How to Present Limitations and Alternatives

13

Now that you have identified the potential sources of bias and confounding in your proposal with the help of Chapter 12, *A Review of Bias and Confounding*, it is time to decide how to best present these limitations to your reviewers.

The Approach section of a proposal should discuss potential study limitations and alternative strategies. Therefore, this chapter describes strategies for presenting study limitations with a focus on techniques to minimize their impact. Part I of the chapter starts with a fourfold approach to strategically presenting limitations. Part II of the chapter applies this approach to the typical study limitations that you are likely to face. Part II goes on to additionally review design and analytic techniques for minimizing these threats to validity along with accompanying examples.

13.1 WHICH LIMITATIONS TO HIGHLIGHT?

One of the goals of writing a dissertation proposal is to demonstrate that you have mastery of the concepts of bias and confounding. Therefore, it is typically expected that a dissertation proposal will cover each potential study limitation listed in the "Issues for Critical Reading" tables in Chapter 12. The proposal will state why it does, or does not, face each limitation. This process demonstrates to the dissertation committee that the student has an understanding of each type of study limitation regardless of whether or not it is a serious threat to their approach.

In contrast, in the context of a grant proposal, there is no room for this type of exercise given space limitations. Instead, you are expected to comment only on the most important/major limitations of your proposal. This gives you the opportunity to address what you anticipate will be the most important threats to validity and to discuss the methods that you will use to minimize these concerns. Finally, as I will demonstrate below, you will also discuss why you dismissed alternative approaches.

13.2 PART I: HOW TO STRATEGICALLY PRESENT LIMITATIONS—A FOURFOLD APPROACH

The key principle in presenting limitations is **transparency**. As mentioned in Chapter 12, instead of trying to hide limitations, you want to identify and present them. You want to be open about your thought process and describe the pros and cons of your study design decisions. Remember that there is no perfect study. All studies face limitations, and being humble and knowledgeable about these limitations will be more impressive to reviewers than ignoring them.

A fourfold approach can be used when presenting limitations as outlined in the Figure 13.1: (1) describe the potential limitation, (2) describe the potential impact of the limitation on your study findings, (3) discuss alternatives and why they were not selected, and (4) describe the methods that you propose to minimize the impact of this limitation.

13.2.1 Step #1: Describe the Potential Limitation

For each important limitation that you identify, specify the type. For example, is it nondifferential misclassification of exposure or outcome (e.g., error), or is it a more dangerous limitation—that is, a differential bias such as selection bias, information bias, or confounding? Or, perhaps the limitation is not related to internal validity, but is instead a matter of external validity such as limited generalizability of study findings.

As a starting point, consider limitations mentioned by the prior literature on your exposure and outcome of interest. Even if you do not face the same limitations, you will want to be sure to highlight this fact as a study strength.

The most important key to success in writing a limitations section is to avoid the use of professional jargon without an accompanying explanation. *Professional jargon* refers to the use of such terms as *selection bias*, *information bias*, *nondifferential misclassification*, and *confounding*. Additionally describing your study limitations in a direct manner using simple terms will show the reviewers that you have a clear grasp

Step 1: Identify the limitation
Step 2: Describe the impact on your findings
Step 3: Discuss alternatives
Step 4: Describe methods to minimize

FIGURE 13.1 A fourfold approach for presenting study limitations in a proposal.

of these limitations—this may be somewhat counterintuitive but it is true. For NIH grant proposals, this is even more important, as not all of your reviewers will have training in epidemiology and preventive medicine; some will have expertise in other pertinent fields.

Imagine a proposal to conduct a prospective study of postmenopausal hormones (hormone replacement therapy [HRT]) on risk of breast cancer.

Original Version
This proposal may face detection bias.
Improved Version
One potential source of bias in our study is detection bias. In other words, those who are taking HRT are more likely to have mammograms and thus more likely to be diagnosed with breast cancer than those women not taking HRT. This would lead to an overestimate of the association between HRT and breast cancer.

Note that the improved example still includes professional jargon (i.e., *detection bias*) but then goes on to define it. To further save space, the term *detection bias* could be removed entirely from the improved example to avoid altogether the use of jargon.

13.2.2 Step #2: Describe the Potential Impact of the Limitation on Your Study Findings

For each limitation, it is important to try to project the:

- Likelihood
- Magnitude
- Direction of the limitation on your study findings

Remember, as discussed in Chapter 12, that some limitations are more likely to bias your findings toward the null value, while others are more likely to bias your findings away from the null. Other limitations may have an unpredictable impact on your findings.

In general, limitations that lead to a bias toward the null are considered less dangerous than limitations that cause a bias away from the null. On the other hand, limitations that lead to a conclusion that your exposure impacts your outcome when it does not (i.e., a bias away from the null) are often considered more dangerous.

Such limitations will lead your reviewers to carefully scrutinize your methods, as well as the alternatives that you considered. The reviewers will assess whether you have minimized these limitations to the extent possible.

Imagine a proposal to conduct a cross-sectional study of acid-lowering agents (ALA) and risk of vitamin B12 deficiency. Participants in this study will be asked to self-report their ALA during a home interview.

It is possible that people with vitamin B12 deficiency will be more motivated to remember ALA use than people without vitamin B12 deficiency. Such a recall bias would result in an **overestimate** of the relationship between ALA use and vitamin B12 deficiency.

Note that the example indicates the likelihood, direction, and magnitude of the study limitation—as indicated by the bold phrase.

A potential pitfall to avoid

As noted earlier in this chapter, in a grant proposal, you are expected to only comment on the most important limitations of your proposal. For example, let's say that you are proposing to conduct a prospective cohort study. Given this design, it is probably not necessary to waste space by saying that this type of design reduces the risk of selection bias because participants are enrolled before the outcome occurs. However, given that your assigned reviewers may not include epidemiologists, and one of your study strengths is the prospective design, it may not hurt to point this out. On the other hand, in a doctoral proposal, you are expected to show mastery of all the potential limitations.

Imagine a graduate proposal that simply states the following:

Original Version

This study is a prospective cohort and therefore is not subject to recall bias.

Improved Version

This study is a prospective cohort, and as such, information on exposure is collected prior to the occurrence of the outcome. Therefore, it is unlikely that the outcome will influence the collection of information on the exposure of interest.

In this example, the first quote would not be sufficient for most dissertation committees, as it does not display that the student understands the concept of recall bias. The improved example clearly defines the concept of recall bias as it relates to the proposed study design and then dismisses it as being unlikely.

Because it is typically considered fair game to ask about any potential limitation at a dissertation defense, considering each potential limitation will provide you with a well-thought-out response for why or why not your study faces each potential limitation.

13.2.3 Step #3: Discuss Alternatives

In any proposal, there will be alternative approaches that you could have, but chose not to, propose. Discuss these alternatives—both their pros and cons—and clearly explain to the reviewer why you chose the approach that you did. In writing this section, be up to date on approaches that prior studies have used and the subsequent impact on their findings. Be sure to cite any review articles or convened panels that make particular recommendations—this can be persuasive evidence in support of the approach that you ultimately chose to take, or it can lead you to reconsider this decision. At the least, it will help you to become adept at defending your decision—both in writing and orally (e.g., most relevant for a dissertation defense).

A word of reassurance

Remember that for many study design and data analysis issues, there are true controversies in the field and even established investigators may disagree on the ideal strategy to take. Therefore, be transparent about your thinking as to why you choose one type of design or analysis, in spite of its limitations, over and above other alternatives. In this manner, you will show that you have a grasp of the current state of the field and thoughtfully considered all the issues in making a final decision. While this decision may not be perfect, you are indicating to the reviewer that you are aware of the alternatives as well as the impact of your decision on the interpretation of your study findings.

13.2.4 Step #4: Describe Methods to Minimize the Limitation

In describing methods to minimize your study limitations, first consult prior studies of your exposure and outcome of interest. Did these studies use design or analysis techniques to minimize limitations that would be prudent for you to adopt as well?

Examples of **design techniques** to minimize study limitations include:

- Choosing a prospective study design over a case–control study design—to avoid such issues as recall bias and selection bias

- Blinding interviewers in a case–control study—to avoid interviewer bias
- Incorporating repeated administrations of questionnaires over the course of follow-up—to minimize nondifferential misclassification of exposure due to changes in behaviors over time
- Use of life events calendars—to boost the accuracy of recall thereby reducing nondifferential misclassification of exposure

Example **analysis techniques** to minimize study limitations include:

- Comparing baseline characteristics of the experimental and standard care group in a clinical trial—to ensure that the randomization was successful
- Performing subgroup analyses among participants with and without missing data on key variables of interest—to address potential selection bias
- Conducting analyses among participants with asymptomatic disease—to address concerns regarding temporality, that is, that whether preclinical symptoms of disease may have influenced exposure

In Part II, I provide specific examples of design and analysis techniques to address each of the classic study limitations in epidemiology and preventive medicine proposals.

13.2.5 Conclusion to Fourfold Approach to Address Limitations

This fourfold approach of identifying the study limitation, describing its potential impact on study findings, discussing alternatives considered, and ending with methods to minimize limitations has a **key strategic benefit**. By ending with the steps that you are taking to minimize your limitations, you leave the reviewer with a **positive impression**. This leads us to the issue of where to place your study limitations in a grant proposal.

13.2.6 Where to Place Your Study Limitations in a Grant Proposal

In general, there are two schools of thought on where to place your study limitations in a dissertation or grant proposal. The first is to place your limitations section near or at the end of the Approach section. The second school of thought is to intermingle your limitations within each relevant subsection of the Approach. Below, I discuss the advantages and disadvantages of each technique. Regardless of which technique you

choose, the Study Limitations section can be titled, *Limitations and Alternatives*. This is a key catch phrase that reviewers will search for—and will criticize proposals for failure to include.

13.2.6.1 Limitations section at the end of the approach section

This technique involves writing **one section** with a subheading titled, *Limitations and Alternatives* in which you discuss **all** the potential limitations of your proposal. For each limitation, you use the above fourfold approach—discussing the source of the limitation, the potential impact on the findings, the alternatives considered, and the methods that you will use to minimize this problem.

The advantage of this technique is that in one centralized section, you can carefully and thoroughly evaluate and discuss each potential limitation.

The first disadvantage of this technique is that, as the reviewer reads your proposal, they will be thinking of limitations in real time. However, the reviewer will be forced to wait until the end of the Approach section to see if you have addressed their concerns. A careful reviewer will be forced to keep a list of concerns as they arise in your application and will then have to cross-check this list with your limitations summary at the end. Therefore, this approach is less *kind* to reviewers.

The second disadvantage of this approach is that you are essentially ending the grant on a fairly negative note. Accumulating all study limitations in one section at the end of the Approach can inadvertently lead to a diminished enthusiasm for the proposal on the part of the reviewer. This can be particularly risky as this section comes at the end of the reviewer's reading of the application—immediately before they need to assign their score.

One way to modestly diminish this concern is to add a final section to the Approach, immediately after this *Limitations* section, titled *Summary of Significance*, where you have a few lines rehighlighting the importance of the application. However, with strict page limitations on grant proposals, it is often difficult to have space for this final upbeat note. In addition, reviewers may find it repetitive of your initial *Significance* section that already appeared earlier in the proposal.

13.2.6.2 Intermingled limitations sections

In contrast, the technique I prefer is to intersperse limitations—as they arise—throughout the Approach section. In this manner, you can address in real time concerns that arise for the reviewer and don't leave them waiting and concerned until the end of the application. This approach is kinder to the reviewer—just as they are about to put pen to paper to note a concern, you immediately address it.

For example, when you are describing the study design, you intersperse a few lines discussing limitations of your study design and your rationale for choosing it. Further on, when you discuss exposure assessment, you insert another small limitation section discussing limitations to your exposure assessment and your rationale for choosing it. In other words, each of these limitations sections is a microversion of the fourfold

approach presented above—dismissing each limitation individually, as it occurs. Each of these subsections can be titled *Limitations and Alternatives.*

13.3 PART II: METHODS TO MINIMIZE CLASSIC LIMITATIONS—DESIGN AND ANALYSIS TECHNIQUES

13.3.1 How to Present Nondifferential Misclassification

There are a number of different techniques that can be used to minimize nondifferential misclassification—both via study design and via data analysis.

13.3.1.1 Design techniques to minimize nondifferential misclassification

Design techniques to minimize nondifferential misclassification of exposure can include shorter recall periods, use of validated questionnaires, interviewer administration of questionnaires, use of calendars to assist participant recall, and many other techniques. Design techniques to minimize nondifferential misclassification of outcome include the use of clear diagnostic criteria to identify disease outcomes (e.g., based on published consensus guidelines).

Imagine a proposal to conduct a prospective study to assess the impact of coffee on bladder cancer. In this study, coffee consumption was measured via an FFQ.

- *Identify the limitation*: Women may generally underreport their coffee consumption.
- *Describe the impact on your findings*: The effect of such misclassification, however, will be to underestimate any true association between coffee consumption and the outcome.
- *Discuss alternatives*: We selected an FFQ, as opposed to 24 h dietary recalls, as FFQs are less prone to error due to the day-to-day variability in diet and have demonstrated relationships between dietary patterns and cancer incidence.[1]
- *Methods to minimize*: Because we collected dietary information every year, nondifferential misclassification will likely be modest. Also, validation studies have indicated that self-reported coffee intake correlates well with true intake.[2]

Of course, in your proposal, you would write this up as one complete paragraph: Women may generally underreport their coffee intake. The effect of such misclassification, however, will be to underestimate any true association between coffee intake and the outcome. We selected an FFQ, as opposed to 24 h dietary recalls, as FFQs are less prone to error due to the day-to-day variability in diet and have demonstrated relationships between dietary patterns and cancer incidence.[1] Because we collected dietary information every year, nondifferential misclassification will likely be modest. Also, validation studies have indicated that self-reported coffee intake correlates well with true intake.[2]

13.3.1.2 Analysis techniques to minimize nondifferential misclassification

One example of an analysis technique to minimize nondifferential misclassification would be to propose to use findings from a validation study to correct for measurement error. Such a validation study may be available from your preliminary studies or from the prior published literature. Measurement error techniques are discussed in detail in several excellent textbooks on the topic, and you could consult a statistician for assistance in this regard.

Imagine a proposal to evaluate physical activity and risk of breast cancer.

Physical activity will be based upon self-report and therefore is subject to misclassification. Due to the prospective nature of the study, this misclassification should not be differential according to breast cancer diagnosis. To the extent that nondifferential misclassification occurs, our observed odds ratios will be biased toward the null. As prior studies have observed strong relationships between self-reported physical activity and diseases such as cancer and cardiovascular disease, this threat should not be substantial. In addition, we will use data from our physical activity questionnaire validation study to evaluate the extent of measurement error (see "Data Analysis" section).

13.3.2 How to Present Selection Bias

Unlike nondifferential misclassification, selection bias cannot be removed in data analysis after it has occurred. Instead, it must be prevented in the design of the study. On the other hand, data analysis techniques such as sensitivity analyses can be used to evaluate the extent of selection bias.

13.3.2.1 Study design techniques to minimize selection bias

eg example

Recall the proposal to conduct a case–control study of the association between multiple sexual partners and HPV presented in Chapter 12. People who have HPV (cases) **and** who have had multiple sexual partners (exposed) may be more motivated to participate because they are concerned that their HPV infection was caused by having multiple sexual partners. The following design techniques could reduce this concern:

Participants will be identified via random sampling of medical records. In addition, we will ensure that participants are blinded to the proposed hypothesis. Finally, questions regarding sexual partners will be embedded in a long questionnaire that includes reproductive history as well as other medical and psychosocial factors.

13.3.2.2 Analysis techniques to minimize selection bias

The following sensitivity analysis could also be proposed to address the extent of selection bias:

In addition, we will compare characteristics of cases and controls to see if they differ on sociodemographic and other medical history variables.

13.3.3 How to Present Information Bias

Just as with selection bias, information bias can only be prevented through study design approaches. Analysis techniques can, however, be used to address the extent of information bias—but cannot remove information bias once it has already occurred.

13.3.3.1 Study design techniques to minimize information bias

The best way to reduce the threat of detection or surveillance bias is to blind the assessor to the participants' exposure (in a cohort study) or to the participants' case/control status in a case–control study. For example, in a prospective cohort study, if medical record abstractors are blinded to exposure status, information on exposure cannot influence the collection of information on the outcome. Similarly, in a case–control study, if interviewers are blinded to case/control status, then information on outcome cannot influence the collection of information on the exposure of interest. In addition, bias is also reduced when the hypothesized association between the exposure and the outcome is not known to the assessor.

Imagine again our proposal to conduct a cross-sectional study of ALA and risk of vitamin B12 deficiency. Participants in this study will be asked to self-report their ALA during a home interview.

It is possible that people with vitamin B12 deficiency will be more motivated to remember ALA use than people without vitamin B12 deficiency. Such a recall bias would result in an overestimate of the relationship between ALA use and vitamin B12 deficiency. **However, the home interviews were conducted by trained interviewers and participants were blinded to the study hypothesis. Additionally, vitamin B12 deficiency was ascertained by serum concentration and results were not shared with participants until after exposure quantification; thus, they were unaware of their disease status at the time of the interview.** Thus, it is unlikely that information bias occurred in this study, and if it occurred, we would expect its effect to be minor**.**

Note that the *bold phrases* indicate the design techniques used to minimize information bias.

13.3.3.2 Analysis techniques to minimize information bias

Sensitivity analyses can be used to examine the extent of information bias. For example, if there are concerns about detection bias or surveillance bias in a cohort study, one approach would be to compare the amount of surveillance applied to the exposed vs. unexposed groups—by comparing such factors as number of medical visits, recency of medical visits, and number of screenings. Another sensitivity analysis to address surveillance bias would be to repeat the analysis after excluding nonsymptomatic cases (i.e., *in situ* cases) as these cases would only tend to be detected during regular medical surveillance. In the examples below, the techniques to minimize information bias are *bold*.

Imagine a proposal to conduct a prospective study of postmenopausal hormone use and risk of breast cancer.

One potential source of bias in our study is the difference in the rates of mammographic screening between hormone users and nonusers. Those who are taking postmenopausal hormones are more likely to have a mammogram and thus more likely to be diagnosed with breast cancer than those women not taking postmenopausal hormones. This would lead to an overestimate of the association between postmenopausal hormones and

breast cancer. **We will address this problem in several ways. We will compare rates of mammography screening among postmenopausal hormone users as compared to nonusers. We will also exclude in situ breast cancers because they are more likely to be diagnosed through mammography.**

Imagine a proposal to conduct a prospective study of dietary factors and their impact on incident diabetes.

Bias could arise if those with early signs of diabetes, but not a formal diabetes diagnosis, started to change their diet in response to these early indicators. This bias would cause an overestimate of the association between diet and diabetes. **To minimize this potential bias, we will perform a subanalysis only among participants without reported symptoms of diabetes**. If we observe a comparable association between diet and diabetes in this subgroup as in the overall sample, this would reduce concerns about the impact of information bias.

13.3.4 How to Present Confounding

13.3.4.1 Study design techniques to minimize confounding

There are a number of study design techniques to minimize the threat of confounding—as summarized in Table 13.1.

1. *Subject restrictions*: Design approaches to address confounding include restricting subjects to particular characteristics. Specifically, you could propose to restrict subjects to particular strata of a confounding factor such that your exposed and unexposed groups will have this factor in common. Because most study designs already limit inclusion criteria, by definition, most proposals are already taking a first step in limiting confounding!

Imagine that you are proposing to conduct a study of depression and risk of preterm birth. You are concerned about parity as a potential confounding factor. Therefore, you propose to restrict the study sample to nulliparous women (women who have not had prior children). In this way, parity cannot act as a potential confounder of the observed association between depression and preterm birth because all the women will have the same level of that potential confounding factor (i.e., no children). That is, having had children cannot be responsible in any part for the observed association between depression and preterm birth.

TABLE 13.1 Study design techniques to minimize confounding

- Subject restrictions
- Collect information on confounders
- Matched design
- Randomization

Even if you cannot fully restrict inclusion criteria to rule out all confounders, you can try to limit the range of a potential confounder. For example, if you were concerned about confounding by age, you could exclude extreme ages (e.g., children or the elderly). This will not remove the need to address potential confounding by age in your analysis, but will limit the potential extent of confounding.

eg example

Imagine a proposal to evaluate vitamin D intake and cataract incidence. You will be using an existing dataset of dental hygienists.

Although we controlled for many cataract risk factors in the analysis, we did not have information on exposure to sunlight. Because sunlight is positively associated with vitamin D, and positively associated with cataract incidence, the lack of control for sunlight may lead to an overestimate of the association between vitamin D and cataract incidence. However, because the cohort is not occupationally exposed, variation in sunlight is not likely to be as large as in a general population sample.

Note that the example ends by minimizing the threat of confounding. The last sentence points out that the study population does not vary significantly according to the level of sunlight. Remember, as described above, that if all participants do not differ according to the confounding factor (e.g., all one gender, or all one age, or in this case, all one level of sunlight exposure), then there cannot be confounding by this factor. That is, differences between participants in levels of this confounding factor will not be responsible for the observed association between vitamin D and cataract incidence. However, some residual confounding is likely to remain.

2. *Collect information on confounders*: The second approach involves designing your study to collect information on potential confounders. By having this data in hand, you will be able to adjust for these potential confounders once you get to the data analysis phase. This approach requires careful consideration of all the potential confounding factors when writing the proposal. Reviewing the prior literature will help to identify potential confounders. The construction of DAGs (see Chapter 10, *Data Analysis Plan*) is also a common approach.

   The flip side of this approach is the potential for heavy participant burden. That is, collecting information on each potential confounder (e.g., either

through questionnaires or biomarkers) may take up an inordinate amount of participant time or require a high amount of biomarker assessment (e.g., multiple blood draws, biopsies).

It is also important to note that this approach does not remove the potential threat of **residual confounding**, but does minimize this concern. For example, if you are concerned that sleep is a potential confounder of the relationship between depression and preterm birth, you may choose to administer a sleep questionnaire to collect information on sleep. However, if this questionnaire has some error associated with it (e.g., reliance on self-report), adjusting for sleep in your analysis will only address a portion of the confounding by sleep and some residual confounding will remain.

3. *Matching*: The third design approach to address confounding is matching participants on potential confounders. Matching is a design technique typically used in case–control studies whereby cases are matched to controls on several key confounding factors (e.g., age, gender, study site). In this way, the cases and controls will not differ on these factors, and in turn, these factors cannot be responsible for the observed association between exposure and disease. However, it is typically not feasible to match on a multitude of factors because logistical concerns come into play. For example, it may become difficult to find a control that matches your case according to a long list of matching criteria.

4. *Randomization*: The fourth design approach involves conducting a randomized trial. Randomized trials include clinical trials in which medical treatments are randomized. Randomized trials can also include behavioral interventions in which, for example, educational programs may be randomized. As long as the investigator is assigning the exposure in a random fashion, the study design qualifies as a randomized trial. Randomized trials are considered the gold standard design because the use of randomization results is not only random distribution of known confounders, but just as importantly, the randomization of unknown confounders as well.

13.3.4.2 Analysis techniques to minimize confounding

There are a variety of analysis approaches to minimize confounding and the most common are listed in Table 13.2. For a more detailed discussion of these techniques, see Chapter 10, *Data Analysis Plan*.

- *Stratification*: Stratification involves analyzing the association between your exposure and outcome separately within individual strata of your confounding variables. In other words, if you are concerned about confounding by

TABLE 13.2 Analysis techniques to minimize confounding

• Stratification
• Matched analysis
• Multivariable regression

gender, you could conduct the analysis only among your female participants and then again among your male participants. Statistical techniques are available to derive a summary measure of association that pools the measure of association across each stratum (e.g., Mantel Haenszel summary odds ratios).

- *Matched analysis*: If you choose to use matching in the design of your study, then your analysis plan has to follow suit. Typically, for a matched case–control study, conditional logistic regression is used. However, there are other approaches to handling a matched study design that can be discussed with your statistician.
- *Multivariable regression*: Lastly, the most common approach to address potential confounding in the data analysis portion of your proposal is to propose to conduct multivariable analyses. Such analyses typically involve the construction of multivariable regression models that include your confounding factors. Chapter 10, *Data Analysis Plan*, discusses techniques for incorporating confounding factors in multivariable models. Even if you have conducted a randomized trial, it will be important to assess whether the random assignment actually worked. If there are any observed differences in covariate status between the treatment groups at baseline, you could consider whether to adjust for these in multivariable analyses. The smaller your study, the more likely that these baseline characteristics will differ in spite of the random assignment of treatment arm.

Imagine a proposal to evaluate physical activity and risk of gestational diabetes.

Women who are more active during or prior to pregnancy could be healthier in some overall way that decreases their risk of gestational diabetes. We will have information on a variety of confounding factors that reflect overall health and will include them in multivariable models. In addition, the study population has excluded women with more severe diseases such as existing diabetes, hypertension or heart disease, and chronic renal disease. In addition, while healthier women may be more likely to engage in sports and exercise, they may have little choice whether to undertake occupational or household activity. Our analyses will include an assessment of the independent contribution of occupational activity and household activity, as well as sports and exercise on gestational diabetes risk.

13.3.4.3 Techniques to minimize lack of data on a confounder

There are several ways that you can address anticipated lack of data on a potential confounding variable in your proposal.

First, you can propose to adjust for a **proxy variable** in place of the confounder of interest. In our cataract example above, you could propose to adjust for geographic region (e.g., northern vs. southern latitude) as a proxy for adjusting for sunlight exposure, your confounder of interest. Or, if you are missing information on income level, you could consider adjusting for highest level of education as a proxy. While a proxy will not be a perfect substitution, it will help to reduce confounding.

A second way to propose to address lack of data on a potential confounder is to propose that you will perform a **sensitivity analysis**. For example, let's say you are conducting a study of exercise during pregnancy and risk of preterm birth but are missing information on history of preterm birth—an important confounder. In this situation, you could propose to repeat the analysis among women with no prior pregnancies (nulliparous women) who therefore have never had the opportunity for a preterm birth. By comparing these findings to those among your entire sample of nulliparous and parous women, you can assess the extent of possible confounding by history of preterm birth.

13.3.5 How to Present Survivor Bias

As described in Chapter 12, survivor bias is a concern typically faced by cross-sectional and case–control studies. It can occur when those with high levels of your exposure may have died from your outcome or are no longer available to participate in your study. This concern can be addressed by comparing survival rates among those with high vs. low levels of your exposure.

Imagine again a proposal to evaluate ALA and risk of vitamin B12 deficiency. You propose a cross-sectional design in which you will recruit participants from an outpatient clinic. Given this design, participants involved in the study will have all, by definition, survived their vitamin B12 deficiency.

If those with high levels of ALA use are more likely to die of vitamin B12 deficiency, they would not be available to be included in our study. This would constitute survival bias and findings would be biased toward null. However, this is not likely to be an important concern as the consequences of vitamin B12 deficiency are not usually life threatening. Therefore, we expect the possibility of survivor bias to be minor.

13.3.6 How to Present Temporal Bias

As discussed in Chapter 12, temporal bias is another typical concern faced by cross-sectional and case–control studies. Because both the exposure and outcome of interest

have already occurred at the time the investigator launches the study, we cannot ensure that the exposure indeed led to the disease and not vice versa.

This concern is minimized if you are studying immutable exposures such as blood type and eye color. For these unmodifiable risk factors, we can be sure that they definitely preceded the disease.

Imagine a proposal to conduct a case–control study of blood type and risk of Asperger's syndrome. You enroll cases of Asperger's syndrome and controls that do not have Asperger's and abstract medical records for their blood type.

Temporal bias is not a concern because Asperger's syndrome could not have led to the blood type of the patient. Instead, we can be sure that blood type came first and diagnosis of Asperger's followed.

13.3.7 How to Present Generalizability

Generalizability was discussed in Chapter 12. Below is an approach for minimizing reviewer concerns regarding the lack of generalizability while clarifying for the reviewers the principles upon which generalizability should be based.

Imagine a proposal to evaluate eating disorders and risk of weight loss among Latinas. You are proposing to recruit a convenience sample of volunteers.

Women who volunteer to participate may not be representative of women who live in other parts of the country. Perhaps those women who agree to participate in the study will have fewer eating disorders than those who decline to participate. However, there is little basis for believing that the biological relation between eating disorders and weight loss observed in this study will be substantially different in our population from that in most American women.

Our decision to focus on one ethnicity (Latinas) is based upon both the methodologic and public health limitations of an ethnic comparison. Comparisons across ethnic groups may be limited in applicability because these groups are often profoundly different. Furthermore, ethnicity is not a modifiable risk factor. Therefore, by selecting Latinas, we will be able to examine gradient of risk within this group and findings from the study will be more closely tied to public health recommendations. Finally, Latinas are an understudied, high-risk population with little representation among the studies of weight loss.

13.4 EXAMPLES

Note that these examples extend the examples included in Chapter 12, with the addition of *techniques to minimize the limitations in bold.*

13.4.1 Example #1

Proposal to Conduct a Case–Control Study of Maternal Heat Exposure and Congenital Heart Defects

Study Limitations

Nondifferential Misclassification of Exposure
Mothers of cases and controls will be asked to recall the period of early pregnancy 3–8 years after delivery has occurred. While women's memory of their pregnancy might be better than for other life periods, inaccuracy is likely to result from the extended time lapse and difficulty in estimating average hours per week of heat exposure over a several-month time period in the past. **To minimize the possibility for such misclassification, mothers were sent individualized, multicolored calendars of their pregnancy periods, which were used as visual aids during phone interviews.**

Another possible source of nondifferential misclassification is in the definition of heat exposures, which requires some judgment by participants. No objective heat exposure measures will be available in this study. However, misclassification resulting from poor participant recall or inaccurate exposure measurement is likely to be nondifferential (i.e., misclassification will not significantly differ between cases and controls), biasing results toward the null value.

Nondifferential Misclassification of Outcome
Congenital cardiovascular malformations will be abstracted from the New York birth defects registry. Inaccuracies in classifying birth defects as congenital cardiovascular malformations are possible, and such misclassification would bias our findings toward the null. **However, a validation study conducted by the New York birth defects registry in 2010 found reasonable validity for major congenital cardiovascular malformations with Spearman correlation coefficients ranging from 0.54 to 0.76 as compared to medical record abstraction.**[1]

Selection Bias
In our pilot study, the response rate was 55.4% due to the difficulty in locating study subjects. Respondents were significantly different from nonrespondents with regard to age, race, ethnicity, and geographic location of residence within New York State. This raises the concern of selection bias, leading to an under or overestimate of our findings. **However, we compared response rates and demographics between cases and controls and found no statistically significant differences, making the possibility of selection bias unlikely.**

Information Bias: Recall Bias

In searching for possible causes for their children's heart defects, mothers of cases may more carefully report exposures as compared to mothers of controls. This recall bias would result in an overestimation of the association between heat exposure during pregnancy and congenital cardiovascular malformations. **However, the hypotheses tested in this study are not well known to the public, and there is no reason to believe that mothers will particularly suspect these exposures as possible causes of their children's heart defects.**

Information Bias: Interviewer Bias

Because exposure information will be collected by an interviewer, it is possible that an interviewer will prompt case mothers differently from control mothers, resulting in an overestimate of the association between physical exposures and congenital cardiovascular malformations. **However, interviewers will be blinded as to case/control status of the subject until the end of the interviews. Their blinded status, in addition to the structured nature of the telephone questionnaire, will help to reduce the likelihood of such interviewer bias. In addition, the questions pertaining to our study exposures will represent a minor part of the overall study questionnaire, and it is possible that neither interviewer nor participant will have preconceived notions of the effects hypothesized for those exposures.**

Confounding

The questionnaire will include information on all known risk factors for congenital cardiovascular malformations, including maternal chronic diabetes, binge drinking during pregnancy, fever during pregnancy, sex of the infant, and family history of congenital cardiovascular malformations. As with the main study exposures, information on these variables will be obtained through self-report. For information that was difficult to recall or associated with social stigma, such as drinking alcohol during pregnancy, some women's answers may be inaccurate. Failure to adequately control for these variables may lead to over- or underestimates of the association between physical exposures and congenital cardiovascular malformations. For example, prior studies have found that heat exposure during pregnancy (e.g., sauna use) is positively associated with binge drinking during pregnancy. In turn, binge drinking during pregnancy is positively associated with congenital cardiovascular malformations. Therefore, any inaccuracies in our measure of binge drinking may lead to an overestimate of the association between heat exposures and congenital cardiovascular malformations.

However, other important covariates in this study will be less likely to be misclassified by participants, such as whether they had chronic diabetes or whether an immediate family member had congenital heart disease.

Generalizability

We do not expect the physiological association between pregnancy heat exposure and congenital cardiovascular malformations to differ according to race, ethnicity, or age. Therefore, in spite of the fact that study participants were African American and Hispanic youth, we will still be able to generalize our findings to pregnant women in the United States.

13.4.2 Example #2

Proposal to Conduct a Prospective Cohort Study of Stress and Risk of Preeclampsia

Study Limitations

Nondifferential Misclassification of Exposure
Trained, bilingual interviewers will administer the Perceived Stress Scale during a structured interview in early pregnancy (mean = 15 weeks gestational age). It is possible that women will over- or underreport their perceived stress. This may occur to the extent that perceived stress may be a sensitive issue for a select group of women. This type of misclassification would bias our results toward the null, thereby reducing our effect estimate for the relationship between perceived stress and hypertensive disorders of pregnancy. We expect this misclassification to be minor.

However misclassification will be minimized through the use of a stress questionnaire that has been validated among Hispanic women.[1] In addition, interviewers who are bilingual and/or native speakers of Spanish will assist women in completing the questionnaire.

Nondifferential Misclassification of Outcome
Cases of hypertensive disorders of pregnancy will be ascertained through medical record abstraction, as well as through a review of ICD codes for hypertension in pregnancy. Nondifferential misclassification could occur if diagnoses are missed by physicians or via the data collection methods employed. This would result in a bias of our results to the null, but we expect the effect to be minimal.

The threat of nondifferential misclassification is minimized because all cases will be confirmed by the study obstetrician. Therefore, it is unlikely that misclassification of the outcome will occur given the comprehensive nature in which diagnoses will be ascertained. Specifically, blood pressure measurements are obtained at every prenatal care visit as part of routine prenatal care, as well as regularly throughout labor and delivery. Therefore, it is unlikely that hypertension will be missed in any woman with complete delivery information. Additionally, women experiencing preeclampsia may have symptoms such as headache and visual disturbances, which would be recognized by the clinician as symptomatic of a hypertensive condition.

Selection Bias: Differential Loss to Follow-Up
Due to the prospective nature of this study, selection bias is unlikely to occur as exposure status (stress) will be collected before the disease (hypertension in pregnancy) occurs. However, selection bias is possible in a prospective study through differential loss to follow-up. For example, if women lost to follow-up were more likely to be in the high stress group and also more likely to be hypertensive in pregnancy, selection bias could occur and bias our results toward the null.

However, in our pilot study, women lost to follow-up were similar to those with complete delivery information, and therefore it is unlikely that selection bias will occur in this cohort.

Information Bias: Surveillance (Detection) Bias
Surveillance bias will be unlikely in this study because women are not monitored differently for hypertension in pregnancy according to their stress levels. The medical record abstractor will also be blinded to stress status.

To reduce the threat of detection bias, the medical record abstractor will also be blinded to stress status.

Confounding
We are not aware of any key confounders that are not available through our dataset. It is possible, however, that we measured one or more of these confounders inadequately. This residual confounding could result in a change in our effect estimate in either direction depending on the direction of the measurement error.

However, given that we are not missing information on any factors that are strongly associated with both stress and hypertensive disorders, we do not expect that uncontrolled confounding will affect our results in a meaningful way.

Generalizability
The results of this study may be generalized to pregnant women as the biological mechanisms through which stress may impact hypertension in pregnancy should not vary by race or ethnic origin.