ERIC Notebook

Second Edition

Confounding Bias, Part II and Effect Measure Modification

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Confounding is one type of systematic error that can occur in epidemiologic studies, and is a distortion of the association between an exposure and health outcome by an extraneous, third variable

Effect measure modification (EMM) is when a measure of association, such as a risk ratio, changes over values of some other variable. In contrast to confounding which is a distortion, EMM is of scientific interest ,answers a research question, and can help identify susceptible or vulnerable populations. Are children with poor nutrition, exposed to water pollution, at higher risk of gastrointestinal symptoms compared with children with good nutrition who are exposed to water pollution?

Both confounding and EMM can be considered in the design phase of research or in the analysis phase. We will discuss both in this notebook.

Calculating and adjusting for confounding

The previous issue of ERIC Notebook, "Confounding Bias, Part I", discussed two criteria for identifying potential confounders in a study. Once potential confounders have been identified, the next step is to evaluate if and how much the confounders bias the study results. To do this, results where confounding is ignored, the *"crude"* measure of association, are compared to results that have been corrected for distortions due to confounding, the *"adjusted"* measure of association.

This methodology makes 2 assumptions:

First, the data are obtained by simple random sampling rather than by some more restrictive subject selection procedure, like matching.

The second assumption is that the exposure, health outcome, and confounder variables are all dichotomous (i.e., having only two strata). If the variables are in a continuous format, they can either be dichotomized, or they must be adjusted for simultaneously to calculate the true measure of association.

Methods to calculate adjusted measures of associations differ by the need to control each confounder individually or all confounders simultaneously.

Before calculating an adjusted measure of association using stratified analyses, one must first assess the presence of *effect measure modification* (EMM). When effect measure modification is present, it can be difficult to ascertain whether or not confounding is occurring.

Two examples of EMM are:

- A breast cancer education program (the exposure) that is much more effective in reducing breast cancer in rural areas than urban areas. Here, the area (rural or urban) is an effect measure modifier.
- The finding that a reduction in regional public transportation services (the exposure) affects individuals with little or no access to a car much more than those individuals with access to a car. In this example, having access to a car is the effect measure modifier.

What is effect measure modification?

When estimates of an exposure-health outcome relationship stratified by a confounder are sufficiently different from one another (i.e., risk ratio level 1=4.0 and risk ratio level 2 =0.2), they suggest that two different exposure-health outcome relationships may be operating, one in each level of the confounder.

EMM is different from confounding, where instead of "competing" with the exposure of interest in explaining the etiology of a health outcome or disease, the effect measure modifier identifies subpopulations that are particularly susceptible to the exposure of interest.

Is effect measure modification present?

To calculate whether EMM may be occurring in the study, first calculate three measures of association:

A = The overall, crude measure of association of the exposure-health outcome

B1 = The measure of the exposure-health outcome association among all study participants who have a history of the confounding variable (C+)

B2 = The measure of the exposure-health outcome association among all study participants who do not have a history of the confounding variable (C-)

Use the Figure 1 below as a guide on how to interpret the meaning of these three measures of associations.

As a general rule, if B1 and B2 are basically equal in value, but different from A, then confounding is present and EMM is not present. EMM is present when B1 and B2 are different from one another, and at least one (B1 or B2) is different from A. Both EMM and confounding can occur simultaneously.

If stratified analysis is used to adjust for EMM, confounders should be addressed using more complex statistical techniques, as stratifying results on more than

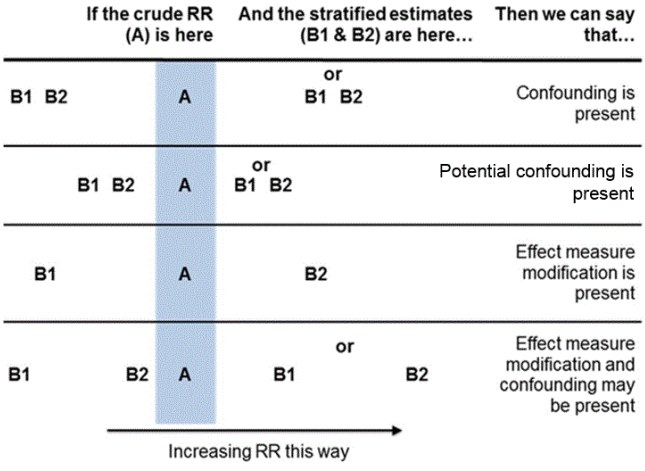

Figure 1

Risk Ratio Example

one variable splits the sample into significantly smaller sample sizes and limits generalizability.

Calculating adjusted summary estimates

If no EMM is present, then stratum-specific estimated effects can be pooled to form a summary estimate of effect across strata. This summary estimate represents an adjusted risk ratio (a risk ratio adjusted for confounding).

Although there are many ways to calculate the adjusted risk ratio, the Mantel Haenszel procedure, is the most common pooling procedure.

Calculating adjusted measures when all confounders are assessed simultaneously

Simultaneous control of two or more variables can give different (and potentially more interesting) results from those obtained by controlling for each variable separately. Simultaneous control of confounders better emulates the natural environment where exposures, diseases, and confounders of interest are found, than does individual control of confounders.

Simultaneous control of several confounders to calculate adjusted measures is done through mathematical modeling.

To control for confounding using mathematical modeling, simply include the confounding variables as independent variables in the model. The simplicity of this method of adjustment for confounding is one of the attractive features of using mathematical models in epidemiology.

Although many types of mathematical models are available, there is generally only one type of model that is appropriate for the goals of a specific data analysis and for the type of data available. The most common mathematical model used in epidemiology is logistic regression.

This model has the general format of

$$y = a + b_{1x} + b_{2z2} + \ldots + b_{izi}$$

Individual-level data need to be provided on:

1. y: the health outcome in a dichotomous format
2. x: the exposure
3. z2 to zi: the confounders

With this information and statistical analysis software, researchers can then calculate the following:

1. a: the y-axis intercept
2. b1: the coefficient for the exposure variable
3. b2 to bi: the coefficients for each confounder that is controlled for in the model.

These coefficients (except for a) are very useful, as they can be transformed into odds ratios. The odds ratio obtained from b1 of this model is an interpretable measure of association describing the relationship between the exposure (x) and the health outcome (y) after adjustment for confounding variables (z_2 to z_i).

The biggest disadvantages to using mathematical models are the assumptions that must be met by the dataset in order to use them – often the data may not conform to all assumptions. It is advisable to do regression diagnostics sometime during the data analysis stage to check these assumptions.

Is adjustment for confounding necessary?

If the adjusted effects are markedly different from the crude effect (typically a 10 or 15% change from crude to adjusted), then confounding is present and should be controlled for. Researchers should report the cut-off they used for their analysis (e.g. 5%, 10%, or 50%) in the selection of confounders for adjustment.

If the adjustment of confounding variables changes the results only slightly (less than 10%), then the tendency would be to ignore this influence, since the more variables controlled for, the less precise (the wider the confidence intervals) the study results will be. The benefits of ignoring the minor confounders would outweigh the costs.

Also consider whether it is important to control for potential confounders such as age, simply because many

readers would not trust results that are not adjusted for age. This distrust stems from knowledge that age is strongly related to disease and mortality rates (similar comments would apply to sex).

Control of confounding

In the analysis phase:

Once data have been collected, there are two options for control of confounding: Stratified analysis or mathematical modeling. Both methods were described above when calculating the effect of confounding on the measure of association. Briefly, stratified analysis pools the measure of association calculated in each strata of the confounder into one summary estimate. Mathematical modeling uses a more complex approach and makes more assumptions than stratified analysis.

In the design phase:

Some confounders should be controlled for in the study design stage of a study, rather than in the analysis stage. It may be necessary to do this if the confounder is very strong and when the anticipated sample size will be large enough to deal with it in the design stage. Some study designs are more favorable for controlling for confounding than others.

Restriction, matching, and randomization are common techniques used to minimize confounding in the design phase. These techniques are not exclusive to one another. Several different control methods may be used at once.

Restriction

Confounding can be controlled for by restricting the study population to those who are unexposed to one or more confounding variables. An example of restriction is to restrict a study population to nonsmokers when studying the association of environmental radon with lung cancer. Restriction is ideal when the exposure-health outcome relationship has strong confounders because it can be an efficient, convenient, inexpensive, and straight-forward method of controlling for confounding. However, the restricted variable, for instance smoking in the given example, cannot be assessed for confounding. Restriction may not always be logistically feasible because the sample size of available study participants is decreased, sometimes to the point that a study cannot be done.

Example

For instance, a group of 30 HIV-positive skydivers of varying age (20% twenty-something, 30% thirty-something, 50% senior citizens) has been identified with which to study behavioral risk factors for HIV infection, independent of age. Therefore, the control group should be 30 HIV-negative skydivers with the same age distribution as the group of HIV-positive skydivers (20% twenty-something, 30% thirty-something, 50% senior citizens). This would be accomplished through matching the controls to the cases by age, by selecting only HIV-negative skydivers who contribute to the pre-determined age distribution.

Matching

Confounding can also be controlled through matching on the confounder variable(s). Matching involves constraining the control group (for case-control studies) or the unexposed group (for cohort studies) such that the distribution of the confounding variable(s) within these groups are similar (or identical) to the corresponding distribution within the index group (the case group for case -control studies or the exposed group for cohort studies). Matching can be viewed as imposing a "partial restriction" on the values of the confounding variables, since only the control or unexposed group is restricted.

Analysis of matched data requires special consideration, because the control, or unexposed, group is not a random sample of study participants; they should be considered to be a biased sample. Techniques for analyzing matched data include conducting the data analysis separately for each level of the confounder (stratified analysis) and using conditional logistic regression.

When considering matching, consider four factors:

1. Precision (generally increased with matching)
2. Cost (generally lowered with matching, because a smaller sample size is needed)

3. Feasibility (can be increased with matching)
4. Flexibility in deciding whether to match

Also keep in mind that variables matched cannot be assessed for confounding.

Randomization

Randomization is an ideal method for controlling for confounding because this method can control both known and unknown confounders. However, because randomization requires that the exposure status of individuals be assigned to study participants, observational study designs such as cross-sectional, cohort, case-control and ecological studies cannot use randomization to control for confounding. For controlled clinical trials however, randomization is a common method to control for confounding.

Use of randomization to control for confounding presumes that random classification of individuals into groups will produce groups that have an equal (or similar) distribution of confounders. For example, the theory of randomization says that given two randomly selected groups of students, each group will have an equal percentage of females, an equal percentage of individuals with white-colored tops, an equal percentage of brown-eyed individuals, and so forth. Thus, randomization, if done correctly, will produce homogeneous groups of individuals. When an exposure is applied to one of these homogeneous groups, but not to the other, the only difference between the two groups is their exposure status. In this situation, confounding, the unequal distribution of a risk factor between exposed and non-exposed groups, cannot occur.

Terminology

Effect measure modification: a variation in the magnitude of a measure of exposure effect across levels of another variable

Randomization: random assignment of subjects to exposure categories

Matching: the selection of controls, or unexposed subjects, that are identical, or nearly so, to the cases, or exposed subjects, with respect to the distribution of one or more potentially confounding factors

From: Modern Epidemiology, Rothman KJ and Greenland S, 1998

The key to proper control of confounding through randomization is having a sufficiently large sample size in each randomized group. Rothman and Greenland (1998) state that having at least 50 subjects, preferably 100 or more, will usually assure that potential confounders are equally distributed among each study group.

Practice Questions
Answers are at the end of this notebook

1) There is a vaccination campaign in effect in some counties of a state to educate parents about childhood diseases and recommended vaccines for their children. Researchers find that the vaccination campaign seems to be effective. Children who live in the counties with the vaccination campaign are 4 times as likely to be vaccinated according to recommendations when compared with children who live in counties without the vaccination campaign. However, even looking only within counties with the vaccination campaign, researchers find that children of families with incomes above the poverty level are twice as likely to vaccinate their children when compared with children of families with incomes below the poverty level. Which of the following can be determined from this example?

Choose all that apply:

a) Family income appears to be a confounder
b) Family income appears to be an effect measure modifier
c) The vaccination campaign appears to be effective
d) The vaccination campaign is the study outcome
e) The vaccination campaign is the study exposure

2) Researchers conducted a cohort study in country B to examine the association between a diet high in fat and the risk of colon cancer. The researchers believe that vitamin use may be a confounder but they first need to examine whether or not vitamin use is an effect measure modifier. Use the 2x2 tables below to determine if vitamin use is an

effect measure modifier or a confounder in the high fat diet- colon cancer association.

	Colon cancer	No colon cancer	Total
Exposed to a high fat diet	254	2220	2474
Not exposed to a high fat diet	98	2300	2398

Among people exposed to a high fat diet:

	Colon cancer	No colon can-	Total
Takes daily	150	1830	1980
Does not take	104	390	494

Among people not exposed to a high fat diet:

	Colon cancer	No colon cancer	Total
Takes daily vitamin	80	1500	1580
Does not take daily vitamin	18	800	818

a) Is vitamin use an independent risk factor for colon cancer?

b) Is vitamin use differentially distributed between the high fat diet and low fat diet groups?

c) Compare the crude risk ratio with the risk ratios stratified by vitamin use.

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Answers to Practice Questions

1. Answer choices b, c and e are correct. In this example, family income appears to be an effect measure modifier because the effect of the vaccination campaign differs markedly between the 2 sub-populations (family income above versus below poverty level). The vaccination campaign does appear to be effective since children in counties with the vaccination campaign were 4 times as likely to be vaccinated as children in counties without the vaccination campaign. In this example, the researchers are studying the outcome of whether or not children are vaccinated according to recommendations. The vaccination campaign is the exposure.

2.

a) Is vitamin use an independent risk factor for colon cancer?

Answer:
Risk ratio of vitamin users getting colon cancer among the non-exposed group:
(80/1580) / (18/818)=2.3

Yes, a risk ratio of 2.3 shows that vitamin use is a moderate predictor of colon cancer.

b) Is vitamin use differentially distributed between the high fat diet and low fat diet groups?

Answer:
Among people who eat a high fat diet there are
1980/2474= 80% vitamin users
Among people who do not eat a high fat diet there are
1580/2398= 66 % vitamin users
So vitamin use is differentially distributed among the high fat and low fat diet exposure groups.

c) Compare the crude risk ratio with the risk ratios stratified by vitamin use.

Answer:
The crude risk ratio (not stratified by vitamin use) is the risk of colon cancer from high fat diet exposure / the risk of colon cancer from low fat diet exposure.
Crude risk ratio = (254/2474) / (98/2398) = 2.51

The risk ratio for colon cancer among vitamin users with a high fat diet is:
Risk ratio = (150/1980) / (80/1580)= 1.50

The risk ratio for colon cancer among non-vitamin users with a high fat diet is:
Risk ratio = (104/494) / (18/818) = 9.6

The crude risk ratio of 2.51 and the vitamin-specific risk ratio of 2.3 (from question 1) are both in between the stratified risk ratios. The 2 stratified risk ratios differ greatly from one another (9.6 for non-vitamin users versus 1.5 for vitamin users). This example shows the presence of effect measure modification.