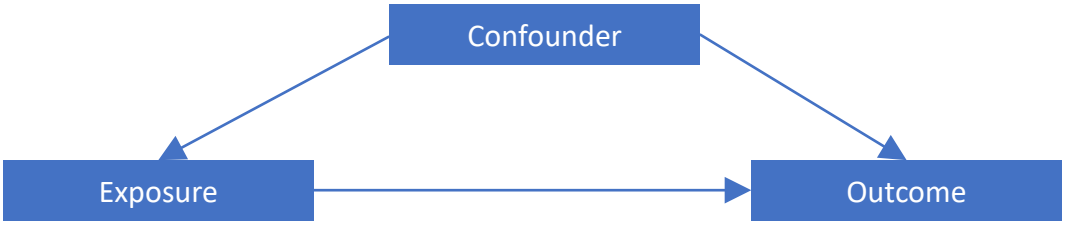
Confounding vs Effect Modification

Since Wednesday's class I've learned that, given broader changes to the MPH curriculum, you've not yet dug deeply into confounding and effect modification in other classes, and that for many students that may have been the first time they've encountered some of the concepts that I mentioned. Accordingly, I've had a number of students ask me questions about this in emails and office hours. With that I wanted to offer more background and put together this summary guide.

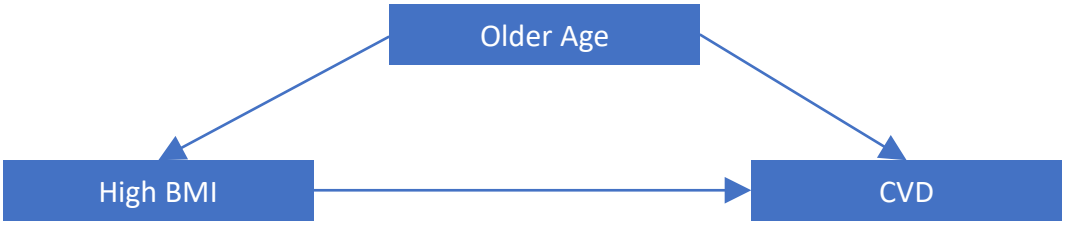
Confounding

What it is…

Confounding occurs when a third variable (the confounder) is associated with both the exposure and the outcome, and these associations distort the apparent association (e.g. the relative risk) between the exposure and outcome. The generic diagram for confounding is as follows:



As an example, imagine we want to study the association between high body mass index (BMI) and cardiovascular disease (CVD). Since older age is positively associated with both increased BMI and increased CVD risk, age will confound the association between BMI and CVD. In this case the effect of confounding will be to exaggerate the strength of the association between BMI and CVD.



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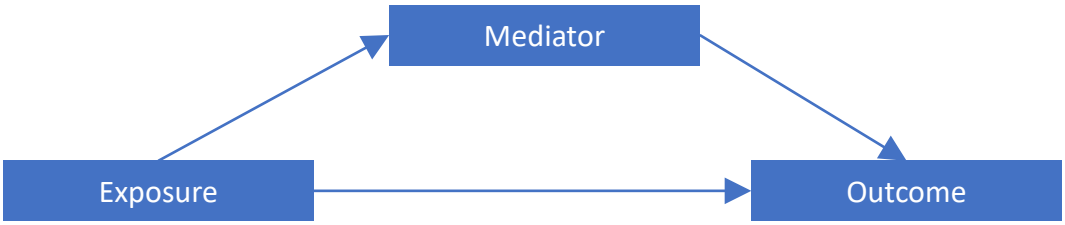
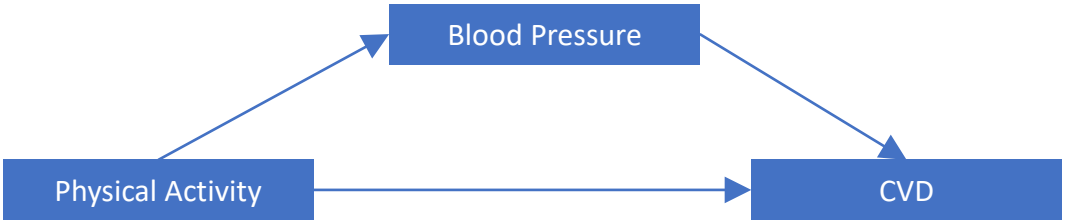
What it isn't…

Note the direction of the arrows. If we reversed the direction of the arrow between exposure and confounder then the third variable would be a mediator and not a confounder. In this scenario the third variable would represent a path through which the exposure is affects the outcome.

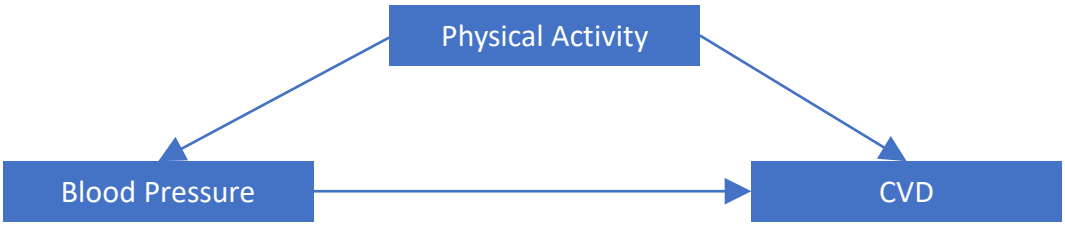


As an example, we might be interested in the association between physical activity and CVD. Here we would also recognize that a third variable, blood pressure, is associated with both physical activity and blood pressure, but if we consider the direction of the association we will see that blood pressure is likely a mediator and not a confounder:



Here, we see that physical activity is associated with reduced CVD risk and that this association is partly attributable to the effect physical activity has on improving blood pressure. This is not a source of distortion or bias, but rather a component of the association of interest.

Note that confounding and mediation depend on perspective and the association of interest. In the example above, blood pressure is a mediator in the association between physical activity and CVD. However, if our research question was about the association between blood pressure and CVD, then physical activity would be a potential confounder:



All this is to say that confounding distorts our estimates of the strengths (or even direction!) of associations and it is a serious problem that must be addressed.

How to identify it

We can identify confounders *a priori*, based on subject-matter knowledge and the results of previous research: where we know that a third variable is associated with both exposure and outcome and that it lies upstream in the causal pathway of both the exposure and outcome (i.e. the arrows point toward both exposure and outcome), then that variable can be assumed to be a confounder. Alternatively, we can identify confounders empirically in our data as any variables that lie upstream of both the exposure and outcome and, when included as an adjustment variable, meaningfully change the estimate of the

strength of the association. For this later approach, some recommend a guideline that a change in the RR (or OR) estimate of 10% or more suggests meaningful confounding. Because we typically don't design studies to be large enough to find statistically significant associations with confounders, and because confounding represents a real problem that must be addressed, we don't use a lack of statistical significance to reject a variable as a potential confounder.

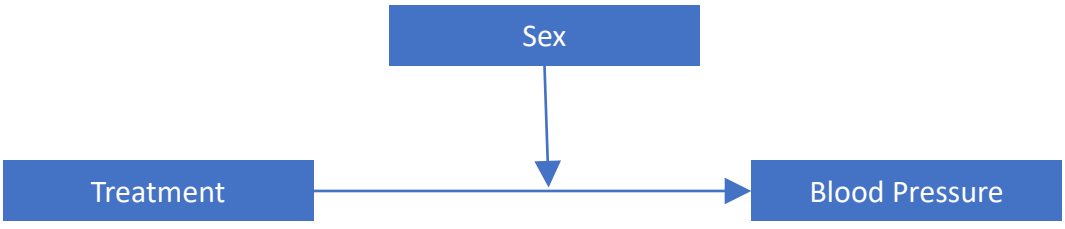
How to address it

If we want to understand the true strength of the association between BMI and CVD, then, we need to deal with confounding. There are several approaches to handling confounding and you'll spend quite a bit of time in the epi program focusing on this issue. Briefly, where the exposure is modifiable (e.g. studying the effect of a medication or interventions to change diet), the gold standard is to assign exposure levels through randomization and this is the core rationale for the randomized trial design. Randomized trials are very expensive and not all exposures can be practically or ethnically modified, so many studies use observational data, rather than data resulting from a randomized experiment. For these studies we must address either through matching (which I'll not address further), or through statistical adjustment. When we conduct a stratified analysis we are using a simple method of statistical adjustment to remove the distortion induced by the confounder. Later in your studies you'll learn regression techniques and these provide richer and more flexible means for adjustment.

Effect Modification

What it is

Effect modification occurs when a third variable modifies the effect of the exposure on the outcome. Effect modifiers are also commonly referred to as interaction terms, especially in the context of regression modelling, and may often be thought of as factors that act either synergistically or antagonistically with the exposure, in more lay terms. Imagine that we were to conduct a double-blind placebo controlled randomized trial of a new blood pressure medication. Given the study design we should not expect the effect of the medication to be confounded by sex (with randomization there should be a roughly equal sex ratio in both the control and intervention arms, and therefore no association between sex and treatment status). Now imagine that we analyze the results of the study and find that the treatment was more effective among males then among females. The way we represent this in a causal diagram is not terribly standardized, but one option to represent this follows:



In this case there is a real biological phenomenon occurring in which the effect of the medication is modified by sex.

What it isn't

Effect modification is a real biological (or social) phenomenon and not a source of bias or distortion. Unlike confounding, effect modification is not a problem that we need to address, but rather a nuance that we want to understand: finding that a drug's effectiveness differs for men and women does not suggest that our estimates are distorted or biased in some way, but provides more insight that may help inform clinical choices and prescribing decisions.

How to identify it

Broadly, to identify effect modification we look for evidence that the strength (or even direction) of an association differs by levels of another variable. Because effect modification is not a form of distortion or bias, an analysis that fails to account of effect modification will not produce an erroneous effect measure estimate: returning to the above example, if we didn't account of sex in our analysis of the drug's effectiveness we wouldn't get an erroneous results, we would simply get the average RR in both sexes combined. With that, we impose a higher standard of evidence with effect modification, where we typically err on the side of assuming no effect modification unless we observe statistically significant evidence of its existence, than we do with confounding, where we tend to err on the side of assuming confounding with no significance threshold. In the context of stratified analysis we use the test of homogeneity to assess whether or not there is statistically significant evidence of effect modification. In the context of regression (which you'll cover extensively in later Biostats courses) we look for statistically significant interaction terms.

How to address it

Where we find statistically significant evidence of effect modification, we will typically prefer to present stratum-specific effect estimates. Returning to our previous example, if the effect of a medication differs by sex, then we'll want to report sex-specific RR estimates. The epi.2by2 package does not display these in its standard output, but it does calculate and return them: if we assign the output of the epi.2by2 function to an object called "x" then the stratum-specific RR estimates can be found in `x$massoc.detail$RR.strata.wald` and the stratum-specific OR estimates can be found in `x$massoc.detail$OR.strata.wald` (see slides 17 and 21 of R session 9 for examples).

TL/DR

	Confounding	Effect Modification
What it is	Distortion of effect estimate induced by a third variable that is associated with (and upstream of) both the exposure and outcome	A real biological or social phenomenon by which an association varies by levels of a third variable
What it isn't	The effect of a mediating pathway in the association between the exposure and outcome	A source of bias or distortion
How we identify it	Either *a priori* based on knowledge and prior research (often combined with causal diagram theory), or empirically be seeing a meaningful difference in crude and adjusted estimates of an association (often defined by a difference of 10% or more)	Stratum-specific estimates that differ significantly (M-H test of homogeneity in stratified analysis, or interaction term in regression)
How we address it	Either through study design (e.g. randomization, matching) or statistical control (e.g. M-H adjustment in stratified analysis)	Report stratum-specific estimates of the measure of association