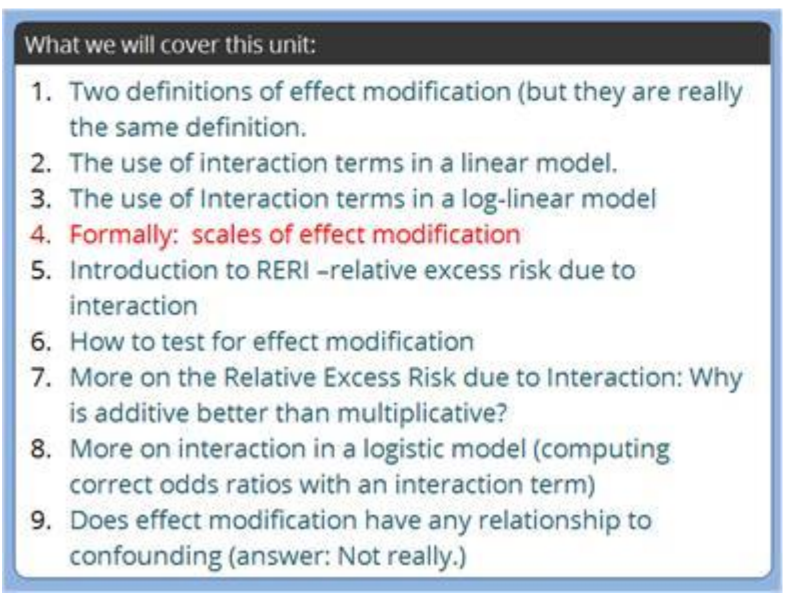
Effect Modification - Part 3

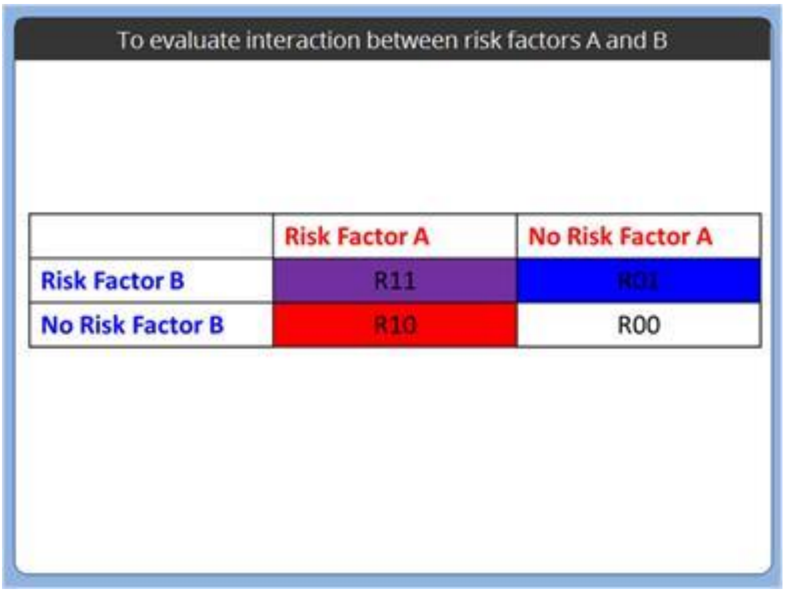
1.1 Effect Modification

We will be formalizing what we have learned so far be introducing equations to examine interaction on additive and multiplicative scales.

1.2 What we will cover this unit:



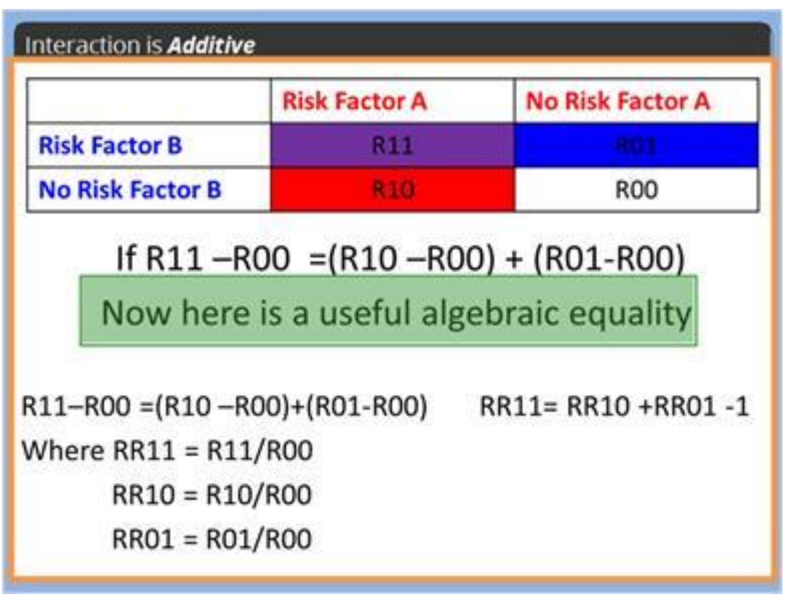
1.3 To evaluate interaction between risk factors A and B



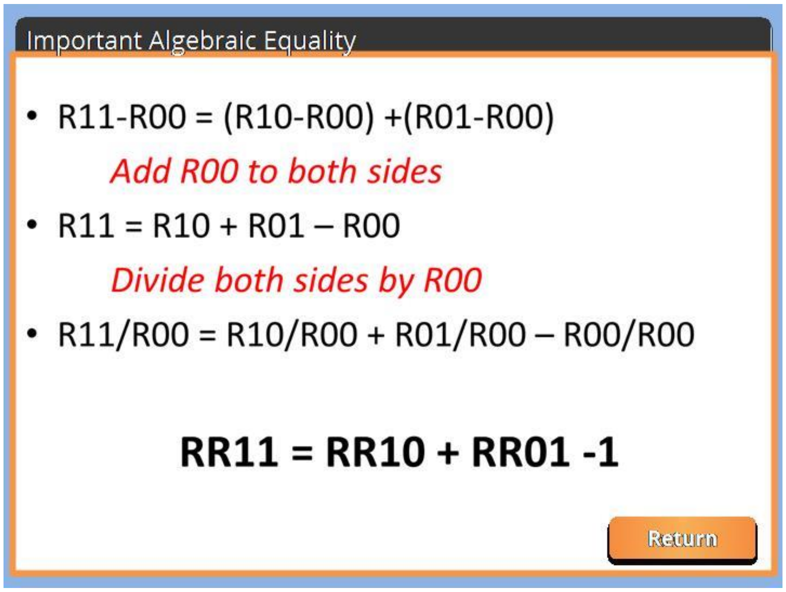
To evaluate where the interaction between risk factors A and B falls on an additive and on a multiplicative scale, you need to divide your population up into four groups of people.

Let's walk through who these four groups are, and the corresponding notation we will use. First, we have people with both risk factors, in the purple color of the two by two table. This risk of outcome in people in this group as R11. Then we have people with factor A and without B, these are R10. THese are in the red color. Next are people without factor A and with factor B. These people are denoted R01 and blue. Finally, we have the people without both risk factors denoted as R00.

1.4 Interaction is Additive

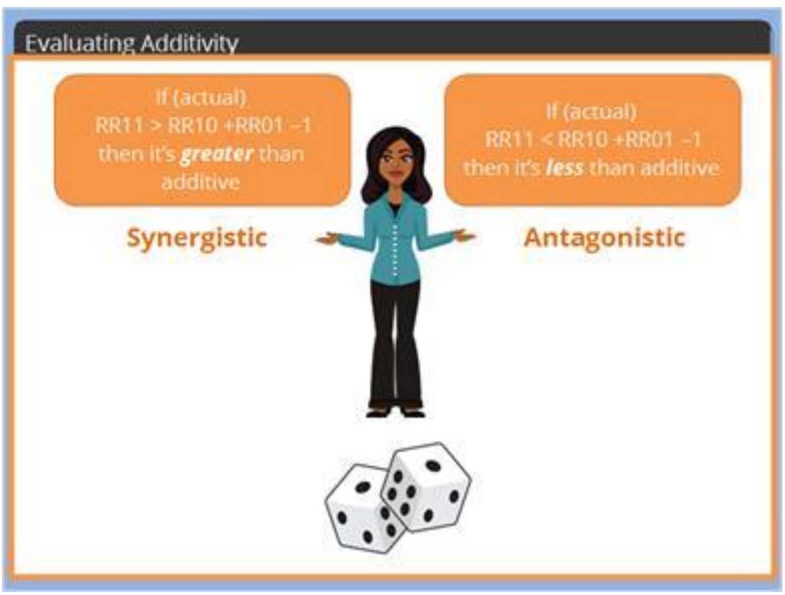


Using the 4 groups of people defined on the previous slide, we use the definition of additive interaction written in notation, to derive a formula that allows us to evaluate additive interaction using risk ratios. This is very useful to us because as epidemiologists we tend to use ratios. Click on the text about algebraic equality to learn more about this topic.



{ this is a layerof the previous slide} So you see all you do to get from the definition of additive interaction to a formula using risk ratios (which are easier for us to use) is to add R00 to both sides and then divide both sides by R00.

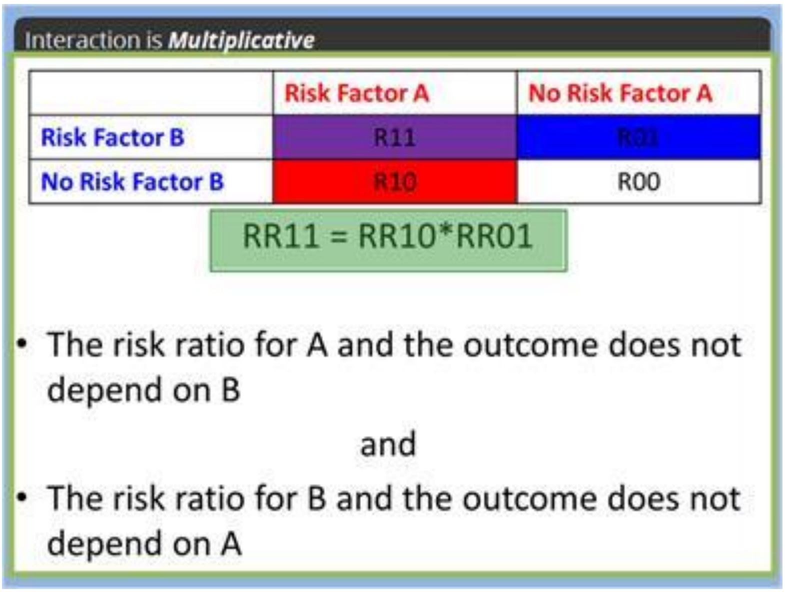
1.5 Evaluating Additivity



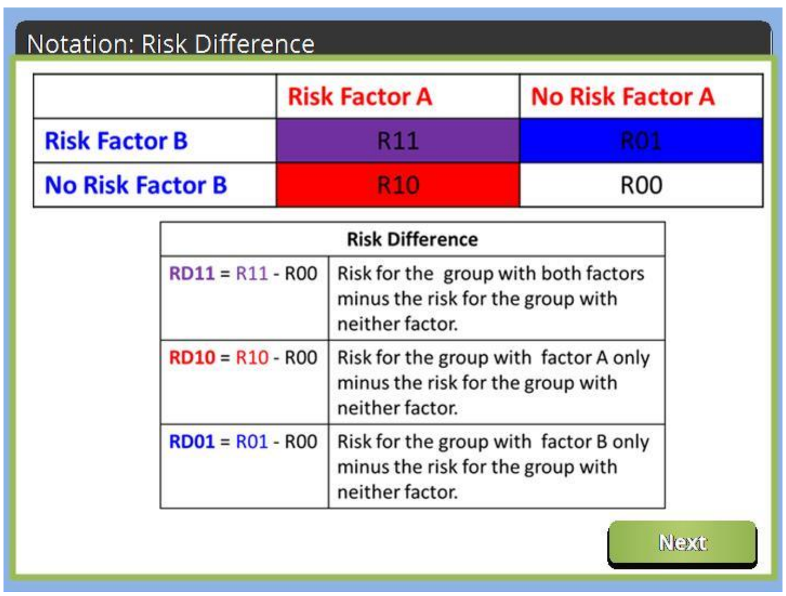
To determine where the interaction falls on the additive scale, we compare the relative risk when both factors are present to the sum of the relative risk when only one factor is present minus 1. Take a moment to study this slide. You will see these inequalities used in a slightly different manner later. Also note that *chance plays a role in the two sides of the equation being different. In the absence of a statistical test, you will have to use your best judgement as to whether the combination of factors is synergistic. For example a 2.3 and a 2.6 are probably not different, but a 2.3 and a 5.6 are.

However, remember that there is chance involved, because you are dealing with different subgroups. Don't pronounce two numbers different based on the eyeball test, unless they are very different.

1.6 Interaction is Multiplicative



Using the notation, here is the equation for multplicative interaction. For multiplicative interaction the risk ratio for A and the outcome does not depend on B and the risk ratio for B and the outcome does not depend on A. Click on the equation to learn more about this notation.

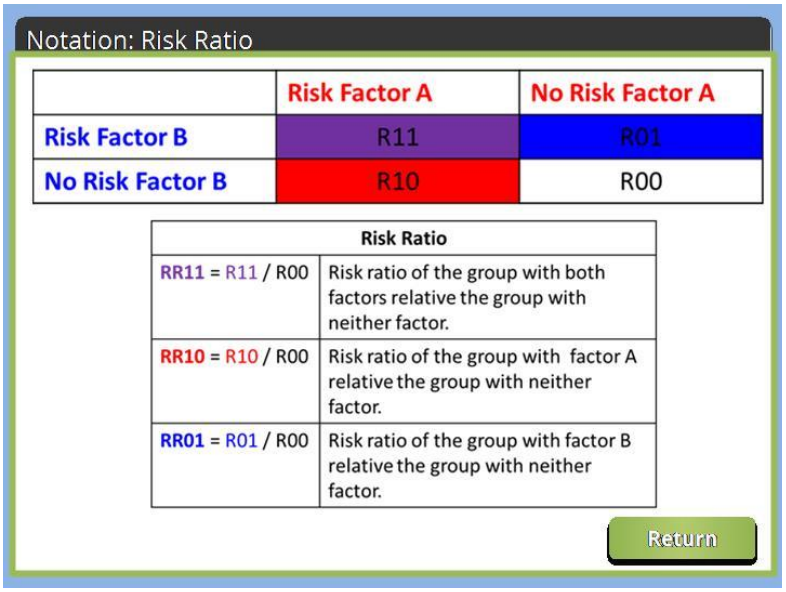


We have a few more equalities about interaction to show you, and they require using notation. You do not have to use this particular notation. You may prefer to use capital and small letters for subscripts, as long as you know what it means.But let's recall what we discussed on the last slide.

Have two factors A and B. Use

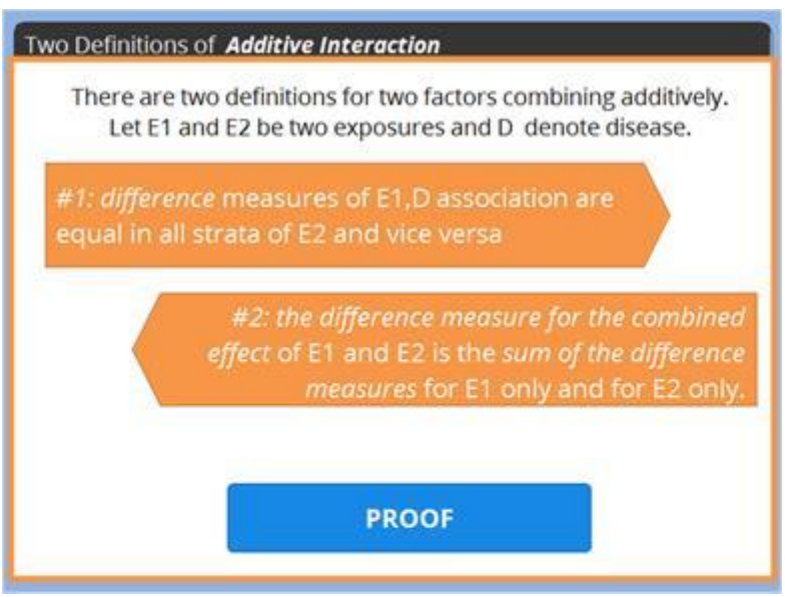
- R11 =Risk of outcome in group with both factors.
- R10 =Risk of outcome in group with factor A, but not factor B
- R01 =Risk of outcome in group with factor B, but not factor A
- R00 =Risk of outcome in group with neither factor ("baseline risk")

We can use the risk difference to understand the risk difference for both factors, the risk for factor A only, and the risk for factor B only. Take some time to review this, then move on to the next page.



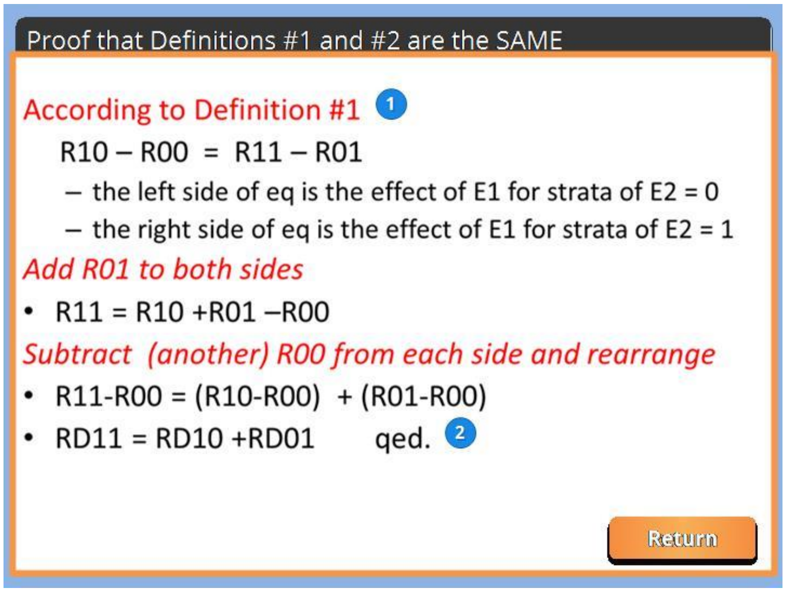
Similarly, we can examine the risk ratio for each of these factors. But this time we are dividing rather than subtracting. Again, take some time to review this table. Once you're done click on the return button.

1.7 Two Definitions of Additive Interaction



Now that we have reviewed the two scales of interaction, additive and multiplicative, let's go into some more detail. For the additive scale, recall there are two definitions of additive interaction. Let E1 and e2 be two exposures and D denote disease. The first definition is the *difference* measures of E1,D association are equal in all strata of E2 and vice versa. The second is the difference measure for the combined effect of E1 and E2 is the sum of the difference measures for E1 only and for E2 only. But fact, 1. and 2. are the same definition. We can use the notation to easily prove this

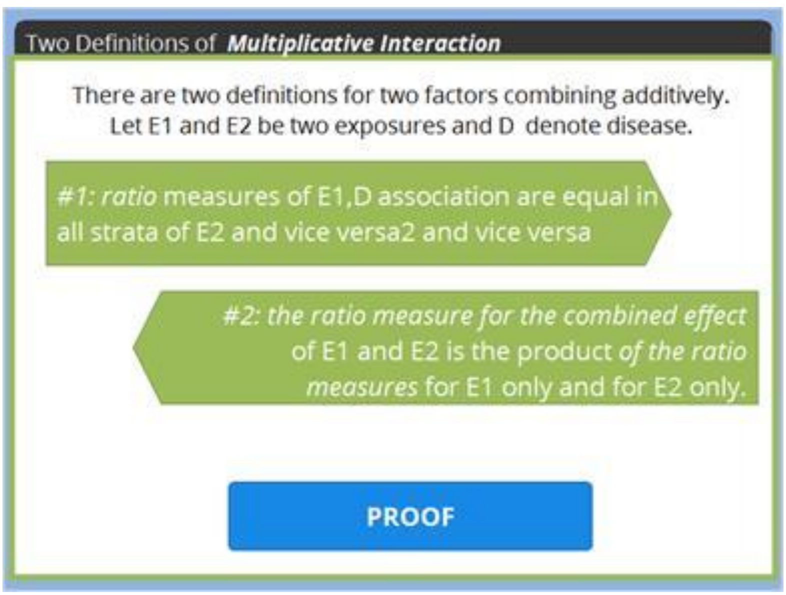
As a reminder, there are two definitions of additive interaction and now we are ready to prove that the two definitions are the same definition. Click on the proof button to learn more.



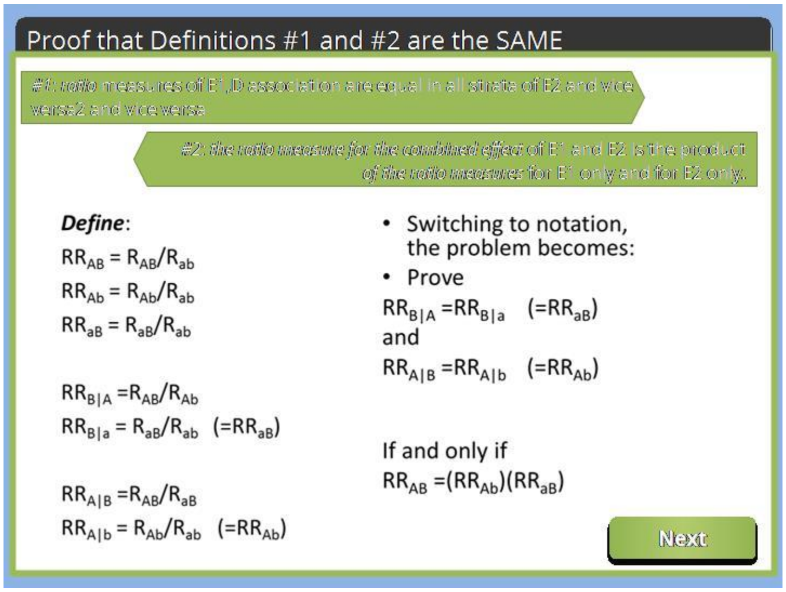
So here is the proof that the definition are the same. If you need to, use the markers to refresh on these definitions.

If you examine the proof, you will see that wego from definition 1 of additive interaction to definition 2in three easy algebraic steps.

1.8 Two Definitions of Multiplicative Interaction



There are also two definitions of multiplicative interaction that are really the same definition. Note specifically that definition 1 is saying that relative risks (or odds ratios) for factor A and the outcome are the same for every strata of B and vice-versa. You probably recall this from Epi 6000. Weleave the proof up to you. Take some time to try this out on your own before moving forward.

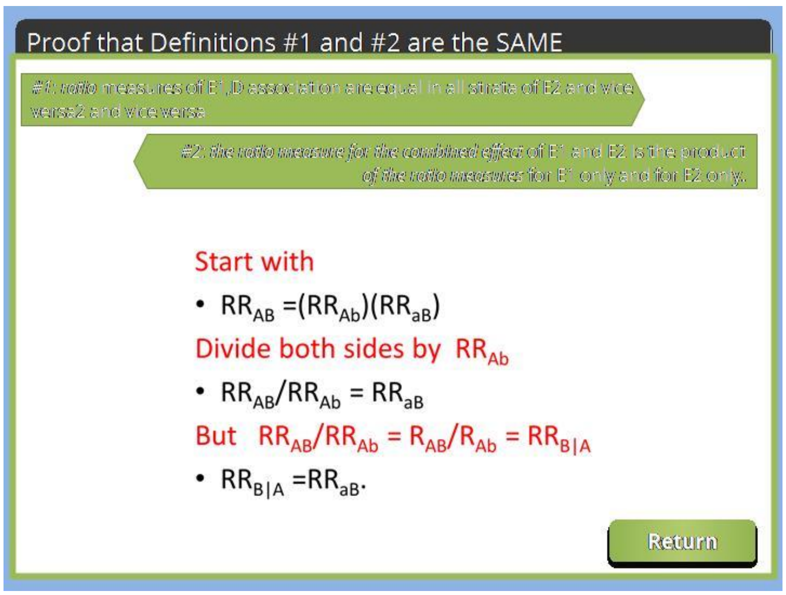


The trick to doing this exercise is to put each of the two conditions into notation. Once they are both in notation, the proof is trivial. Notation: Use capital letters if the factor is present and small letters if the factor is absent.

- Condition 1. Ratio measures of E1,D association are equal in all strata of E2 and vice versa

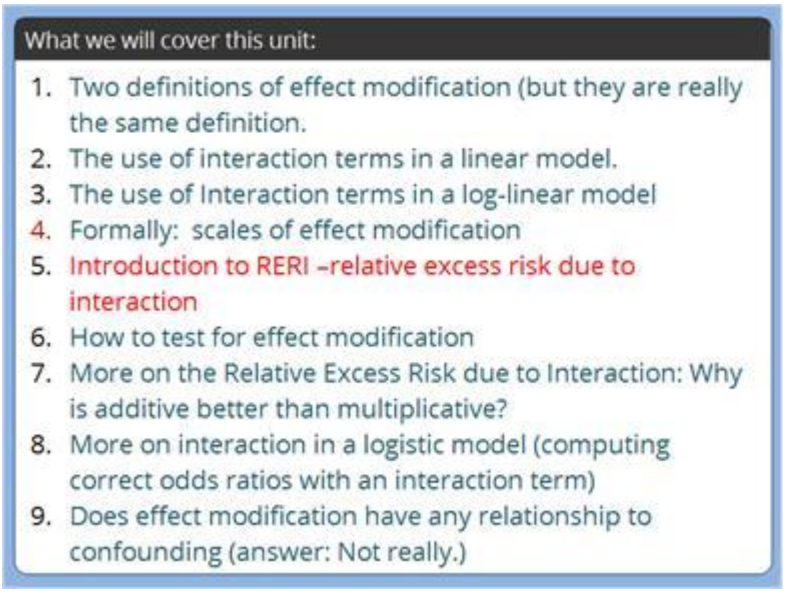
If and only if

- Condition 2 .*the ratio measure for the combined effect*of E1 and E2 is the product *of the ratio measures*for E1 only and for E2 only.



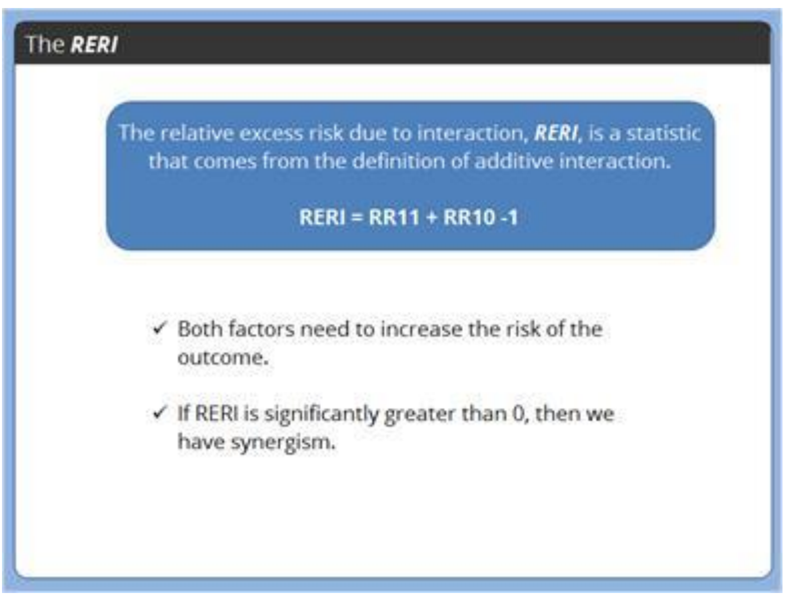
In our notation this means:

1.9 What we will cover this unit:



Now let's move on to talking about the fun acronym - RERI, which stands for the relative excess risk due to interaction.

1.10 The RERI



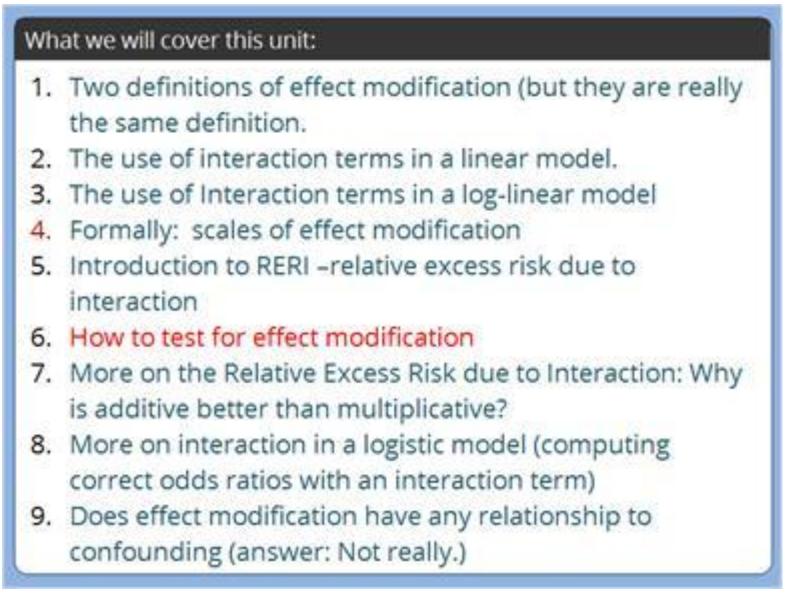
The relative excess risk due to interaction, RERI, is a statistic that comes from the definition of additive interaction. It is often used by epidemiologists.

A couple things to keep in mind about the RERI *To use, both factors have to increase risk of outcome.

If RERI is significantly greater than zero we have synergism between the factors.

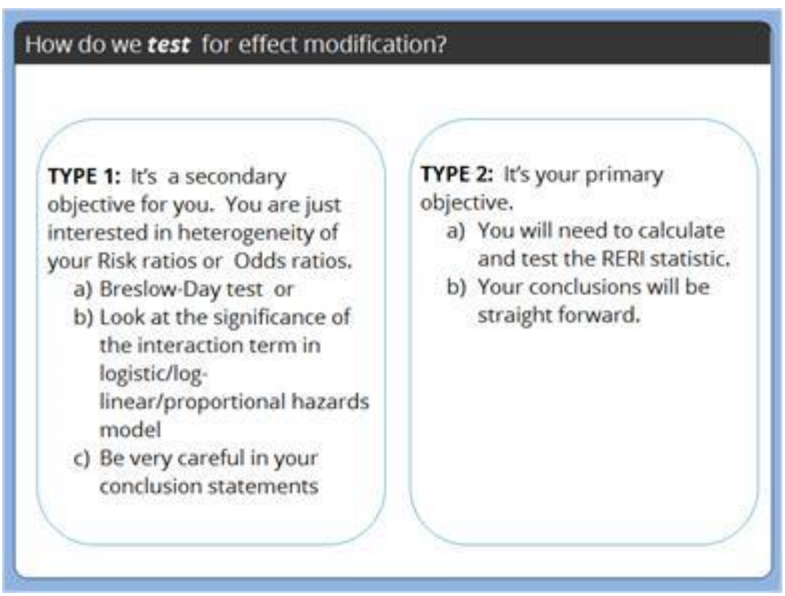
Unfortunately the calculation of the variance of RERI is outside the scope of the class.

1.11 What we will cover this unit:



Wehave spent a lot of time going over various definitions of effect modification. How do we statistically test for it? When do we statistically test for this?

1.12 How do we test for effect modification?

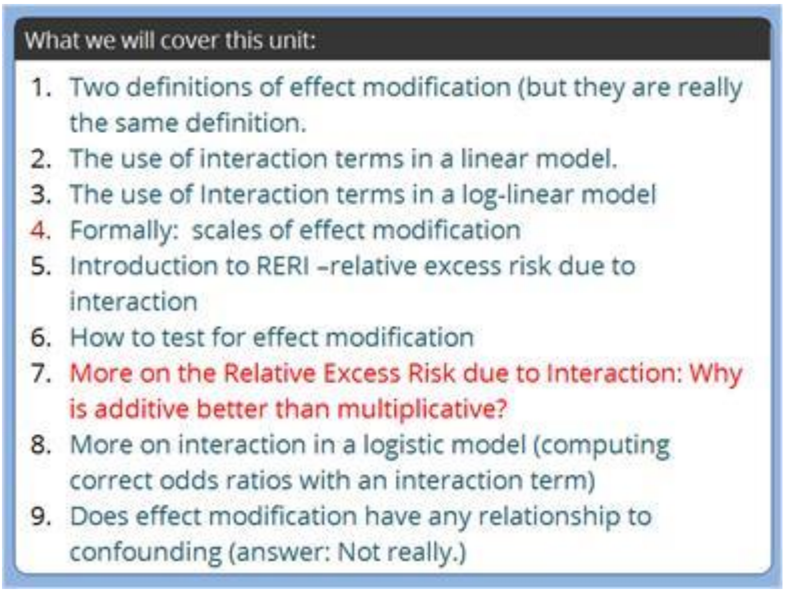


There are two scenarios of how we would test for effect modification.

READ

TheBreslow-Day test tests whether risk ratios or odds ratios are the same across strata; This is the same as testing for interaction on a multiplicative scale. SAS Proc Freqwill put out the Breslow-Day test when doing an adjusted analysis. The significance of the coefficient of an interaction term in a multiplicative model also is a test of multiplicative interaction. However, you need to be aware that if you are truly interested in whether there is synergism between two factors, you need to calculate RERI.

1.13 What we will cover this unit:

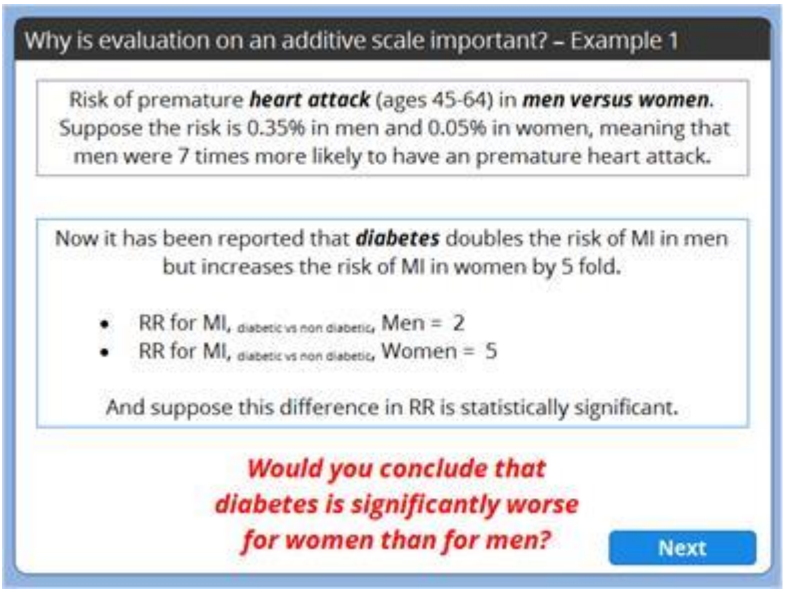


Okay, we reviewed how to test for effect modification, but let's return to our favorite, RERI and answer the question, why is additive better than multiplicative?

1.14 Evaluate on additive scale

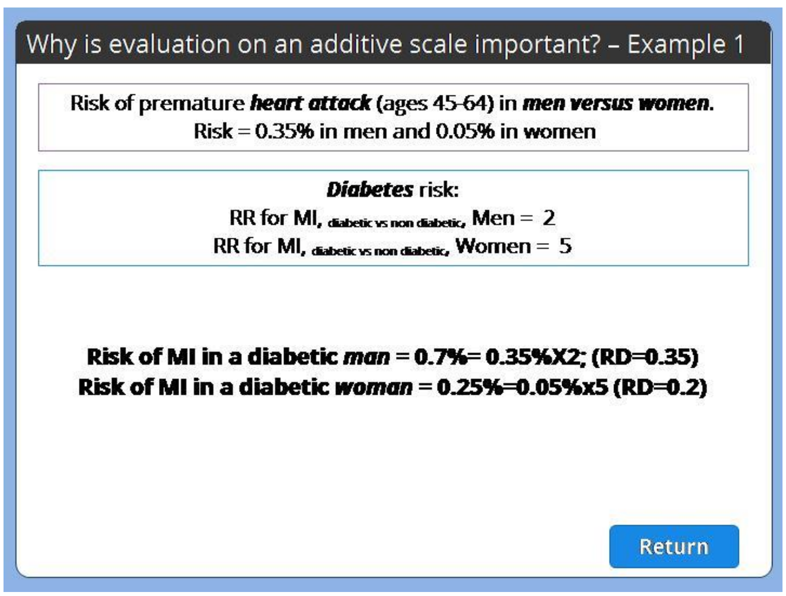
Wehave said several times in this lecture that interaction should really be examined on an additive rather than a multiplicative scale. We go through some examples now to try to give you an intuitive feeling as to why this may be true. In fact, we hope to show you that evaluating interaction on a multiplicative scale may lead to ridiculous conclusions.

1.15 Why is evaluation on an additive scale important? – Example 1



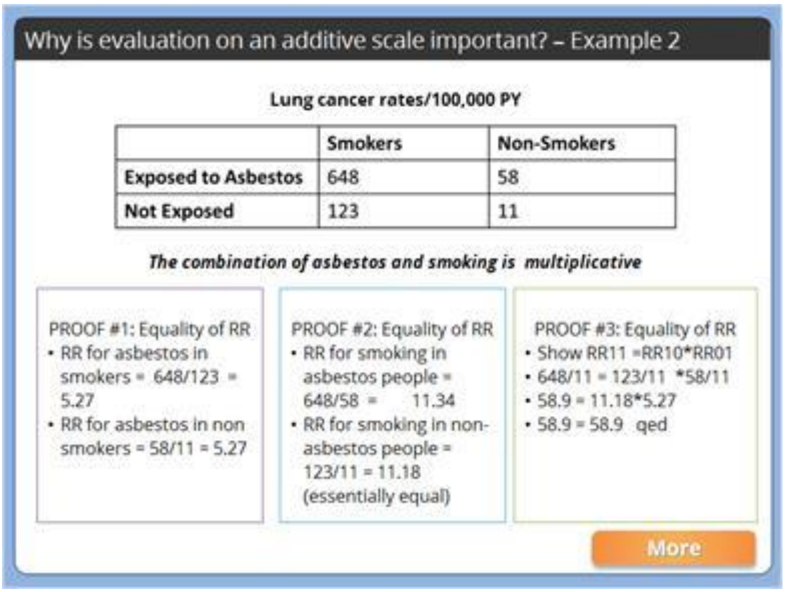
We start with an example ofMI in men and women ages 45-64. Suppose that in this age range being male is a strong risk factor as men are seven times more likely to have a heart attack than women.

Suppose now what we are really interested in is the association between diabetes and MI in this middle aged age group. We decide to stratify on gender. We find that Risk ratio for diabetes and MI among men is 2.0, but among women it's 5.0 and the Breslow Day test (or interaction term in a logistic model) is highly significant. We conclude diabetes is worse for women than for men. What is the problem with that?



Here's the problem. If we take the baseline risk of MI in mean and women and multiply it by the relative increase in risk with diabetes, the **Risk of MI in a diabetic man is 0.7% . The Risk of MI in a diabetic woman is 0.25%. Do you really want to say that diabetes is significantly worse for women than for men when men get a greater increment in risk and a diabetic man is still almost 3 times as likely to have an MI than a diabetic woman????**

1.16 Why is evaluation on an additive scale important? – Example 2

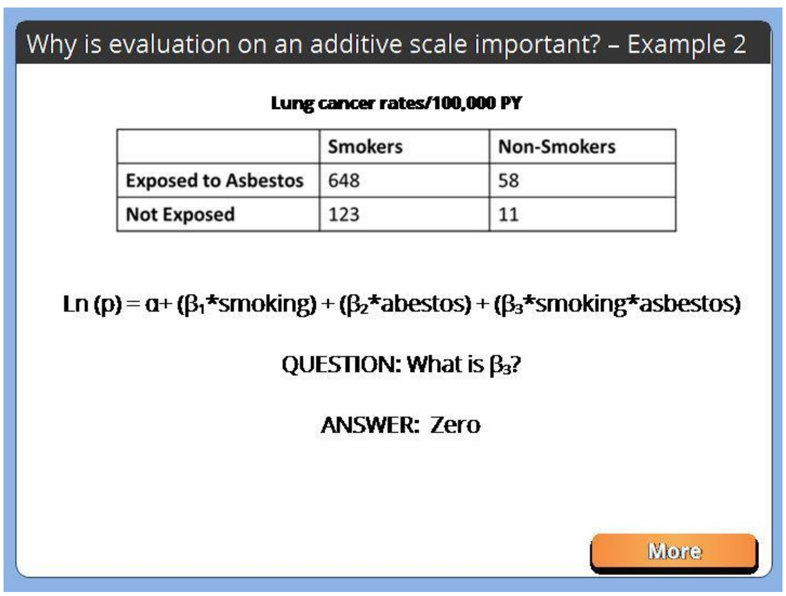


For example #2 lets go back to the asbestos and smoking example.

In example 2, we create a table such that asbestos and smoking is exactly multiplicative.

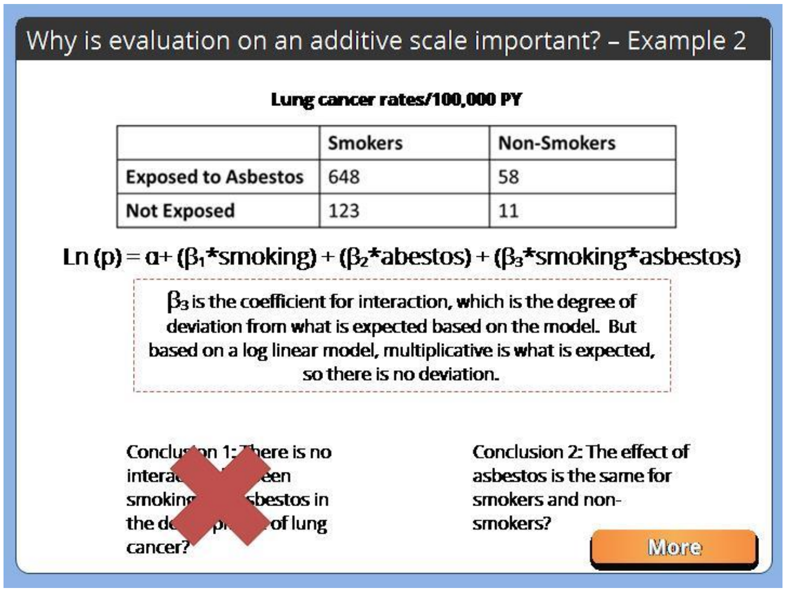
Note that I changed the smoking-asbestos cell to 648 for illustrative purposes.

The combination of asbestos and smoking is multiplicative (except for rounding in the table to whole #s) ***and we will prove this not once <u>but three times</u>.***



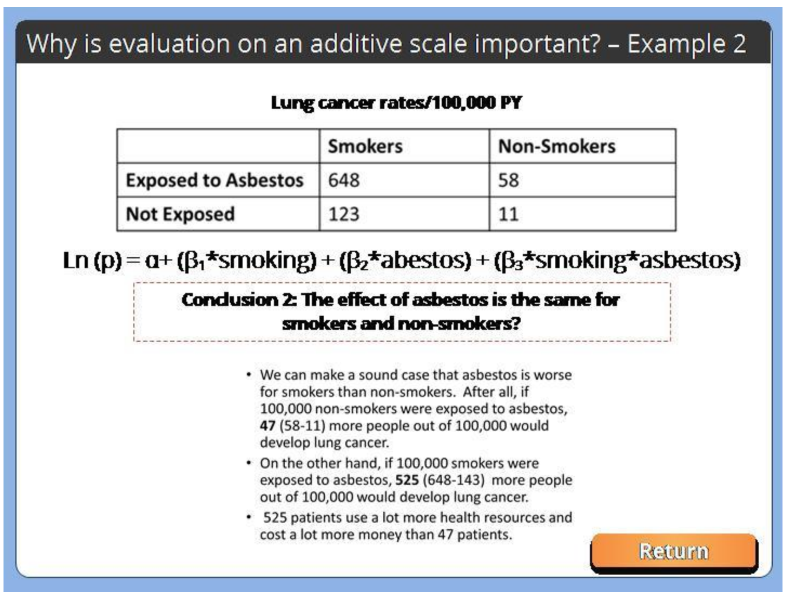
We evaluate the RR for asbestos in eachsmoking stratum, and the RR for smoking in each asbestos stratum. We find that the RR for asbestos doesn't depend on smoking and vice-versa

Here we show that the RR when both factors are present equals the product of the individual RRs



If we ran the following model

Now werun a log-linear model putting in an interaction term. What is the coefficient on the interaction term? The answer is zero, of course, because the interaction is exactly multiplicative.

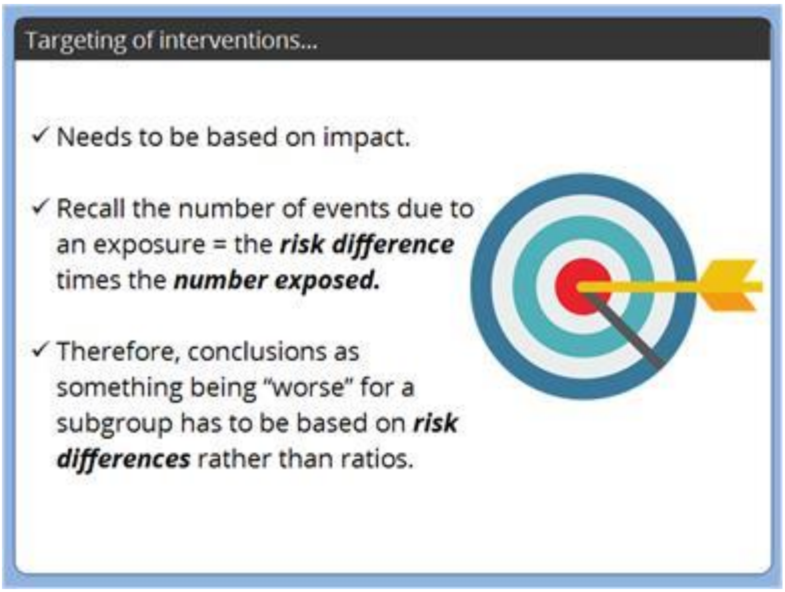


What can we then conclude about B3?

Conclusion 1 no: ***Hahahaha.Only if you wanted to do standup comedy. Everyone would laugh at you for refuting a very well known synergistic effect.***

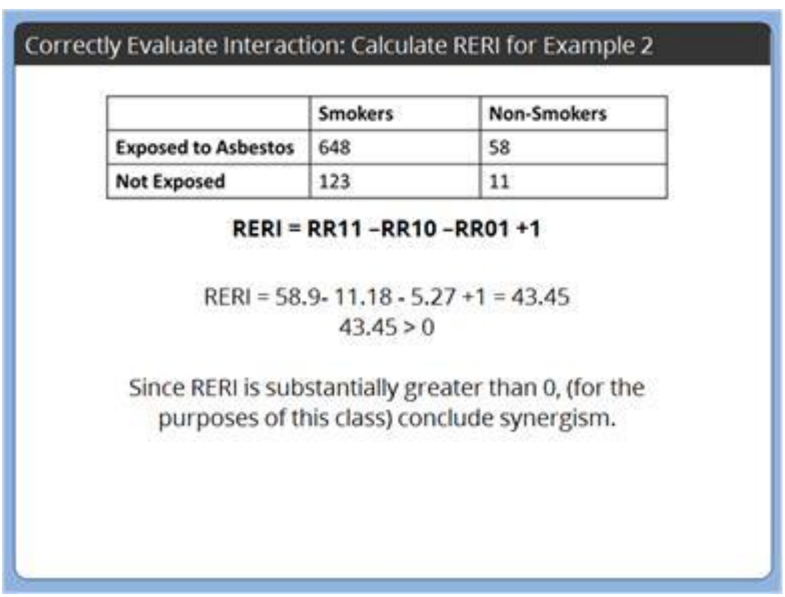
Based in the numbersin the table, I can make a sound case that asbestos is worse for smokers than non-smokers. If 100,000 non-smokers were exposed to asbestos, more people out of 100,000 would develop lung cancer. If 100,000 smokers were exposed to asbestos, more people out of 100,000 would develop lung cancer. So how can I get awaywith saying that asbestos has the same effect for smokers and non-smokers based on zero interaction term?

1.17 Targeting of interventions…



Conclusions as to arisk factor being"worse" for one subgroup rather than another have to be based on risk differences rather than risk ratios.

1.18 Correctly Evaluate Interaction: Calculate RERI for Example 2



To correctly evaluate interaction, calculate RERI. In this smoking/asbestosexample RERI comes out to 43, which is a lot bigger than 0. We conclude that asbestos and smoking are synergistic.

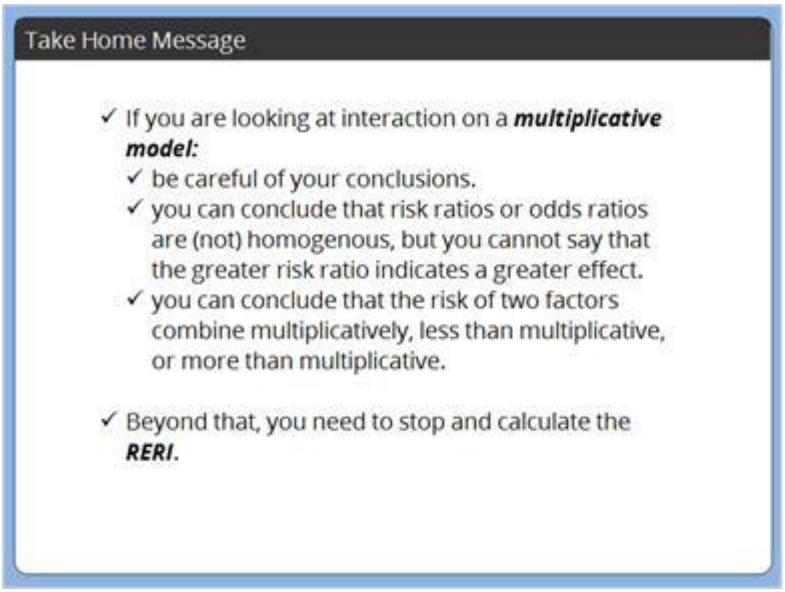
If RERI is substantially greater than 0, (for the purposes of this class) conclude synergism.

RERI = 58.9- 11.18 - 5.27 +1 =43.45

Does 43.45 =0 ? I guarantee you it does not, so you may conclude asbestos and smoking are synergistic. ***Give up your career in comedy.***

Unfortunately the test of RERI = 0 is beyond the scope of this class. You will have to take Advanced Research Methods.

1.19 Take Home Message

<table>
<tr>
<td>


</td>
<td>
If you are looking at interaction in a multiplicative model

The take-away message is be careful when examining interaction.
</td>
</tr>
</table>