Box 1. Assessing additive interaction using ratio measures

Often times we may not be able to estimate risk or rate differences when assessing interaction. For example, when our study design is to collect a purposive sample of diseased individuals and non-diseased individuals, we cannot estimate population parameters for risks and rates directly because our study design dictates the number of diseased and non-diseased participants. We have learned, in Chapter 6, that the odds ratio is an appropriate measure of association for these types of study designs.

We can estimate interaction with ratio measures such as the odds ratio (or risk ratio or rate ratio, should there be a reason to estimate these measures rather than risk or rate differences). To illustrate how to do this, let us consider an example.

We conduct a study in Farrlandia of the association between consumption of aspartame and stroke. We collect a purposive sample, including 200 cases of stroke newly diagnosed at Farrlandia hospitals, and 600 individuals who have never had a stroke from the surrounding hospitals in different Farrlandia communities. We hypothesize that individuals with a family history of stroke may be particularly vulnerable to the effects of aspartame, suggesting that aspartame and family history may be causal partners in a marble jar that causes stroke.

Because we sampled our participants based on their disease status (200 with stroke and 600 without stroke), we cannot estimate risk of stroke conditional on aspartame use or family history (see Chapter 6). Rather, we can estimate the odds ratio for the association between aspartame, family history, and stroke.

One way in which to assess interaction would be to stratify the association between aspartame use and stroke by family history. In Figure 4, aspartame consumers will be noted in black and non-aspartame users in grey, and family history of stroke with be noted in dots on the individuals.

Box 1, Figure 1. Association between aspartame consumption and stroke, stratified by having family history of stroke

Dots = family history
Black = aspartame user

Association between aspartame and stroke among those without a family history of stroke

	Health indicator present	Health indicator absent	Total N
Exposed	25	85	110
Unexposed	103	363	466
Total N	128	448	576

$$\text{Odds ratio} = \frac{\frac{25}{128}}{\frac{103}{128}} \Big/ \frac{\frac{85}{448}}{\frac{363}{448}} = \frac{25 * 363}{85 * 103} = 1.04\ [95\%\ \text{CI}\ (0.63, 1.70)]$$

Association between aspartame and stroke among those with a family history of stroke

	Health indicator present	Health indicator absent	Total N
Exposed	53	87	140
Unexposed	19	65	84
Total N	72	152	224

$$\text{Odds ratio} = \frac{\frac{53}{72}}{\frac{19}{72}} \Big/ \frac{\frac{87}{152}}{\frac{65}{152}} = \frac{53 * 65}{87 * 19} = 2.08\ [95\%\ \text{CI}\ (1.13, 3.85)]$$

Among those without a family history of stroke, there is little relation between aspartame use and stroke incidence [OR=1.04, 95% CI (0.63,1.70)]. Among those with a family history of stroke, those who use aspartame have 2.08 times the odds of stroke (95% CI 1.13, 3.85). This certainly suggests that family history and aspartame use operate conjointly to influence stroke.

However, this does not give us information about the presence of an additive interaction between aspartame use and family history, because we are examining variation in the odds ratio, which is a multiplicative measure.

To assess whether additive interaction is present, we will divide the sample into four groups: (1) Family history of stroke and regular aspartame use; (2) No family history of stroke and regular aspartame use; (3) Family history of stroke but no regular aspartame use; (4) No family history of stroke and no regular aspartame use.

Next, we need to estimate three odds ratios. We will compare each of the first three categories to the fourth category of unexposed to both family history and aspartame. We will label each of these odds ratios with a new notation: OR_{A+F+} is the odds ratio comparing those exposed to both family history and aspartame to those who are exposed to neither family history nor aspartame. OR_{A+F-} is the odds ratio comparing those exposed to aspartame but not family history to those who are exposed to neither family history nor aspartame. Finally, OR_{A-F+} is the odds ratio comparing those exposed family history but not aspartame to those who are exposed to neither family history nor aspartame. Box 1, Figure 2 contains our study data.

Box 1, Figure 2. Association between aspartame consumption, family history, and stroke, each group compared to no family history and no aspartame use

Dots = family history
Black = aspartame user

Association of stroke with family history and aspartame use compared with no family history and no aspartame use

	Health indicator present	Health indicator absent	Total N
Exposed	53	87	140
Unexposed	103	363	466
Total N	156	450	606

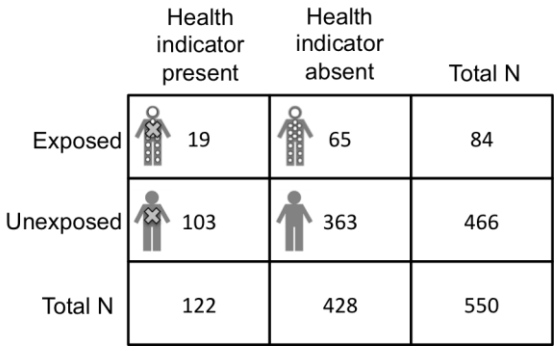
$$\text{Odds ratio (A + F+)} = \frac{\frac{53}{156}}{\frac{103}{156}} \Big/ \frac{\frac{87}{450}}{\frac{363}{450}} = \frac{53 * 363}{87 * 103} = 2.15\ [95\%\ \text{CI}\ (1.43, 3.22)]$$

Association of stroke with aspartame use but no family history compared with no family history and no aspartame use

	Health indicator present	Health indicator absent	Total N
Exposed	25	85	110
Unexposed	103	363	466
Total N	128	448	576

$$\text{Odds ratio (A + F}-\text{)} = \frac{\frac{25}{128}}{\frac{103}{128}} \Big/ \frac{\frac{85}{448}}{\frac{363}{448}} = \frac{25 * 363}{85 * 103} = 1.04\ [95\%\ \text{CI}\ (0.63, 1.70)]$$

Association of stroke with family history but no aspartame use compared with no family history and no aspartame use:



$$\text{Odds ratio (A}-\text{F+)} = \frac{\frac{19}{122}}{\frac{103}{122}} = \frac{19 * 363}{65 * 103} = 1.03\ [95\%\ \text{CI}\ (0.59, 1.80)]$$

Notice that the row describing unexposed individuals for each of the three 2x2 tables in Box 1, Figure 2 are identical (103 individuals who have the health indicator and are unexposed; 363 individuals who do not have the health indicator and are unexposed) – each group is always compared to those with no family history and no aspartame use. When comparing those with family history and aspartame use to those with neither, the resulting odds ratio (OR_{A+F+}) indicates that the former had 2.15 times the odds of stroke compared with the latter (95% CI 1.43,3.22). When comparing those with aspartame use but no family history to those without either family history of aspartame use, the resulting odds ratio (OR_{A+F-}) provides little evidence of an increased odds of stroke [OR=1.04, 95% CI (0.63, 1.70)]. Finally, when comparing those with family history but not aspartame use to those without either family history of aspartame use, the resulting odds ratio (OR_{A-F+}) provides little evidence of an increased odds of stroke [OR=1.03, 95% CI (0.51, 1.80)].

We can use these three odds ratios, all with the same comparison group of no family history and no aspartame use, to estimate the magnitude of the interaction between family history and aspartame use with the following formula:

The general formula for estimating the magnitude of interaction for a ratio measure is termed an 'interaction contrast ratio' (ICR) and is then:

$$\text{ICR} = \text{OR}_{++} - \text{OR}_{+-} - \text{OR}_{-+} + 1$$

Where the "+" and "-" subscripts indicate whether the comparison group has both factors (++), or one factor only (+- or -+), always compared to those with neither factor.

In our hypothetical study, the interaction contrast ratio would be estimated as:

$$2.15 - 1.03 - 1.04 + 1 \; = \; 1.08$$

This measure can be interpreted as the excess odds due to the interaction of aspartame use and family history, relative to those without either exposure. An ICR of 0 would indicate no evidence of interaction. Our ICR of 1.08 indicates that there is interaction present in these data between family history of stroke and aspartame use in association with stroke.

Some caution needs to be exercised when using odds ratios to estimate additive (or any) interaction, given that the odds ratio will often over-estimate the risk ratio as the disease becomes more common. We provide additional detail on odds ratios and interaction in the Box 2 of the online material that accompanies Chapter 11.

Box 2. Caution needed when proceeding with additive interaction using ratio measures

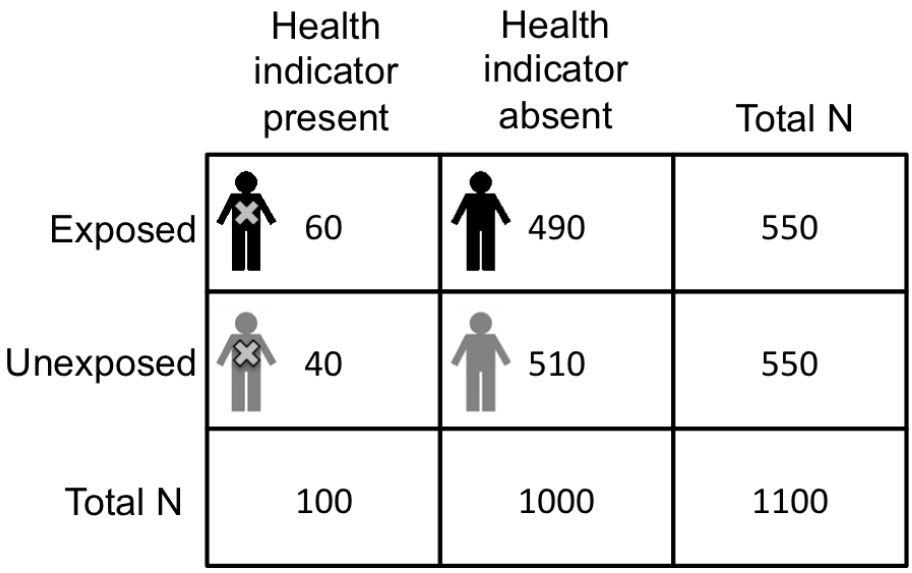
We have demonstrated above how we can assess additive interaction with ratio measures. However, particular caution needs to be taken when using odds ratio measures to assess interaction.

When odds ratios are used to approximate the risk ratio (as we often do when we sample diseased individuals and non-diseased individuals), the magnitude of the incidence of the outcome should be considered for proper interpretation. We have previously demonstrated, in Chapter 6, that the odds ratio will always be slightly stronger in magnitude than the risk ratio. As the incidence of the outcome becomes more common, the odds ratio will be increasingly stronger in magnitude than the risk ratio.

When we conduct stratified analysis (i.e., examining the exposure disease relationship across levels of a third variable), there could be the appearance of an interaction if the disease is common in one stratum and rare in another stratum. Let us review a short example.

We conduct a study in Farrlandia of the potential association between neighborhood violence and risk of developing depression. We collect a random sample of Farrlandians, screen out those with prior histories of depression, and divide them into two groups based on whether or not they live in a violent neighborhood. We then follow individuals forward in time for one year, estimating incidence of depression in the sample. We sample 1,100 individuals, and of these, 100 have the genetic variant believed to increase the risk for depression. Box 2, Figure 1 contains our data.

Box 2, Figure 1. Association between neighborhood violence and depression in the full sample



$$\mathrm{P(D|E+)} = \frac{60}{550} = 0.11$$

$$\mathrm{P(D|E-)} = \frac{40}{550} = 0.07$$

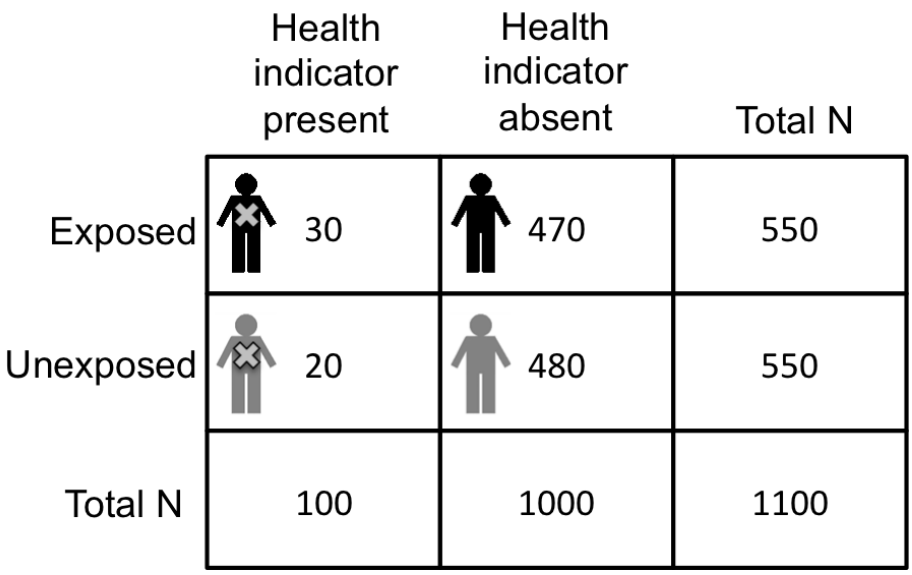
$$\text{Risk ratio} = \frac{0.11}{0.07} = 1.50\ [95\%\ \mathrm{CI}\ (1.02, 2.20)]$$

$$\text{Odds ratio} = \frac{\frac{\frac{60}{100}}{\frac{40}{100}}}{\frac{\frac{490}{1000}}{\frac{510}{1000}}} = \frac{60 * 510}{490 * 40} = 1.56\ [95\%\ \mathrm{CI}\ (1.03, 2.37)]$$

In our sample, individuals in violent neighborhoods had 1.5 times the risk (95% CI 1.02, 2.20) and 1.56 times the odds (95% CI 1.03, 2.37) of developing depression over one year.

In Box 2, Figures 2 and 3, we then stratify our analyses by whether individuals in the study have a particular genetic variant that is believed to increase the risk of depression.

Box 2, Figure 2. Association between neighborhood violence and depression among those without the genetic variant



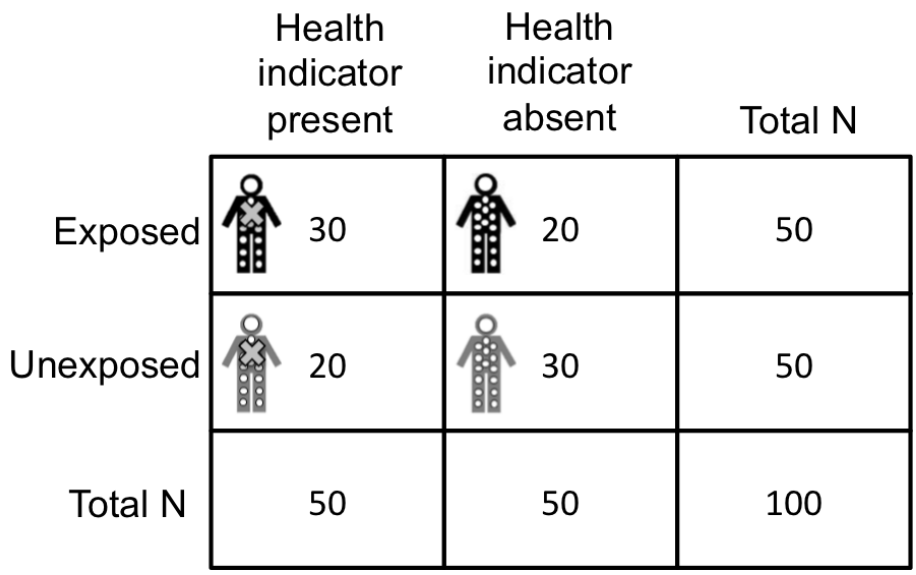
$$\mathrm{P(D|E+)} = \frac{30}{500} = 0.06$$

$$\mathrm{P(D|E-)} = \frac{20}{500} = 0.04$$

$$\text{Risk ratio} = \frac{0.06}{0.04} = 1.50\ [95\%\ \mathrm{CI}\ (0.86, 2.61)]$$

$$\text{Odds ratio} = \frac{\frac{30}{50}}{\frac{20}{50}} = \frac{30 * 480}{470 * 20} = 1.53\ [95\%\ \mathrm{CI}\ (0.86, 2.74)]$$

Box 2, Figure 3. Association between neighborhood violence and depression among those with the genetic variant



$$\mathrm{P(D|E+)} = \frac{30}{50} = 0.60$$

$$\mathrm{P(D|E-)} = \frac{20}{50} = 0.40$$

$$\text{Risk ratio} = \frac{0.60}{0.40} = 1.50\ [95\%\ \mathrm{CI}\ (1.00, 2.26)]$$

$$\text{Odds ratio} = \frac{\frac{30}{50}}{\frac{20}{50}} = \frac{30 * 30}{20 * 20} = 2.25\ [95\%\ \mathrm{CI}\ (1.01, 5.01)]$$

When we stratify the data, we see that the risk ratios do not change. The risk of depression is 1.5 times higher among those in violent neighborhoods as in non-violent neighborhoods, regardless of the presence of a genetic variant. The odds ratio, however, does change. Among those with the genetic variant, the odds of depression are 2.25 times higher among those exposed to neighborhood violence versus those who are not (95% CI 1.01, 5.01).

Comparing the two strata, it might appear that there is an interaction between neighborhood violence and genetic risk, since the odds ratio is 1.53 (95% CI 0.86, 2.74) in one strata compared with 2.25 in other strata.

However, within the stratum of those with the genetic variant, 50% develop depression over the course of the study (50 out of 100). This makes depression very common within this stratum. It is rare in the other stratum of those without the genetic variant, at 5% (50 out of 1,000). Thus, odds ratios will increasingly over-approximate the risk ratio when the disease becomes more common. Thus, when we do stratified analysis, it is critical to ensure that the disease incidence or prevalence does not preclude proper interpretation of the odds ratio measure.