EFFECT MODIFICATION

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Welcome to this presentation focused on effect modification.

Effect Modification

Learning Objectives:

- Discuss the distinction between confounding and effect modification
- Use stratification to evaluate potential effect modifiers

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After viewing this module, you will be able to
Discuss the distinction between confounding and effect modification
Use stratification to evaluate potential effect modifiers

Effect Modification

- The effect of the exposure on the outcome differs depending on the level of another variable, the effect modifier.
- Effect Modification = Interaction
- Example: An association that is stronger in older people than in younger people; age is an effect modifier

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We begin our discussion on effect measure modification with a few definitions and examples.

When the measure of effect or measure of association changes over the value of some other factor we say that that effect is modified or in other words we have effect modification. You may also see the term “interaction” used to describe effect modification.

As an example, a drug treatment effect on a particular health outcome may be stronger in males than females, in which case, gender is acting as an effect modifier. Or if we consider driving and alcohol consumption as risk factors for injury, alcohol is likely to increase the impact of driving on the risk of injury. Alcohol is said to modify the association between driving and injury.

Don’t confuse this with confounding. Effect modification doesn’t distort the data like confounding.

Consider the example provided on this slide, if an association is stronger in older people than in younger people, we say that age is acting as an effect modifier.

Interaction

- When the incidence rate of disease in the presence of two (or more) risk factors differs from the incidence rate expected to result from their individual effects.
- Differences in the effect of one (or more) factors according to the level of the remaining factors.

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We defined effect modification in terms of measures of association such as odds ratios or risk ratios.

But we want to point out that we can also think of interaction in terms of incidence rates and comparisons of incidence rates such as cumulative incidence or incidence density.

Another definition of effect modification is when the incidence rate of disease in the presence of two (or more) risk factors differs from the incidence rate expected to result from their individual effects. For example, the effects are synergistic.

Another way to think of effect modification is that an interaction occurs when there is a difference in the effect of driving on injury depending on the level of another factor, such as alcohol.

Example:

Deaths from lung cancer (per 100,000) among individuals with and without exposure to cigarette smoking and asbestos

	Asbestos exposure	
Cigarette smoking	No	Yes
No	11.3	58.4
Yes	122.6	601.6

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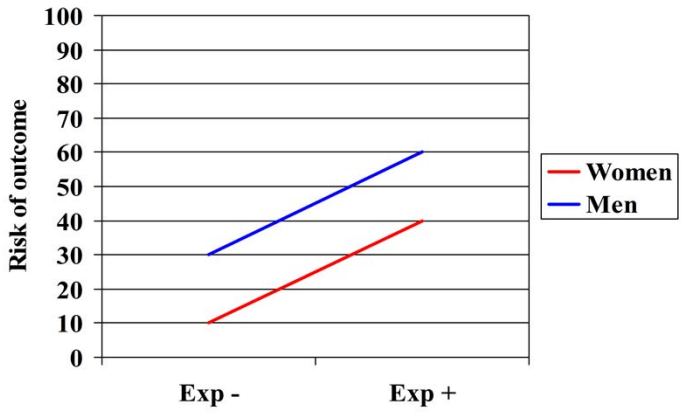
Consider a numeric example of effect modification. In this study, investigators studied the impact of smoking on deaths from lung cancer among individuals with and without asbestos exposure.

We see that the risk of death from lung cancer is increased with cigarette smoking among those with no asbestos exposure, but is even more dramatically increase with cigarette smoking among those with asbestos exposure.

Graphical Example of No Interaction



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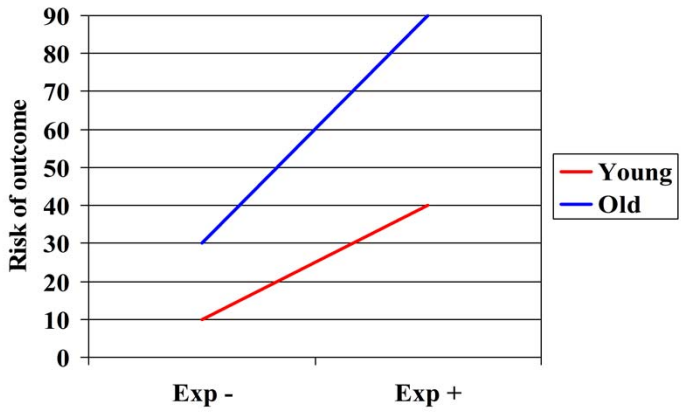
We can also assess the presence or absence of the interaction by examining the association graphically.

In this example, we see the incidence of an outcome graphed according to levels of exposure (positive and negative). In addition, we have separate risk lines for men and women.

Let's say that our outcome is incidence of high blood pressure and our exposure would be something like obesity. The graph then summarizes the incidence of high blood pressure for obese and non-obese men and women.

In this example, the two lines for each of our subgroups are parallel. This means that the difference in the incidence of high blood pressure when comparing obese to non-obese individuals is the same regardless of gender. Even though we have different starting points if we were to calculate the attributable risk or risk difference for men, we would have an attributable risk among obese men of 30 (calculated as 60-30). Similarly, among women, we would have an attributable risk of 30 (calculated as 40 – 10). Therefore, the risk difference is the same regardless of the value of our third factor gender so this would be a graphical example of no interaction.

Graphical Example of Interaction



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Now, let's consider the same relationship between the incidence of an outcome and exposure status but now we consider subgroups defined by age.

If we were to take a look at this relationship by age we can see that in this example the lines are not parallel. What does this mean?

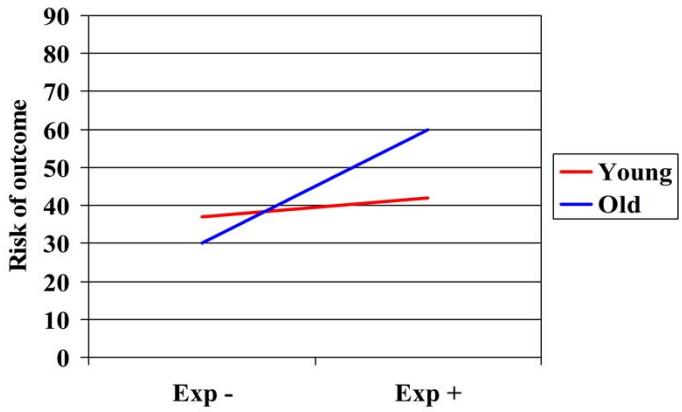
If we were to calculate the attributable risk for the older age group, we would have an attributable risk of 60 (calculated as 90 minus 30) as compared to the attributable risk among the younger age group which would be 40-10, an attributable risk of 30.

We observe an attributable risk that is higher when our study subjects are in the older age category.

In this example, we are observing a difference in the risk of the outcome in the exposed and the non-exposed group depending on a third factor, age. In this case, we see a greater difference among the older age category compared to the younger age category. This is an example of the presence of interaction.

We could say that the incidence of high blood pressure or the cumulative incidence of high blood pressure differs between those who are obese and not obese and it differs to a greater extent among those who are older compared to those who are younger.

Graphical Example of Interaction



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In this example we have a more extreme situation where our lines are crossing or intersecting. So what's happening here?

This is another example of the presence of interaction. If we again consider an outcome of high blood pressure now consider age to be the primary exposure. We see that among the non-obese (non-exposed), the incidence rate is slightly higher for young individuals than old individuals while among obese (exposed), the incidence rate is higher among older than younger participants. This is an example of an interaction. The effect of age on the risk of high blood pressure differs depending on the obesity status of the individual.

Types of Interaction

- Synergistic effect (positive interaction) = The effect modifier potentiates or accentuates the effect of the exposure of interest.
- Antagonistic effect (negative interaction) = The presence of the effect modifier diminishes or eliminates the effect of the exposure of interest.

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So just like we were able to describe the direction of confounding as either positive or negative, we can also describe the types of interaction as either positive or negative but we use the term synergistic and antagonistic.

A synergistic effect occurs when the effect modifier is accentuating the effect of the exposure of interest. So the example we gave earlier concerning drinking and driving on the risk of injury would be a synergistic effect. The effect of alcohol is accentuating the effect of driving on risk of injury.

An antagonistic effect however would occur when the presence of the effect modifier is diminishing or eliminating the effect of exposure. An example of this would be the effect of folic acid levels during pregnancy on the effect of a certain mycotoxin on the risk of neural tube defects. A mycotoxin called Fumonisins is a type of mold that contaminates corn. It can be present in corn-based products like tortillas and has been associated with an increased risk of neural tube defects in infants. This association has been observed to exist; however, when the mother has high folic acid levels, the effect of mycotoxin Fumonisins on nueral tube defects appears to be eliminated. So the B-vitamin folic acid has an antagonistic effect on the association between Fumonisins and neural tube defects.

In summary, synergistic factors magnify the effect and antagonistic factors weaken

the effect.

Using Stratification to Identify Presence of Effect Modification

1) Calculate the crude overall estimation of the exposure-disease association
2) Stratify the data by levels of the third factor
3) Calculate the stratum-specific estimates
4) Compare the stratum-specific estimates to one another and to the crude measure of association
5) Determine whether the magnitude of the stratum-specific estimates is different across strata

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When assessing effect modification in our data, we can use the technique of stratification to identify whether effect modification is present or absent.

We recall that this is the same method that we used to assess confounding.

We begin by calculating the crude overall association between exposure and disease.

Then, we stratify the data by levels of the third factor that you suspect may be an effect modifier. You then calculate the stratum-specific estimates and compare those estimates to one another and to the crude measure of association.

You are comparing the stratum-specific estimates to determine whether the magnitude of the association is different across strata and if it is different, we would conclude that the association differs according to the level of that third factor. Therefore, there is evidence of effect modification.

Note that this approach differs from the approach we used to assess confounding in that when we are comparing our stratum specific estimates

we compare them to one another first to ensure that they are similar or that they are the same because that rules out effect modification. Then, if they are the same, we can assess confounding by comparing those stratum-specific estimates to the crude.

The main comparison for confounding is between the strata specific estimates and the crude measure of association to determine if there's a difference after adjusting for that factor whereas the primary comparison for assessing effect modification is to compare the stratum specific estimates to one another to determine if there is a difference.

Example: Case control study of association between alcohol consumption and bladder cancer

	Bladder cancer	
Alcohol consumption	Yes	No
Yes	233	297
No	128	360
Crude OR = 1.73		

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Let's now consider an example from a case-control study of the association between alcohol consumption and bladder cancer.

Based on these data, we estimate a crude odds ratio of 1.73 suggesting that the odds of alcohol consumption are 73% higher among bladder cancer cases compared to controls without bladder cancer.

Example: Case control study of association between alcohol consumption and bladder cancer, **stratified by race**

	White		Black		Asian		Total	
	Ca+	Ca-	Ca+	Ca-	Ca+	Ca-	Ca+	Ca-
Alc+	72	106	93	113	68	78	233	297
Alc-	41	105	54	113	33	142	128	360
	OR=1.74		OR=1.72		OR=3.75		OR=1.73	

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Now, let's determine if there is evidence that race modifies the association between alcohol consumption and bladder cancer.

In this slide we see that within each race group, the odds ratio is similar with the exception of the estimated odds ratio among Asian individuals where the odds ratio is 3.75 instead of the value of 1.72 to 1.74 seen in the other race groups.

This higher odds ratio in the Asian group suggests that race modifies the association between alcohol consumption and bladder cancer.

Interpretation

- Clear evidence of interaction by race for the association between alcohol consumption and bladder cancer because the effect is strong in Asians, but less so in Whites and Blacks.
- Thus, the effect of alcohol consumption on bladder cancer is modified by race

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In this example, there was a clear interaction between race and alcohol consumption relative to bladder cancer.

The association between alcohol consumption and bladder cancer is stronger among Asians than among Whites or Black participants.

The association between alcohol consumption and bladder cancer is modified by race.

Effect Modification

	Smoker		Nonsmoker		Total	
	BC	No BC	BC	No BC	BC	No BC
OC	188	612	12	188	200	800
No OC	5	195	45	775	50	950
	OR=11.98		OR = 1.1		OR = 4.75	

Crude OR = 200 (950) / 800 (50) = 4.75
OR for Smokers = 188 (195) / 612 (5) = 11.98
OR for Nonsmokers = 12 (775) / 45 (188) = 1.1

Conclude: The effect of OC use on breast cancer is modified by smoking. (Smoking is an effect modifier.)

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Now, let's consider an example case-control study investigating the association between oral contraceptive use and breast cancer. We are concerned that smoking may act as an effect modifier.

To investigate the impact of smoking status on the association between oral contraceptive use and breast cancer, we estimate stratum-specific odds ratios first among smokers and then among non-smokers.

The OR among smokers is 11.98 while the OR among non-smokers is 1.1.

The OR values are very different between the smokers and non-smokers suggesting that the effect of oral contraceptive use on breast cancer is modified by smoking. Smoking is an effect modifier.

Effect Modification

- The aim is to describe and report it, not control it
- Assessed by comparing the magnitude (and direction) of stratum-specific estimates
- Use stratification to evaluate and describe

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When effect modification is present, we want to emphasize that our aim is to identify it to describe it and to report it but not to control for it.

This approach differs from what we discussed with confounding. Confounding is something that we want to remove and something we want to control. That is not the case with effect modification. The presence of effect modification or interaction represents a different association that exists among subgroups of the population and so our goal then is to investigate whether an interaction is present and if so, we want to describe it and we want to report it.

After we find an interaction, it is appropriate to keep our data stratified to assess our associations between exposure and disease separately among those groups.

With effect modification you are not going to control it but instead, want to describe it. We assess it by comparing the magnitude of association across the strata specific estimates.

We can use stratification to evaluate and describe this association so the method of stratification is utilized both to assess confounding and effect

modification. When considering stratified estimates, we compare across the stratum-specific estimates to evaluate effect modification. If the stratum-specific estimates are similar and we rule out effect modification, then we will address confounding by comparing the stratum-specific estimates to the crude estimate. If there are differences between the stratum-specific and the crude measure, we would conclude that the third factor (the stratification factor) is acting as a confounder and needs to be adjusted for in our analysis.

Key Points

- Confounding and effect modification are different concepts
- Effect modification is present if the estimate of the measure of association differs according to the level of another variable
- Confounding is present when the observed effect is distorted by the influence of another variable
- When assessing interaction and confounding in the same study, it is possible to have one with or without the other.

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It is important to keep in mind that confounding and effect modification are different concepts even though they both involve the influence of some third factor on an association between exposure and outcome.

Effect modification is present if the estimate of the measure of association differs according to the level of another variable.

Confounding is present when the observed effect is distorted by the influence of another variable.

When assessing interaction and confounding in the same study, it is possible to have one with or without the other.

We will now consider some numeric examples to distinguish effect modification from confounding.

No Confounding and No Interaction

Data Set	Stratum 1 RR	Stratum 2 RR	Crude RR
1	4.15	4.21	4.20
2	1.07	1.04	1.05
3	1.84	1.82	1.83

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This slide includes three different scenarios where there is no confounding and no effect modification or interaction.

You can see in each case that the stratum-specific estimates are nearly identical to one another.

In practice, the stratum-specific and crude measures won't be exactly equal. Instead, we are looking for evidence that they differ substantially.

In these examples, the stratum-specific estimates are very similar in stratum one to stratum two and of course they also do not differ from the crude values. So we have no evidence of interaction because this stratum-specific estimates are similar to one another and furthermore, there is no evidence of confounding because the stratum-specific estimates are also similar to the crude estimate.

Confounding and No Interaction

Data Set	Stratum 1 RR	Stratum 2 RR	Crude RR
1	1.2	1.3	4.0
2	3.4	3.4	1.0
3	0.85	0.81	1.80

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In this example we have evidence of confounding but no interaction.

We begin by comparing the stratum-specific estimates to each other and find in each case that they are similar to one another; however, the stratum-specific estimates differ from the crude measure and therefore, would conclude that confounding is present.

In the first case, the confounding results in bias away from the null; in the second case, the confounder results in bias towards the null; and in the third case, the apparent increased risk of the outcome with exposure is reversed following adjustment for the confounder such that the exposure appears to be protective after adjustment for the third factor.

Confounding and Interaction

Data Set	Stratum 1 RR	Stratum 2 RR	Crude RR
1	1.0	1.9	4.0
2	1.7	3.0	1.0
3	0.9	0.5	1.8

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In each of these examples, there is an indication of effect modification, because the stratum-specific estimates differ from each other, and furthermore, there is an indication of confounding, because the stratum-specific estimates differ from the crude relative risk. In each case, we would want to report the stratified estimates.

Strong Interaction, Confounding Irrelevant

Data Set	Stratum 1 RR	Stratum 2 RR	Crude RR
1	1.0	9.4	4.0
2	0.3	3.0	1.0
3	0.4	6.0	1.8

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In this series, the third factor again acts as both an effect modifier and a confounding factor; however, the impact of effect modification is much greater than the impact of confounding. Again, we would report the stratum-specific estimates instead of the adjusted or crude estimates.

Problem

- A case-control study was conducted to study the relationship between oral contraceptive use and ovarian cancer. The crude OR was calculated as 0.77. Given the data provided on the next slide, is there evidence that age is a confounder of the relationship between oral contraceptive use and ovarian cancer?

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Now, let's consider a case-control study that was conducted to investigate the relationship between oral contraceptive use and ovarian cancer.

The crude OR was calculated as 0.77.

Given the data provided on the next slide, is there evidence that age is a confounder of the relationship between oral contraceptive use and ovarian cancer?

Data Example

	Ages 20-39		Ages 40-49		Ages 50-59	
	OCs	No OCs	OCs	No OCs	OCs	No OCs
Case	46	12	30	30	17	44
Control	285	48	463	301	211	331

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The results have been stratified by age group. In order to investigate the impact of effect modification, we will need to estimate the stratum-specific odds ratio values.

- Ages 20-30

OR = 46(48) / 12(285) = 2208/3420 = 0.65

- Ages 40-49

OR = 30(301) / 30(463) = 9030/13890 = 0.65

- Ages 50-54

OR = 17(331) / 44(211) = 5627/9284 = 0.61

Conclusion: The crude OR of 0.77 is meaningfully different from the stratum-specific estimates. Thus, there is evidence that the association between OC use and ovarian cancer is confounded by age.

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We can use the observed data to estimate the stratum-specific odds ratio values. In each stratum, we find an estimated odds ratio that is roughly similar with values ranging from 0.61 to 0.65. Based on these data, there is no indication of effect modification.

However, the crude OR of 0.77 is meaningfully different from the stratum-specific estimates. Thus, there is evidence that the association between OC use and ovarian cancer is confounded by age.

Is the confounding positive or negative confounding? Toward or away from the null value?

Answer: negative confounding, toward the null value

Problem

- A measles vaccine may be highly effective in preventing disease if given after a child is 15 months of age, but less effective if given before 15 months of age.

What does this example illustrate?

A. confounding

B. effect modification

C. selection bias

D. information bias

E. random error

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Let's now consider some additional review problems.

A measles vaccine may be highly effective in preventing disease if given after a child is 15 months of age, but less effective if given before 15 months of age. What does this example illustrate?

This is an example of effect modification; age modifies the association between vaccine exposure and measles prevention.

Problem

- A measles vaccine may be highly effective in preventing disease if given after a child is 15 months of age, but less effective if given before 15 months of age.

- In this example, the exposure is _____Vaccination_____, the outcome is _____Measles_____, and the effect modifier is _____Age of the Child_____.

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A measles vaccine may be highly effective in preventing disease if given after a child is 15 months of age, but less effective if given before 15 months of age.

In this example, the exposure is VACCINATION, the outcome is MEASLES, and the effect modifier is AGE OF THE CHILD.

Confounding versus Interaction?

Data Set	Stratum 1 RR	Stratum 2 RR	Crude RR	Interaction?	Confounding?
1	1.0	3.5	6.0	Yes	Yes
2	1.0	1.0	4.1	No	Yes
3	4.0	4.1	4.2	No	No

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Now, let's consider three data sets and determine if an interaction is present and if confounding is present.

In the first case, the stratum-specific estimates are notably different from each other and therefore, an interaction is present. Furthermore, the stratum-specific estimates differ from the crude estimate and therefore, the third factor also acts as a confounder.

In the second case, the stratum-specific estimates are the same and therefore, an interaction is NOT present. However, the stratum-specific estimates differ from the crude estimate and therefore, the third factor acts as a confounder.

In the third case, the stratum-specific estimates are similar to each other and therefore, an interaction is NOT present. Furthermore, the stratum-specific estimates are similar to the crude estimate and therefore, the third factor is not acting as a confounding factor either.

Coffee, Caffeine, and Risk of Depression Among Women

Michel Lucas, PhD, RD; Fariba Mirzaei, MD, MPH, ScD;
An Pan, PhD; Olivia I. Okereke, MD, SM;
Walter C. Willett, MD, DrPH; E´ilis J. O'Reilly, ScD;
Karestan Koenen, PhD; Alberto Ascherio, MD, DrPH

Arch Intern Med. 2011;171(17):1571-1578

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Let's now consider an example of effect modification from the published study investigating the association between coffee consumption and the risk of depression.

Modification by Smoking

- Smoking status may modify the association between coffee consumption and depression (p=0.06)

RR of depression per 2 cup increase in coffee:

- Among Current Smokers:
  0.78 (95% CI: 0.66 – 0.93)
- Among Never/Past Smokers:
  0.95 (95% CI: 0.89-1.01)

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In the results, the authors note that smoking status may modify the association between coffee consumption and depression and they provide a test for the interaction between these factors in the model predicting depression.

We see that among current smokers, an increase in coffee consumption by two cups is associated with a 22% reduction in the risk of depression (calculated as 1 – 0.78) and furthermore, based on the confidence interval, this reduction is statistically significant because the confidence interval does not include the value 1.

In contrast, when we consider never or past smokers, we see that there is no significant association between coffee consumption and depression. An increase in coffee consumption by two cups is associated with a 5% reduction in the risk of depression among never or past smokers and this reduction is not statistically significant as indicated by the confidence interval that includes 1.

Summary

- Discuss the distinction between confounding and effect modification
- Use stratification to evaluate potential effect modifiers

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In this module, we introduced effect modification, which occurs when the effect of a particular exposure on an outcome differs depending on the level of a third variable. Note that effect modification differs from confounding. We aim to control or adjust for confounding factors, while we describe the impact of effect modification. Finally, we introduced the use of stratification to evaluate the potential for effect modification. In summary, our reporting of the association between an exposure and outcome will often involve either adjustment or reporting of the influence on this association by a third factor that is acting as a confounder or an effect modifier.

This concludes this series.