate this situation is to conduct analyses excluding both case participants and control participants who were not mobile phone users (Cardis et al., 2007). In this study, the odds ratios for meningioma were only slightly changed, whereas those for gliomas became mostly close to (and above) 1 (Saracci and Samet, 2010); the odds ratio for the top decile of cumulative call time increased from 1.40 to 1.82. Saracci and Samet (2010) comment that the direction of these corrections again indicates a contribution of non-participation (selection) bias to the observed low odds ratios. (text continues on page 142)

**Example 5.26.** Using external data on exposure prevalence to examine potential selection bias in a case–control study of pesticide exposure

In a study of pesticide exposure and soft tissue sarcoma (Smith et al., 1984), control participants who had cancers other than soft tissue sarcoma were recruited, to minimize information bias (because the control participants also had cancer and would have gone through a similar thought process to that of the case participants in terms of the potential causes of their cancer). However, if some of the cancer types in these control participants were also caused by pesticide exposure, selection bias would have occurred due to overrepresentation of pesticide exposure among control participants, thus leading to bias downwards in the estimated odds ratios. Information on pesticide exposure in the general population was not available, but such exposures occur mainly in farming, and information was available on the proportions of workers in various farming groups in the general population. Thus, it was possible to compare the proportions of control participants who were farmers with the expected proportion based on the general population; this comparison showed that it was unlikely that this form of selection bias was occurring (Pearce et al., 1983). (text continues on page 142)

**Example 5.27.** Using external data on exposure prevalence to examine potential selection bias in a case–control study of opium exposure

As described in Examples 4.14, 5.18, and 5.22, Shakeri et al. (2012) compared the results of two different case–control studies of opium use and oesophageal cancer conducted in the same region by a single research group. In one study, hospital-based control participants were recruited, whereas the other study involved control participants drawn from the neighbourhood. The prevalence of opium use was also estimated from a cohort that was enrolled in the same geographical area and therefore probably represented the source population for the study. The standardized opium consumption prevalence was 0.17 in the cohort, 0.16 in the neighbourhood control participants, and 0.23 in the hospital-based control participants, suggesting that the neighbourhood control participants were more representative of the study base population for this exposure. (text continues on page 142)

### *(e) Tool S-6: using several control groups*

It is unusual for studies to involve more than one comparison or control group, but when this is done the information obtained can be used to assess the potential for selection bias. This applies particularly when the various control groups are expected to produce biases in opposite directions, as in Example 5.28.

### *5.4.3 Tool S-7: assessment of selection bias through comparisons across studies*

Selection bias can also be assessed by making comparisons across studies (Example 5.29). This applies particularly when similar studies have been conducted in the same population (e.g. cohort studies involving the same industry or the same group of workers, or case–control studies conducted in the same populations). However, comparisons can also be made between studies conducted in different populations where it is reasonable to assume that the strength of the main exposure–outcome association is likely to be similar. For example, one might compare the findings from studies in which control participants were recruited from the general population with those from studies in which control participants with diseases other than the disease

**Example 5.28.** Using triangulation of findings from different control groups to examine biases in a case–control study of pesticide exposure

In a study conducted in New Zealand to investigate a possible association between phenoxy herbicides and non-Hodgkin lymphoma (Pearce et al., 1986), control participants were recruited from the general population and also from among people who had other cancers. The assumption is that if there were any recall bias, this would be more likely in the general population control participants (who may not recall all of their exposures), and the comparison with this control group would produce artificially high odds ratios (i.e. bias upwards). Conversely, the recruitment of control participants who had other cancers would be expected to minimize recall bias, but there might be selection bias and hence a bias downwards in the estimated odds ratio (see previously) if some of the cancer types in these control participants were also caused by phenoxy herbicides. A key issue is that these biases would operate in different directions, allowing the possibility of triangulation of the findings with the two control groups. In fact, the study produced similar results for each control group, indicating that both recall bias and selection bias were unlikely to be important problems in this study. (text continues above)

**Example 5.29.** Comparisons across studies to examine potential biases in case–control studies

As described in Examples 4.14, 5.18, 5.22, and 5.27, Shakeri et al. (2012) compared the results of two different case–control studies of opium use and oesophageal cancer conducted in the same region by a single research group. Case definition and enrolment of case participants were the same in the two studies. However, the selection of control participants differed: in one study, hospital-based control participants were recruited, whereas the other study involved control participants drawn from the neighbourhood. The prevalence of opium use was found to be significantly different between the hospital and neighbourhood control participants, but the prevalence of tobacco use did not differ between these groups. Consequently, the inference drawn for the association between oesophageal cancer and tobacco use did not differ between the studies, but that for opium use did (IARC, 2021). In the study with neighbourhood control participants, opium use was associated with a significantly increased risk of oesophageal cancer (adjusted OR, 1.8; 95% CI, 1.2–2.7), while in the study with hospital control participants, this was not so (OR, 1.1; 95% CI, 0.6–1.9). This indicates that selection bias is likely to have occurred, and to have been substantial, in the study with hospital control participants, although the possibility that neighbourhood control participants may be prone to other selection factors cannot be ruled out. (text continues above)

under investigation were enrolled. Such comparisons across studies (triangulation) are discussed further in Chapter 6.

### 5.4.4 Tool S-8: selection bias adjustment

In this section, an approach to conducting sensitivity analyses for selection bias is demonstrated, with a detailed worked example using methods described in more detail in Fox et al. (2021), beginning with Example 5.30a.

Selection bias is, mathematically, the easiest bias to adjust for. Table 5.1 illustrates a common way in which selection bias occurs in case–control studies. If $A$ = 100 people are eligible for recruitment to the exposed case group in the population but only $s_{11}$ = 70% of them participate in the study, we would have $a$ = 70 participants. The bias parameter $s_{11}$ is the selection probability for exposed case participants. There are three other selection probabilities – for the unexposed case participants, exposed control participants, and unexposed control participants – that determine which data are observed in a study. These types of parameters, which dictate the extent of the bias in the data, are referred to as bias parameters (Side Box 5.6).

If these four selection probabilities are known, it is easy to divide the observed cell counts by the selection probabilities to recover the 2 × 2 table that would have been observed in the absence of selection bias (assuming that the correct selection probabilities are specified): $A = a/s_{11}$, $B = b/s_{10}$, $C = c/s_{01}$, and $D = d/s_{00}$. Unfortunately, these bias parameters are generally unknown, because they require information on the exposure prevalence among case and control participants in the general population – information that, if it were available, would generally obviate the need to conduct a bias adjustment in the first place. In some situations, selection probabilities may be available from ancillary studies, but these situations are limited. When precise information on selection probabilities is lacking, it is common to choose a range of plausible values for each of the four parameter values and conduct a bias analysis over the combination of values. This is referred to as a multidimensional bias analysis (introduced in Section 4.3.2).

Often, study publications give an overall response or participation rate for case and control participants, and this can be used to reduce the number

**Example 5.30a.** Identifying potential selection bias in a nested case–control study of breast cancer

The Working Group for *IARC Monographs* Volume 124, on night shift work and cancer (IARC, 2020), noted a potential for selection bias in the findings of O'Leary et al. (2006), who had conducted a case–control study of shift work and breast cancer as part of the larger Long Island Breast Cancer Study Project. Case participants were residents of Long Island, New York, who had received diagnoses of incident occurrences of breast cancer between 1 August 1996 and 31 July 1997. Control participants were age-matched to case participants. Control participants younger than 65 years were recruited through random-digit dialling, and those aged 65 years or older were selected from Medicare enrolment lists. Both case and control participants were restricted to people who had lived at the same residence for 15 years or longer. O'Leary et al. (2006) reported that any overnight shift work was inversely associated with breast cancer (OR, 0.55; 95% CI, 0.32–0.94). These results are implausible, based on other reported findings, and it is therefore useful to consider whether the observed protective effect could in part be due to selection bias. The original Long Island Breast Cancer Study Project, within which this study was nested, reported response rates of 82.1% for case participants and 62.8% for control participants (Gammon et al., 2002). O'Leary et al. (2006) reported participation rates for their substudy of 87% for case participants and 83% for control participants. The overall participation rates in the shift work study were unavailable, because the original Long Island Breast Cancer Study Project did not limit enrolment to people who had lived at the same residence for at least 15 years, whereas the substudy on shift work did. Nonetheless, overall rates can be approximated by multiplying the two sets of response rates, yielding an overall response rate of 71.4% for case participants and 52.0% for control participants. Thus, there is certainly a potential for selection bias. (text continues above)

**Table 5.1.** True and observed cell counts in a case–control study with selection bias[a]

| | True cell counts | | Observed cell counts | |
|---|---|---|---|---|
| | **Exposed** | **Unexposed** | **Exposed** | **Unexposed** |
| Case participants | *A* | *B* | $a = A \times s_{11}$ | $b = B \times s_{10}$ |
| Control participants | *C* | *D* | $c = C \times s_{01}$ | $d = D \times s_{00}$ |

[a] Uppercase letters, unobserved true cell counts; lowercase letters, observed cell counts; $s_{ce}$, selection probability by case status ($c$ = 0, 1) and exposure ($e$ = 0, 1).

**Side Box 5.6.** Information that should be reported to enable the assessment of selection bias using sensitivity analysis

The key parameters that should be reported to enable the post-publication assessment of selection bias using sensitivity analysis are the bias parameters shown in Table 5.1, i.e. the selection probabilities for exposed case participants, unexposed case participants, exposed control participants, and unexposed control participants. In some studies, it may be possible to report this information, or proxies for it, if it is available for the source population, and the distribution of these factors (case or control status; exposed or unexposed status) in the study population and the source population can be compared. However, this is rarely the situation; typically, the best that can be done is to hypothesize the probable values (or a range of values) for the four bias parameters shown in Table 5.1 and then conduct the sensitivity analyses covered in this section. (text continues on page 145)

of bias parameters that need to be specified in a sensitivity analysis. For instance, if the overall response rate among case participants is $s_{case}$ and a value for the participation rate among exposed case participants, $s_{11}$, is specified, then the participation rate among unexposed case participants, $s_{10}$, can be calculated as

$$s_{10} = \frac{b}{\frac{a+b}{s_{\text{case}}} - \frac{a}{s_{11}}} \qquad (5.1)$$

A similar equation exists for the control participants, if the overall response rate among control participants, $s_{control}$, is known:

$$s_{00} = \frac{d}{\frac{c+d}{s_{\text{control}}} - \frac{c}{s_{01}}} \qquad (5.2)$$

These two equations can be used to implement a sensitivity analysis for selection bias that only requires plausible values to be specified for two remaining unknown parameters: the selection probability among exposed case participants ($s_{11}$) and the selection probability among exposed control participants ($s_{01}$), as in Example 5.30b.

These methods enable the researcher to judge how much the point estimate can change after adjusting for selection bias, assuming that the bias parameters are correctly specified, but they do not incorporate uncertainty due to random error. Fortunately, relatively simple procedures can be used to produce interval estimates around the bias-adjusted effect estimates; indeed, the typical variance estimates (e.g. using the delta method) for the log odds ratio that would be calculated from the biased data can be used directly (Example 5.30c).

Quantitative bias analysis methods to adjust effect estimates for selection bias are easily implemented, but the user should be cautious, for several reasons. The first is that the methods rely on accurate specification of the bias parameters. Incorrect guesses of the selection probabilities will result in incorrect bias adjustments. Furthermore, although it may be tempting to assume that if the specified selection probability is close to the truth then the bias-adjusted result will be close to unbiased, this turns out not to be true in general. Having a bias parameter that is close to the true selection probability may still result in a badly biased adjusted effect estimate. The best solution to this problem is to conduct a multidimensional bias analysis (such as that in Table 5.2) and determine the sensitivity of the adjusted effect estimate to changes in the bias parameters.

**Example 5.30b.** Quantitative bias analysis to examine potential selection bias in a nested case–control study of breast cancer

The estimated response rate among case participants ($s_{case}$ = 0.714) and among control participants ($s_{control}$ = 0.520) can be used to implement a quantitative bias analysis for selection bias in the shift work study of O'Leary et al. (2006). To begin the quantitative bias analysis, the crude 2 × 2 data are abstracted from the paper ($a$ = 26, $b$ = 313, $c$ = 50, and $d$ = 321). As reported in O'Leary et al. (2006), control participants who reported a history of overnight shift work were younger, had a lower household income, and were less likely to have had a mammogram than control participants who had never engaged in overnight shift work. It is assumed that both eligible case participants and potential control participants who had engaged in overnight shift work were less likely to participate in the study than women who had not engaged in overnight shift work. That is, it is assumed that $s_{11} \leq s_{10}$ and $s_{01} \leq s_{00}$. Furthermore, it is assumed that women with incident breast cancer are at least as likely to participate in the study as those without breast cancer: $s_{11} \geq s_{01}$ and $s_{10} \geq s_{00}$. To conduct a sensitivity analysis, we choose a range of values of the bias parameters $s_{11}$ and $s_{01}$ compatible with these assumptions. For example, the selection probability among exposed case participants is specified as slightly lower than the overall response rate among case participants, $s_{11}$ = 0.7. Similarly, the response rate among exposed control participants is specified as slightly lower than the overall response rate among control participants, $s_{01}$ = 0.5. With these values, the selection probability among unexposed case participants can be calculated as

$$s_{10} = \frac{313}{\frac{26+313}{0.714} - \frac{26}{0.7}} = 0.715 \qquad \text{(E5.1)}$$

Similarly, the selection probability among unexposed control participants can be calculated as

$$s_{00} = \frac{321}{\frac{50+321}{0.520} - \frac{50}{0.5}} = 0.523 \qquad \text{(E5.2)}$$

With the four selection probabilities specified, a selection-bias-adjusted odds ratio can be calculated:

$$\mathrm{OR}_{\mathrm{adj}} = \frac{\frac{a}{s_{11}} \times \frac{d}{s_{00}}}{\frac{b}{s_{10}} \times \frac{c}{s_{01}}} = \frac{\frac{26}{0.7} \times \frac{321}{0.523}}{\frac{313}{0.715} \times \frac{50}{0.5}} = 0.52 \qquad \text{(E5.3)}$$

For this set of bias parameter values, one would expect that in the absence of selection bias, approximately the same protective effect of overnight shift work would have been observed ($OR_{adj}$ = 0.52 vs $OR_{crude}$ = 0.53). Note that the second odds ratio is calculated directly from the cells of the observed 2 × 2 table and does not adjust for any confounders. This result is the first row of Table 5.2. This calculation is repeated for $s_{11}$ = {0.7, 0.6, 0.5, 0.4} and $s_{01}$ = {0.5, 0.4, 0.3}. The spreadsheet used in this example is provided in Annex 2 (online only; available from: https://publications.iarc.who.int/634#supmat). No combination of these selection probabilities leads to a bias-adjusted odds ratio that supports a harmful effect of overnight shift work. Most bias parameter combinations lead to more protective bias-adjusted effects; only bias parameters that may be viewed as less plausible, such as those with higher participation rates among exposed control participants than among exposed case participants, lead to adjusted effects near the null. These results suggest that for these bias parameter values, selection bias is not likely to be responsible for the observed protective effect of shift work.

**Example 5.30b.** Quantitative bias analysis to examine potential selection bias in a nested case–control study of breast cancer (continued)

**Table 5.2.** Sensitivity analysis for overnight shift work and incident breast cancer from a case–control study[a]

| Bias parameters | | | | Bias-adjusted OR[b] | 95% confidence interval |
|---|---|---|---|---|---|
| $s_{11}$ | $s_{10}$[b] | $s_{01}$ | $s_{00}$[b] | | |
| 0.7 | 0.715 | 0.5 | 0.523 | 0.52 | (0.32–0.86) |
| 0.7 | 0.715 | 0.4 | 0.545 | 0.40 | (0.24–0.66) |
| 0.7 | 0.715 | 0.3 | 0.587 | 0.28 | (0.17–0.46) |
| 0.6 | 0.725 | 0.5 | 0.523 | 0.62 | (0.37–1.01) |
| 0.6 | 0.725 | 0.4 | 0.545 | 0.47 | (0.29–0.78) |
| 0.6 | 0.725 | 0.3 | 0.587 | 0.33 | (0.20–0.54) |
| 0.5 | 0.740 | 0.5 | 0.523 | 0.75 | (0.46–1.24) |
| 0.5 | 0.740 | 0.4 | 0.545 | 0.58 | (0.35–0.95) |
| 0.5 | 0.740 | 0.3 | 0.587 | 0.40 | (0.25–0.66) |
| 0.4 | 0.764 | 0.5 | 0.523 | 0.97 | (0.59–1.60) |
| 0.4 | 0.764 | 0.4 | 0.545 | 0.75 | (0.45–1.23) |
| 0.4 | 0.764 | 0.3 | 0.587 | 0.52 | (0.32–0.86) |

OR, odds ratio.
[a] Using an overall response rate among case participants of $s_{case} = 0.714$ and an overall response rate among control participants of $s_{control} = 0.520$ and the observed cell counts ($a = 26$, $b = 313$, $c = 50$, and $d = 321$).
[b] $s_{10}$ and $s_{00}$ and the adjusted odds ratio are calculated using the formulae given in this section, conditional on the observed cell counts and overall response rates.
*Source:* O'Leary et al. (2006).

(text continues on page 146)

**Example 5.30c.** Confidence interval estimation when quantifying selection bias for a nested case–control study of breast cancer

In the study by O'Leary et al. (2006), the variance estimated from the crude data is

$$\mathrm{Var}(\log \mathrm{OR}) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d} = \frac{1}{26} + \frac{1}{313} + \frac{1}{50} + \frac{1}{321} = 0.06 \quad \text{(E5.4)}$$

This variance can be used in conjunction with the bias-adjusted effect estimates derived in Example 5.30b. For example, in the first row of Table 5.2, the bias-adjusted odds ratio is 0.52, and the 95% confidence interval can be calculated as

$$\ln(0.52) \pm 1.96 \times \sqrt{0.065} = (0.32, 0.86) \quad \text{(E5.5)}$$

Similar calculations can be included for each row of Table 5.2 to generate bias-adjusted interval estimates. (text continues on page 146)

A second cause for concern is that the methods presented here admit no uncertainty about the bias parameters; they assume complete confidence in the parameter value. It is possible to specify a distribution for each bias parameter, with that distribution representing the investigator's uncertainty regarding the value of the bias parameter, and then to conduct a probabilistic bias analysis (Example 5.30d).

In a probabilistic bias analysis, uncertainty is incorporated into the bias parameter by repeatedly sampling selection probabilities from each of the four bias parameter distributions. Each set of sampled bias parameters is used to bias-adjust the observed table, as before. Finally, to incorporate the conventional random error, the variance should be based on the non-bias-adjusted cell counts, as calculated previously. This approach is iterated a large number of times, and the resulting estimates are summarized by an overall bias-adjusted estimate (the median of the bias-adjusted results) and an uncertainty interval (the 2.5th and 97.5th percentiles of the bias-adjusted results). This approach can easily be implemented in Excel, R, Stata, or SAS. To find the bias analysis estimate given in Example 5.30e, Excel spreadsheets were used, with 1000 iterations (https://sites.google.com/site/biasanalysis/Home; Fox et al., 2021); the spreadsheet is provided in Annex 2 (online only; available from: https://publications.iarc.who.int/634#supmat).

## 5.5 Other miscellaneous biases

In this final section, several biases are considered that do not necessarily fit neatly into the categorization of biases comprising selection bias, information bias, and confounding.

**Example 5.30d.** Probabilistic bias analysis to examine potential selection bias in a nested case–control study of breast cancer

In the study by O'Leary et al. (2006), one might believe that the selection probability among the exposed case participants is between 0.6 and 0.8, with 0.7 the most likely selection probability; one could then parameterize this belief as a triangular distribution with a minimum of 0.6, a maximum of 0.8, and a mode of 0.7. This distribution should capture a well-informed belief about the distribution of plausible selection probabilities among the exposed case participants. Similarly, a distribution for each of the three other selection probabilities could be parameterized. For the purposes of this example, the selection probabilities from the first row of Table 5.2 are used. It is assumed that the mode of each distribution is the selection probability given in the table ($s_{11}$ = 0.7, $s_{10}$ = 0.715, $s_{01}$ = 0.5, and $s_{00}$ = 0.523). For simplicity, it is assumed that the minimum of each of the distributions is 0.1 below the mode and the maximum is 0.1 above the mode (e.g. the distribution for $s_{01}$ is centred at 0.5 and has a minimum of 0.4 and a maximum of 0.6). (text continues above)

**Example 5.30e.** Applying probabilistic bias analysis results to estimated odds ratios in a nested case–control study of breast cancer

For the study by O'Leary et al. (2006), the probabilistic bias analysis returns an odds ratio of 0.52 (95% credibility interval, 0.29–0.91). The point estimate is identical to the point estimate obtained from the simple bias analysis; this will generally be the situation whenever the bias parameter distribution is symmetrical around the mode. The interval estimate for the probabilistic bias analysis is larger than that for the simple quantitative bias analysis; this will generally be the situation, because the intervals for the former analysis incorporate additional uncertainty around the bias parameters. (text continues above)

### 5.5.1 Healthy worker biases

There are two types of healthy worker bias. The first type is healthy worker hire bias, which occurs when relatively healthy individuals in an occupational population are compared with the general population; it may lead to downward bias in relative mortality measures (e.g. for all causes or for all cancers) (Checkoway et al., 1989, 2004). The second type is healthy worker survivor bias, which occurs because workers who are healthy are more likely to stay employed for longer, thus experiencing the greatest amount of exposure (Pearce et al., 1986). Because of these two selection processes, an occupational population is usually inherently non-comparable with the general population with which it is typically compared in occupational cohort studies. This occurs even if participants continue to be followed up after they leave employment, because they are likely to have lower lifetime cumulative exposure than those who remain in employment. Although healthy worker bias is most commonly discussed in terms of occupational cohort studies, the same issues of bias apply to other study designs (such as nested case–control and cross-sectional studies) that are based on the experience of a cohort over time.

Some authors regard healthy worker bias as an example of selection bias, because of the selection of an inappropriate comparison population (i.e. comparing the general population with a healthy employed population) or conditioning on employment in the industry. Others regard it as an example of confounding, because employed people and those who remain in employment are generally healthier than the rest of the source or general population with which they are being compared (Checkoway et al., 2004; Keil et al., 2015). In the context of this book, healthy worker bias can be regarded as confounding, because it arises from inherent differences between employed and non-employed subgroups in the source population. Therefore, it is also addressed in Chapter 3.

### 5.5.2 Immortal time bias

Immortal time bias arises if the definition of one of the two exposure groups that are compared within a study is specified incorrectly, such that there is a period during which members of that exposure group accumulate person-time but will not be included in the study if they experience the outcome (Hanley and Foster, 2014). A good example of this was presented as far back as the 1840s by William Farr: generals and bishops live longer than curates and soldiers, but only because one has to reach a certain age to hold such a position (Farr and Humphreys, 1885). This can be regarded as a type of selection bias (related to time-zero specification, described in Section 5.2.3), because some study participants are only included in the analysis if they survive up to a certain time point, but if they do, their person-time up to that point is incorrectly included in the data analysis. Although this issue may seem obvious, this error seems to reappear in epidemiology, and immortal time bias has led to seriously flawed results (Example 5.31).

### 5.5.3 Reverse causation and protopathic bias

Reverse causation occurs when the exposure changes after the disease of interest occurs or is caused by the diagnosis of the disease. This can be viewed as a type of differential information bias, because exposure has been measured at the wrong time (i.e. too close to the occurrence of disease) and is therefore misclassified. The easiest way to avoid reverse causation is to use a prospective cohort study design, in which a condition of enrolment in a study is not having cancer, perhaps after an initial period to allow for the appearance of cancers that were latent but not yet diagnosed, and then to assess exposure. In case–control studies, reverse causation may occur when there is not careful assessment of the timing of exposure and confirmation that the disease occurs after the occurrence of exposure. One method of evaluating the effect of reverse causation is to exclude individuals who only recently experienced the exposure of interest (Example 5.32).

Protopathic bias is related to reverse causation and is often included in the definition of reverse causation. However, it differs in that the occurrence of disease does not directly affect exposure status. Rather, protopathic bias occurs indirectly when a symptom of the undiagnosed disease causes a change in the exposure of interest in the case participants. Protopathic bias can occur in both cohort and case–control studies (Example 5.33).

In cohort studies of cancer types for which survival is poor, the exclusion of patients who were diagnosed within the early period of follow-up can provide evidence about the extent of

**Example 5.31.** Immortal time bias in a registry study related to solar radiation exposure

Immortal time bias was observed in a registry study of skin cancer in Denmark (Brøndum-Jacobsen et al., 2013; Lange and Keiding, 2014). The researchers aimed to investigate any beneficial effects of sun exposure on longevity, but because they did not have access to information on sun exposure, they chose people with a diagnosis of skin cancer as a proxy for high sun exposure. The comparison group was all people in Denmark without a diagnosis of skin cancer, and follow-up started at age 40 years. Whereas people in the comparison group were at risk of dying from this age onward, it was impossible for people in the skin cancer group to die before the age of diagnosis, which was, on average, 68 years. The immortal time bias led to people with skin cancer having half the mortality risk of people without skin cancer (relative risk, 0.52), and the study received great attention in the media in Denmark, with front pages stating that sunbathers live longer. In such a study, the correct analysis would be to allow people to change exposure status as they proceed through the study period (this is equivalent to using a time-dependent variable in a Cox model; Pearce et al., 1988). Thus, in this situation, the people with skin cancer should have been considered as part of the unexposed group until they received a diagnosis, and the results of the analysis would have been very different. (text continues on page 150)

**Example 5.32.** Examining reverse causation in a case–control study of oesophageal cancer

In a case–control study of oesophageal cancer and opium use, there was concern that reverse causation may partially explain the odds ratio of 2.00 (95% CI, 1.39–2.88), if people who developed cancer had a subsequent increased likelihood of taking up opium use. Therefore, Nasrollahzadeh et al. (2008) restricted the analysis to users who had reported use earlier than 1 year before cancer diagnosis; this gave an odds ratio of 1.92 (95% CI, 1.30–2.84), indicating that reverse causation is unlikely to explain the association. (text continues on page 150)

**Example 5.33.** Examining protopathic bias in case–control studies of opium use and cancer

Opium consumption is an excellent example of an exposure that may be affected by protopathic bias in studies of cancer. In this case, the symptoms of undiagnosed cancer may motivate the patient to self-medicate with opium, making it appear that opium use increases the risk of disease. In studies of opium use and lung cancer, one of the causes of protopathic bias is related to the antitussive properties of opium. Because one of the early symptoms of lung cancer is coughing, the use of opium to ameliorate these symptoms may introduce protopathic bias. In this situation, because tobacco smoking is related to both coughing and lung cancer, controlling for smoking will minimize the risk of protopathic bias. (text continues on page 150)

protopathic bias (Example 5.34). The impact of protopathic bias is more difficult to assess for cancer types for which survival times are longer.

### 5.5.4 Inappropriate control for a collider (other than selection into the study) in the analysis

Bias can also arise from inappropriate control for a collider (other than selection into the study) (Pearce and Lawlor, 2016), even if 100% of the source population has been recruited into the study (and therefore there cannot be selection bias). Briefly, controlling for any collider can open a backdoor pathway involving that collider, and the resulting bias can only be controlled by controlling for at least one other variable on the same backdoor pathway (Example 5.35).

### 5.5.5 Biases in biomarker exposure measures

Biomarkers are now extensively used in cancer epidemiology. Within the concept of the exposome, their application has widened to incorporate new high-throughput techniques to evaluate exposure or intermediate pathways and preclinical disease markers (e.g. Wild, 2005). In the context of this book, we consider mostly biomarkers of exposure, i.e. measurements in body fluids or other tissues that correlate with an environmental exposure or an exposure mixture. Biases arising from the use of biomarkers can most commonly be regarded as information bias, but these issues are considered here because they also relate to reverse causation. In contrast, the appropriate use of biomarkers can help to avoid or minimize information bias.

Biomarkers can be used as direct measures of exposure in study participants and are frequently used in a subpopulation to develop exposure models that are then applied to the whole study population by modelling using proxies of exposure (Example 5.36).

Like for any other exposure measured through questionnaires or other methods, errors in biomarker measurements can result from both non-differential and differential misclassification (Fig. 5.4).

#### *(a) Non-differential errors in biomarker measurements*

In a case–control study of breast cancer (Mukherjee Das et al., 2022), using urinary concentrations of short-lived chemicals (e.g. phthalates) would introduce non-differential misclassification because of extreme time-related misclassification. The time window of interest for a chronic disease, such as breast cancer, could be 10–20 years before clinical disease diagnosis, while the biomarker would measure exposure only during the previous few weeks. It is unlikely that breast cancer status would affect the performance of the biomarker test or alter levels of phthalates; thus, this is a non-differential misclassification mechanism. Chapter 4 describes tools to assess the direction and magnitude of non-differential biases in continuous exposures.

**Example 5.34.** Evaluating the potential impact of protopathic bias in a study of pancreatic cancer

In a cohort study of prognostic factors for pancreatic cancer, for which survival is poor, Sheikh et al. (2020) evaluated the potential impact of protopathic bias by excluding any participant who had started using opium in the 2 years before receiving a diagnosis. They found minimal impact on the results when the few participants who had started using opium recently before diagnosis were excluded. (text continues above)

**Example 5.35.** Inappropriate adjustment for a collider

Richiardi et al. (2008) provide an example of inappropriate adjustment for SES in occupational cancer studies. They consider the scenario where SES is not a cause of the cancer under study but is associated with other occupational factors (apart from the main exposure) that are causes of the cancer under study. In this situation, adjustment for SES can open a backdoor pathway involving the other occupational factors, and thus bias the effect estimate for the main occupational exposure under study. (text continues above)

**Example 5.36.** Modelling using biomarker-based proxies of exposure in a study of herbicide exposure

In the IARC cohort of phenoxy herbicide (Agent Orange) workers who were exposed to dioxins that are contaminants of the herbicides (Saracci et al., 1991; Kogevinas et al., 1997), several studies were conducted among industrial workers and professional sprayers to measure the most toxic dioxin compound, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), in blood samples. In most workers, measurements were made several years after the end of employment (IARC, 1997). Measurement after the end of employment can be problematic for most chemical exposures, because of the short half-life of most compounds; the chemicals are eliminated from the body during a relatively short time (hours, days, or a few months). Dioxins, like other persistent organic compounds and some metals and radionuclides, have a long half-life, frequently longer than 5 years. In the dioxin cohorts, levels of TCDD since first exposure could be reconstructed by modelling, using information from individual job records and individual measurements of blood levels of TCDD (Fig. 5.3). The studies in subsamples indicated a strong correlation of TCDD levels with duration of employment in jobs or industries with potential exposure to TCDD; it was also observed that TCDD levels increased only after substantial exposure to the herbicides, approximately after at least 1 year of exposure. Exposure models were then developed for all the cohort participants, based essentially on information on duration of exposure. (text continues on page 152)

**Fig. 5.3.** Serum levels of TCDD, adjusted for lipids, in 253 workers in the USA, as a function of years of exposure

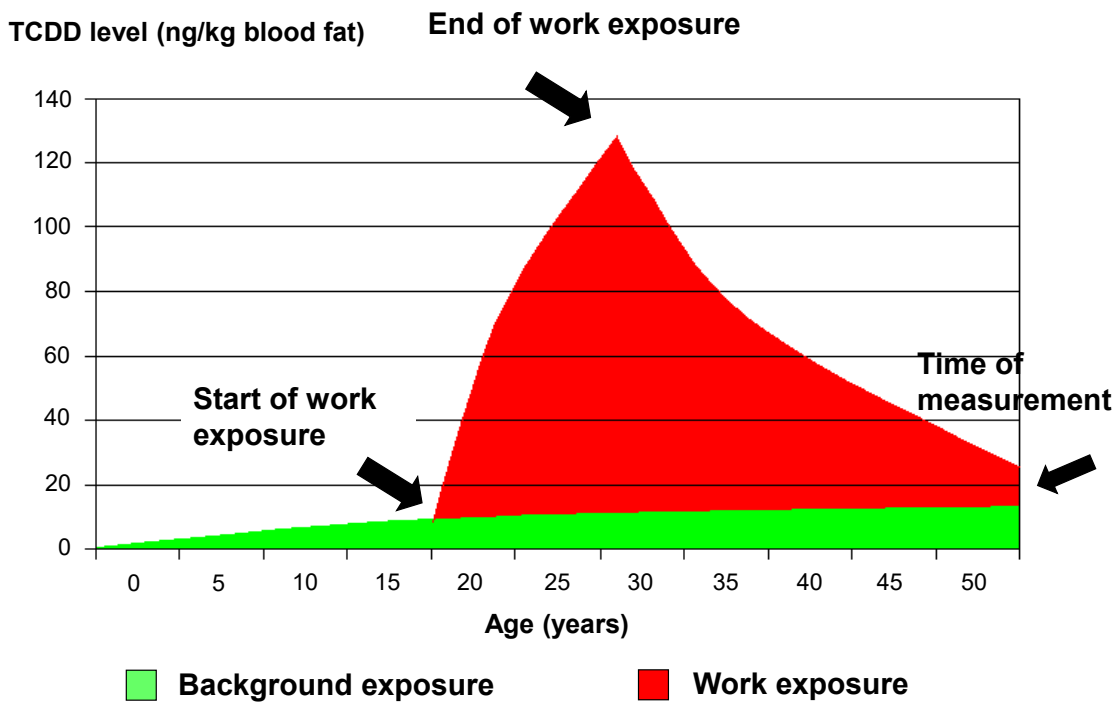
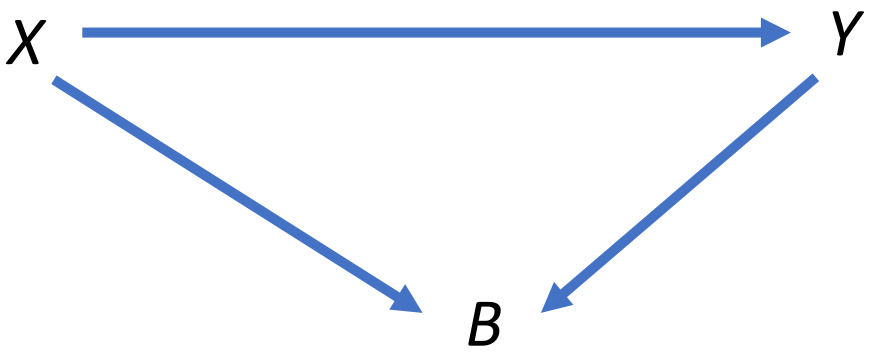


**Fig. 5.4.** If *X* (exposure) is associated with *B* (biomarker) and there is measurement error of *B*, this would induce non-differential misclassification. If the disease (*Y*) affects the levels of *B*, this would induce differential misclassification.




### *(b) Differential errors in biomarker measurements*

If the biomarker levels were affected by the disease, this could also introduce differential misclassification in a case–control study, because levels among case participants would depend on disease status. This has been described in relation to measurements of chemicals in cancer types with poor prognosis, for example where disease could have affected weight and consequent mobilization of fat tissue, where several persistent compounds are stored in the body. Similarly, the possibility of differential misclassification has been raised in relation to tumours affecting immune status, for example measurements of infectious agents through antibodies, the production of which could be affected by the disease (Aguilar et al., 2017), as in Example 5.37. Section 4.2.3 describes tools for assessing the direction and magnitude of bias from differential exposure.

## 5.6 Summary

In summary, selection bias can occur because of differences between the study population and the source population. Selection bias can arise through various mechanisms, such as incomplete recruitment from the source population or loss to follow-up. This selection bias is distinct from issues of representativeness or generalizability or transportability, which relate to comparisons between the target population and the source population.

In general, selection bias occurs as a result of incomplete recruitment, if selection depends differentially on exposure and disease status (e.g. if exposed case participants are more or less likely than other groups to be recruited) and if this incomplete

**Example 5.37.** Differential errors resulting from use of biomarkers in studies of Burkitt lymphoma

Infection with Epstein–Barr virus is a primary cause of endemic Burkitt lymphoma, a common neoplasm in children in Africa. An ecological association has been reported between endemic Burkitt lymphoma and the prevalence of malaria due to infection with *Plasmodium falciparum* (IARC, 2013). In a case–control study of Burkitt lymphoma in children in Malawi, blood levels of antibodies to both Epstein–Barr virus and *P. falciparum* were evaluated, and it was found that there was a strong association with Epstein–Barr virus, a moderate association with *P. falciparum*, and an additive interaction of both infections. However, the observed associations with the two infections could be due to differential misclassification, because antibody levels could be different for children with and without Burkitt lymphoma, particularly if reverse causation was involved, i.e. if having Burkitt lymphoma increased the risk of being infected with malaria. (text continues above)

recruitment is not adjusted for in the analysis. In cohort studies, important mechanisms for selection bias include non-response at baseline, loss to follow-up, left truncation, right truncation, and immortal time bias. In case–control studies, all of these biases are possible; in addition, bias could occur through inappropriate selection of control participants (e.g. a control group that does not provide a valid estimate of the exposure history in the source population).

Qualitative tools for assessing the existence, direction, and magnitude of selection bias include the use of negative control exposures, negative control outcomes, ad hoc reanalyses of published data, comparisons with external data, and the use of several control groups. All of these can be regarded as types of triangulation. Quantitative methods also exist for sensitivity analyses that involve adjusting for hypothesized selection bias. Although these calculations are relatively easy to implement, it is often the situation that there will not be adequate information to specify bias parameters for a range of possible selection effects.

Thus, as noted in Chapter 1, one of the primary questions posed to *IARC Monographs* Working Group experts is, "Can we reasonably rule out selection bias as an explanation for an observed exposure–cancer association?" This can be particularly difficult to assess, because most published studies provide little or no discussion of the potential for selection bias, in contrast to the usually more extensive discussions of the potential for confounding (Chapter 3) or misclassification (Chapter 4). Therefore, it is important that authors, and editors, are encouraged to report the information that is required for a valid assessment of the potential, direction, and magnitude of possible selection bias, as described in Chapter 7.

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