TITLE: SPECIAL ISSUES: Confounding and Effect Modification

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Slide 1: In the previous lecture on interpretation of epidemiologic studies, we talked a bit about confounding, the mixture of effects between an exposure and a disease that could be an explanation for the findings. What I'd like to do is talk a little bit more in detail about the special issue of confounding and a complementary but different issue called effect modification.

Slide 2: Confounding just to review what we talked about before is a mixture of effects between the association under study and a third variable. This third factor, the confounder has to be both associated with the exposure under study and independently the exposure, it has to be a risk factor or a correlate of the risk factor for the disease. And the result of this confounder is that it may be responsible, either in part or totally for the association seen in the data.

Slide 3: Just to look at it pictorially, we think we're looking at the relationship between the risk factor and the disease, between smoking and lung cancer for example. But instead of that, we are looking at the relationship through another variable. Let's say age, where smokers and non-smokers differ with respect to age. Age is a risk factor for lung cancer. Therefore, whatever relationship that we see between smoking and lung cancer is in part or totally due to the relationship with this third variable, the confounder of age.

It's important to realize that a confounder is actually population specific. So, I just said that smokers and non-smokers differ with respect to age. That may be true in my population but may not be true in yours. And if in your population that variable is not related to the exposure or not a risk factor for the outcome in your population, then it cannot be a confounder, because it must have that relationship, must fulfill that relationship to be a confounder.

Slide 4: So again, for example to think of a variety of variables that stay with smoking and lung cancer for right now that ever smokers have an increased risk of lung cancer, then potential confounders would be as we said age. So, if the ever smoker is more likely to be older, older people are more likely to have lung cancer. Then, in fact this confound will work to over estimate the harm of smoking.

Because smokers are more likely to have another variable, another characteristic, increased age, which in itself will increase risk of the outcome of lung cancer. So if we do not control for the confounder of age, we will make smoking look actually worse than it truly is.

Gender would be the same kind of direction. If smokers are more likely to be men, men are more likely to develop lung cancer independently of smoking. But again, smoking will look worse than it actually is because smokers will have another characteristic which independently affects the risk of developing lung cancer.

Other variables we would want to look at, pollution. Are smokers more likely to live in an urban area rather than a rural? Are smokers more likely to have an occupational exposure to asbestos than the non-smokers do? If these are true, either more likely or less likely, and those factors are also related to lung cancer which they are independent of smoking, those would be confounders we would need to take into account. What would not be any confounders would be any variable that is not associated with the exposure of smoking does not differ between smokers and non-smokers, or is independently not related to the outcome under study.

So, if for example exercise which is associated with smoking is not an independent risk factor of lung cancer, then in fact it would not be a confounder. And any variable which is an intermediate factor, a link in the causal chain, the way that smoking works on the outcome of lung cancer would not be a confounder, we would not control for that, because to control for it, we'd actually be controlling for the exposure.

Slide 5: Well, what then are potential confounders? Potential confounders are factors which are known to be related to the exposure of interest and known to be related to the disease, but are not part of the mechanisms by which the exposure is postulated to affect the disease of interest, and not part of the causal pathway. Often all of this is unknown; we don't know what's related to smokers or non-smokers. We might know some stuff about the risk factors for the disease, but we don't know everything.

So, the best way to do it if we do not know what is related to the exposure is just make sure to collect information on all known risk factors for the outcome. And the important thing is to collect information on them in the design of the study, because in the majority of epidemiologic studies, we will not be able to correct for confounders that have not been collected in the design of the study. The randomized trial which we'll talk about in another lecture is the only exception to that rule.

Slide 6: So, what are the methods for the control of confounders? Well, we can do it in the design of the study. We can do it by restriction. So, in other words, if we are concerned that smokers might be more men and being a man is associated with an increased risk of lung cancer, we could actually restrict the study to just men, and then we don't have to worry about the fact that there is a different distribution of men and women among smokers and among non-smokers. And it will work very well for the control of confounding. But, we might say, but I want to understand the relationship between smoking and the outcome in both men and women, and by restricting, we wouldn't be able to do it because through genders would not be in the study.

We can also do it by matching. For every smoker who comes in who is a man, we match to a non-smoker who is also a man. And then, the next smoker comes in who is between the ages of 50 and 55, and we

control for age by having a non-smoker between the ages of 50 and 55. That again will control for confounding.

But, the problem is we waste so much information by doing that. We throw away so many potential participants in the study because they do not have the exact characteristics of a person we are trying to match to. So, except for special circumstances like when we want somebody's sibling to be their comparison or we want someone's spouse to be or we want someone's twin to be, we are never going to be able to identify those people unless we do match.

But, for the majority of the variables, matching used to be much more popular than it is because we have a number of analytic techniques which will allow us to take care of this in the analysis. So, matching is now pretty restricted to variables that we would not get any other way if we did not match.

Then, if we were doing a randomized trial, randomization, the method of allocating the intervention by randomization, if a sample size is big enough, will result in all confounders known and unknown being evenly divided between the two groups. So, the process of allocating the exposure by randomization is the process by which confounding will be dealt with in a randomized trial as long as the sample size is big enough, but again, only in trial, not in a case control study, not in a cohort study, only in a trial can you randomize because you are assigning the exposure.

Slide 7: In the analysis of the study, if you did match in the design of the study, then you need to consider doing an analysis that is matched. If you didn't match, then you can use stratification and multivariable analysis.

Stratification is an analytic technique to look at one possible confounding factor at a time. Multivariable analysis is mathematical modeling to control for many confounders simultaneously.

So, for stratification, you break down your overall association by levels of one confounding factor. In a multivariate analysis, you put it into a model to look at the relationship between the exposure and the outcome controlling for all the confounders that you put in the model.

Slide 8: And how do you know if a potential confounder was a real confounder? You compare the overall, the crude, relative risk, the association between smoking and lung cancer, between the exposure and the outcome, and then you adjust for the confounding factor you are concerned about, such as age or such as gender. And you compare the crude relative risk, the unadjusted relative risk to the adjusted relative risk for the confounding factor. And if there is a difference between these two values, it is due to the effects of that confounding factor. And you would report and use and work with the adjusted relative risk because that’s a more valid estimate, not due to confounding.

So, as an example, in a study of low fat diet and coronary heart disease, the overall crude association is 0.6. Meaning, that those who have a low fat diet have six-tenths of the risk of coronary heart disease or 40% less risk of coronary heart disease than those who have a usual fat diet, and then you are concerned about body mass index, related to a low fat diet and independently a risk factor for coronary heart disease.

So you adjust for it let's say by a multivariate technique or a stratification, and you find that the adjusted relative risk is now 0.80, that those who have a low fat diet has eight-tenth of the risk or only 20% less

risk. The difference between the 0.6 which is your crude estimate and the 0.8 which is adjusted for body mass index, that difference is due to the effects of confounding by body mass index. So it will control for that one variable, just that one variable, but when we report our findings, we would want to report the 0.8 because it's the relationship once you have taken that confounder into account.

Slide 9: So, a confounder is a factor which because of its relationship with the exposure and the disease, it is actually just going to distort the magnitude of the association relating those two variables, relating smoking to lung cancer. It's just a problem. It's going to depend on the relationships of the factors in your population; it's a nuisance factor, not some biological insight into the relationship between smoking and lung cancer. The fact that smokers are more likely to be men is not giving us great insight; it is just something to get rid of when we are looking at the relationship between smoking and lung cancer. So, you need to remove the effect of the confounder, you want to control for confounding.

Slide 10: But, there is a different relationship that the same variables can also have in the interpretation of your findings. If you have an overall association between smoking and lung cancer, and if there is confounding by age and gender, and urban, rural and occupation and you take that into account so you have a relative risk estimate of smoking and lung cancer unconfounded by those variables, and that one adjusted relative risk is the one best number to represent that relationship between smoking and lung cancer, taking confounders into account.

But, what if one number doesn't represent everybody? What if the magnitude of the relationship between smoking and lung cancer is not the same for everybody? Those who are 80 years old do not have the same magnitude of association between smoking and lung cancer as those who are 20 years old. In that case, the variable age is something called an effect modifier. When the overall magnitude of the relationship between the exposure and the disease for the entire population, that overall adjusted value is modified by, differs in size by the level of a third variable like age, called the effect modifier.

So, in other words, if someone asks you, does the magnitude of the overall association observed between smoking and lung cancer apply to everybody or does the magnitude of the effect depend in size or even the direction on what type of people you are referring to? Then, this relationship is actually effect modification.

Slide 11: So, we see this often without even knowing that it's called effect modification. I just happen to pick an advertisement out of the newspaper, out of a magazine on a birth control pill called Yaz. And that the first part, the part that's in black, they said that it was going to be 99% effective when taken, and it treated different conditions and it treats acne, all the things it is effective for. But, there is a bottom section that says who should not take Yaz? And it says don't take Yaz if you smoke and are over age 35.

The next part is effect modification. Smoking increases your risk of serious side effects from the pill, statement of fact. But, the next segment that's in blue, this risk increases with age and number of cigarettes smoked.

So overall, we know that smoking increases the risk of side effects. But, the relationship between the pill and those side effects is different in size, if the woman reports to you that she is 40 years old versus 20 years old or if she is a smoker. That's effect modification; age and number of cigarettes. The overall

association between the pill and the side effects is modified by or differs for people with different characteristics in particular age and smoking.

Slide 12: So, the difference between a confounder and effect modifier; an effect modifier is a factor that modifies, alters the relationship between the exposure and the disease. This isn't a nuisance like confounding is; this is actually insight into the nature of the biologic relationship between the exposure, and the disease. You don't want to control effect modification, you want to explore it and report it.

Slide 13: So, how do we find out if there is confounding and effect modification? As we said before for confounding, we compare the crude or the unadjusted estimate between the exposure and the outcome to the adjusted estimate between the exposure and the outcome. If there is a difference between it, then that will adjust for that confounding factor and we report the adjusted unconfounded factor.

To assess effect modification, we compare the stratum-specific estimates of the measure of the effect. We look at the relationship between the pill and side effects just among older people, then we look at it just among younger people, we look at it among smokers, we look at it among non-smokers. Those are stratum-specific estimates. And if those stratum-specific estimates are different, it means the magnitude of the association between Yaz and side effects differs by the level of these possible effect modifiers. And if there is a difference, then we are actually going to report this, and we are going to discuss it to understand why the pill would work differently on side effects in a body of someone who is a smoker as opposed to someone who is a non-smoker.

Slide 14: So just to again summarize how we look for the assessment of confounding and effect modification, we have a 2×2 table up at the top, it's the crude analysis, the exposure and to the outcome; relative risk is crude, not adjusted for anything.

Then we do a stratified analysis where we take that 2×2 table and we break it down by level of the potential confounder or a potential effect modifier. So each stratum is a relationship for example between Yaz and side effects for different ages of women or different smoking levels.

We put each one of those stratum-specific analyses is unconfounded by what you divided the stratum in to. So, if you did it by age, then each of those 2×2 tables for each of the age groups is unconfounded within that age group. So you take those unconfounded estimates, you statistically put them back together again using a Mantel–Haenszel technique and you now get a relative risk adjusted for that confounding factor. It's as if the two groups of exposed and non-exposed people have the same distribution of this confounding factor. To assess confounding, you compare the crude to the adjusted relative risk. To assess effect modification, you compare those stratums to fit relative risk to see if they differ or not.

Slide 15: So, confounding and effect modification are independent concepts. But, the complexity of it is in an analysis that same variable can be a confounder, an effect modifier, both a confounder and effect modifier, or neither a confounder nor an effect modifier.

Slide 16: So again just as an example, if we have data on oral contraceptive use and myocardial infarction in women of childbearing age, the crude overall association is 2.0. Women of childbearing age who use oral contraceptives have twice the risk of developing a myocardial infarction. And we worry

about smoking because oral contraceptive users may differ from non-users in terms of their smoking habits. We also worry about let's say alcohol, oral contraceptive users again may differ, I don't know in what direction, but they may differ with respect to their other lifestyle, so alcohol maybe different. And we know that both smoking and alcohol are independent risk factors for myocardial infarction.

And when we adjusted for both smoking and alcohol, we still had a relative risk of 2. So, that means in this study, there was not confounding by alcohol or smoking. The oral contraceptive users and non-users were the same with respect to their patterns of smoking and alcohol which are other risk factors for myocardial infarction.

But now we want to say the 2.0 is a two-fold increased risk the number that I should be thinking about for everybody, every woman of childbearing ages who uses oral contraceptives, or is there any possibility that the action of the oral contraceptive in the body of a woman of childbearing age works differently if they have another factor like smoking or like alcohol.

So, then I look at the stratum-specific estimates. I look at the relative risk again for oral contraceptives and myocardial infarction, but first, just among people who don't drink, and then just among people who do drink. And I noticed that those two relative risks are exactly the same; 2.0. The relationship between oral contraceptives and myocardial infarction is two-fold increased risk regardless if you drink or don't drink. That will make no difference.

But then I say, let's look at it now among non-smokers and smokers. And we note that the relative risk for the pill, oral contraceptives and MI is about 2, 1.9 if you don't smoke, that's fine, just the same. But, if you are smoking, then you have a 41 fold increased risk of developing a myocardial infarction if you are a woman of childbearing age who uses the pill.

Now remember, on an absolute scale it's still going to be very low because most women of childbearing age don't have a myocardial infarction. But, on a relative scale, there is a modification of the effect of the oral contraceptive on the heart if you also are smoking, which from a public health standpoint or a clinical standpoint will have tremendous implications in terms of advising a woman, and certainly in terms of understanding mechanism of how a pill is harmful, that information about smoking being an effect modifier would advance our knowledge.

Slide 17: And let's look at one more thing; current use of postmenopausal hormones and coronary heart disease. The crude relative risk is 0.4, women who use postmenopausal hormones has four-tenths of the risk or 60% less risk of developing coronary heart disease. And after adjusting that for all the risk factors for coronary heart disease that we can get information on in this study, age, body mass index, diabetes, hypertension, smoking, oral contraceptive use, parental history of myocardial infarction, the relative risk was 0.5; 50% lower risk.

Now, you might say, well 0.4 isn't that different from 0.5 and it's not, so there is not much confounding, but there is a little confounding. So, it would be better for us to report the adjusted relative risk and now start working with that.

Is there effect modification? Well, it turns, there is by age. Over the age of 60, there is actually no benefit of hormones on coronary heart disease, the adjusted relative risk is 0.95. But, if you are under the age of 60, that adjusted relative risk falls to 0.35; a 65% lower risk. So, in the study of whether the

use postmenopausal hormones will reduce coronary heart disease in an observational study, the overall finding is actually different depending on the woman's age.

Slide 18: And finally, one more way, I am trying to show you different ways that you will be seeing effect modification. In this, it's this relationship of you taking low-dose aspirin to prevent cardiovascular disease and primary prevention among people who have not had evidence of cardiovascular disease to date. And we're trying to look at the prevention of myocardial infarction as well as stroke.

And if you look at everybody overall, aspirin reduces risk of a first myocardial infarction by 24%, and it really doesn't reduce risk of stroke; 0.97, so a 3% reduction, not statistically significant.

But, is that clear benefit on myocardial infarction and really not much on stroke, is that true for everybody? Let's just do gender, let's just look at men and women. And what we can see when we look at men is that there is a very clear reduction in risk of first myocardial infarction for men; 0.68 is the relative risk.

But, in fact not only is there no benefit on stoke, there is even a little bit of an increased risk of stroke, again not statistically significant, but that relative risk is greater than 1. For women, the pattern is completely reversed. There is no benefit on first myocardial infarction, relative risk 0.99. But, in fact, there is a statistically significant benefit on stroke, 0.81.

So, those overall associations, all participants together is masking the fact that the relationship is actually different from men and women, there is effect modification, and that biologic insight is incredibly important both for our understanding of the relationship as well as advising people as to what's next to do.

Slide 19: And how different is different enough for effect modification? We actually can test to see if the stratum-specific estimates are different, maybe the Breslow-Day Test that you can use, or you can put an interaction term and the multivariate modeling and see if the interaction is significant or not.

But the other way you can do it is just think about it. Compare those stratum-specific estimates and say, would my public health or clinical message be different based on these numbers? Would I tell men something different than I would tell women with respect to the risk benefit ratio if they are using aspirin for the primary prevention of cardiovascular disease? And if so, then whether it's statistically significant or not? You really would like to communicate that, raise it for people to think about, and put into their thoughts as they think about recommendations or clinical decision-making?

Slide 20: So, how do we present results? In the presence of effect modification we actually present the stratum specific results in addition to the overall association, not just the overall association alone, because we're going to feel that a single relative risk cannot reflect the different effects in the different stratum.

Slide 21: So overall, how do we present our final results? We report the crude, the overall measure of effect; we report the adjusted measure of effect to assess confounding. If there is a large amount of confounding present, we're going to be very cautious in our interpretation of the findings because if there is that much confounding we know about, then what about the effects of unknown or unmeasured confounding? We're just going to be more anxious that what we are seeing could be due to

confounders that we didn't have information on. And if effect modification is present, then we report the stratum-specific estimates and we discuss it in terms of the biology as to what could be happening in our association.

Slide 22: Thank you!