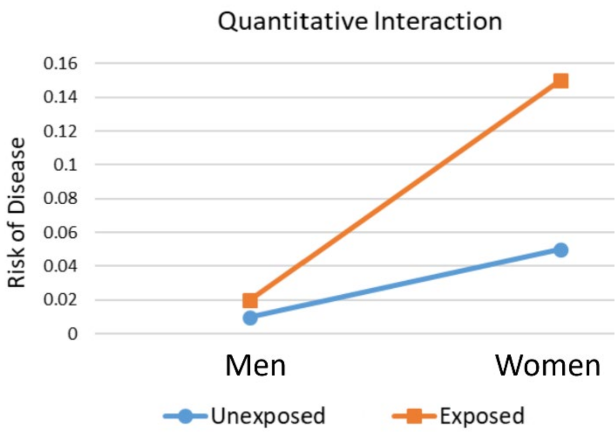
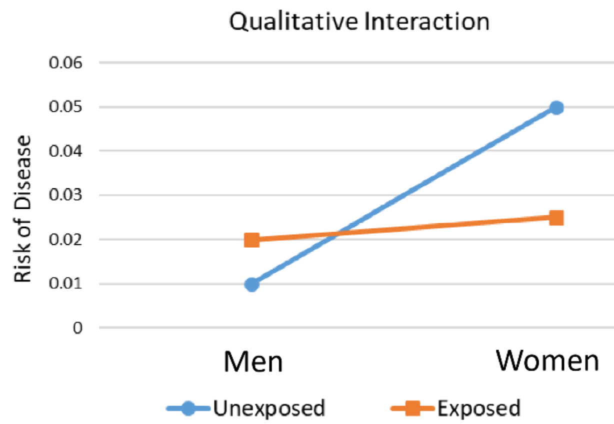
Interaction/Effect Modification

treatment effect is different over different strata of the population defined by a baseline covariate
e.g. age, sex, study center, region, baseline prognostic factors
not due to imbalance in the data

Quantitative Interaction
direction of effect stays the same over strata
magnitude differs over strata



Qualitative Interaction
direction of effect differs over strata



Potential Issues
treatment may be beneficial to some subgroups but harmful to others
can't provide a single summary measure, perform separate analysis for each stratum
sample size for each strata will be smaller than the whole trial population, so there will be less power to detect an effect
multiple testing will cause inflated Type 1 error

Continuous Outcomes

Testing for Interaction

H_0: The difference in means between the treatment and placebo is the same for all strata.
H_A: The difference in means between the treatment and placebo is not the same for all strata.

use F test to test for interaction
if interaction term is not significant, remove it from the model and slope between the strata will stay parallel

Dummy Variables for Categorical Predictors

$$X_1 = \begin{cases} 1 & Treatment \\ 0 & Placebo \end{cases}$$

$$X_2 = \begin{cases} 1 & Female \\ 0 & Male \end{cases}$$

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2$$

β_1 = difference in intercept between the response variable for treatment and placebo
β_1 = difference in intercept between the response variable for females and males
$\beta_3 X_1 X_2$ = interaction term between treatment and sex

treatment and female $E[Y] = \beta_0 + \beta_1(1) + \beta_2(1) + \beta_3(1)(1) = \beta_0 + \beta_1 + \beta_2 + \beta_3$
treatment and male $E[Y] = \beta_0 + \beta_1(1) + \beta_2(0) + \beta_3(1)(0) = \beta_0 + \beta_1$
placebo and female $E[Y] = \beta_0 + \beta_1(0) + \beta_2(1) + \beta_3(0)(1) = \beta_0 + \beta_2$
placebo and male $E[Y] = \beta_0 + \beta_1(0) + \beta_2(0) + \beta_3(0)(0) = \beta_0$

H_0: $\beta_3 = 0$ There is no interaction between treatment and sex.
H_A: $\beta_3 \neq 0$ There is interaction between treatment and sex.

Dummy Variables for Continuous Predictors

$$X_1 = \begin{cases} 1 & Treatment\ N \\ 0 & Otherwise \end{cases}$$

$$X_2 = \begin{cases} 1 & Treatment\ A \\ 0 & Otherwise \end{cases}$$

$$Y = \beta_0 + \beta_1 trtN + \beta_2 trtA + \beta_3 age + \beta_4 trtNage + \beta_5 trtAage$$

treatment N $E[Y] = \beta_0 + \beta_1(1) + \beta_2(0) + \beta_3 age + \beta_4(1)age + \beta_5(0)age = \beta_0 + \beta_1 + \beta_3 age + \beta_4 age$
treatment A $E[Y] = \beta_0 + \beta_1(0) + \beta_2(1) + \beta_3 age + \beta_4(0)age + \beta_5(1)age = \beta_0 + \beta_2 + \beta_3 age + \beta_5 age$
placebo $E[Y] = \beta_0 + \beta_1(0) + \beta_2(0) + \beta_3 age + \beta_4(0)age + \beta_5(0)age = \beta_0 + \beta_3 age$

H_0: $\beta_4 = \beta_5 = 0$ There is no interaction between treatments by age and by sex.
H_A: $\beta_4 \neq 0, \beta_5 \neq 0$ There is interaction between treatments by age or by sex.

Binary Outcomes

Testing for Interaction

H_0: The difference in proportion between the treatment and placebo is the same for all strata.

H_A: The difference in proportion between the treatment and placebo is not the same for all strata.

Male	**No Disease**	**Disease**	
Placebo	a	b	m_0
Treatment	c	d	m_1
	n_0	n_1	n

Female	**No Disease**	**Disease**	
Placebo	a	b	m_0
Treatment	c	d	m_1
	n_0	n_1	n

Cochran-Mantel-Haenszel Approach

analyzes the relationship between treatment and outcome stratified by another variable

Breslow-Day Test: H_0: $OR_{male} = OR_{female}$ There is no interaction between treatment and sex.
H_A: $OR_{male} \neq OR_{female}$ There is interaction between treatment and sex.

Breslow-Day-Tarone test if lots of cell counts are below 5

Mantel-Haenszel OR $\left(m\widehat{OR}\right)$ = weighted average of the OR for each stratum

$$m\widehat{OR} = \frac{\sum \frac{ad}{n}}{\sum \frac{bc}{n}} = \frac{\sum \left(\frac{ad}{bc}\right)\left(\frac{bc}{n}\right)}{\sum \frac{bc}{n}} = \frac{\sum OR \times \left(\frac{bc}{n}\right)}{\sum \frac{bc}{n}}$$

Mantel-Haenszel RR $\left(m\widehat{RR}\right)$ = weighted average of the RR for each stratum

$$m\widehat{RR} = \frac{\sum \frac{an_0}{n}}{\sum \frac{cn_1}{n}} = \frac{\sum \left(\frac{\frac{a}{n_1}}{\frac{c}{n_0}}\right)\left(\frac{cn_1}{n}\right)}{\sum \frac{cn_1}{n}} = \frac{\sum RR \times \left(\frac{cn_1}{n}\right)}{\sum \frac{cn_1}{n}}$$

if no interaction, perform Mantel-Haenszel chi-Square test

H_0: There is no association between the treatment and the disease, after adjusting for the confounding variable.

$$OR_1 = OR_2 = \ldots = OR_k = 1$$
$$mOR = 1$$

H_A: There is an association between the treatment and the disease, after adjusting for the confounding variable.

$$OR_1 = OR_2 = \ldots = OR_k \neq 1$$
$$mOR \neq 1$$

$$\chi^2_{MH} = \frac{\left(\sum \frac{ad - bc}{n}\right)^2}{\sum \frac{n_0 n_1 m_0 m_1}{n^2(n-1)}}, 1\ df$$

Logistic Regression

$$logit(p) = log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 trtA + \beta_2 female + \beta_3 trtAfemale$$

$$odds(x) = \frac{p}{1-p} = e^{\beta_0 + \beta_1 trtA + \beta_2 female + \beta_3 trtAfemale}$$

treatment and female $E[Y] = \beta_0 + \beta_1(1) + \beta_2(1) + \beta_3(1)(1) = \beta_0 + \beta_1 + \beta_2 + \beta_3$
treatment and male $E[Y] = \beta_0 + \beta_1(1) + \beta_2(0) + \beta_3(1)(0) = \beta_0 + \beta_1$
placebo and female $E[Y] = \beta_0 + \beta_1(0) + \beta_2(1) + \beta_3(0)(1) = \beta_0 + \beta_2$
placebo and male $E[Y] = \beta_0 + \beta_1(0) + \beta_2(0) + \beta_3(0)(0) = \beta_0$