

Statistics 305/605: Introduction to Biostatistical Methods for Health Sciences

Chapter 19, part 4: Statistical Interaction and Confounding

Jinko Graham

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Overview

- ▶ What is the relationship between a response variable, Y , and explanatory variable, X_1 , adjusted for other variables?
- ▶ Example: Study of low-birthweight babies.
 - ▶ Y is head circumference and X_1 is gestational age.
 - ▶ Interested in the effect of X_1 on Y as summarized by the slope term in the linear model.
 - ▶ However, an extraneous variable X_2 , such as birth weight, can **modify** (change) the effect of X_1 on Y .
- ▶ Earlier, we looked at **effect modification**, when studying association between a categorical outcome variable, Y , with two levels and a categorical exposure variable, X_1 , with two levels.
 - ▶ In this context, the effect of X_1 on Y was summarized by the odds ratio (rather than the slope term).
 - ▶ When the effect of X_1 on Y was different depending on the value of X_2 , then X_2 was a modifier of the effect of X_1 on Y .
 - ▶ If X_2 was not an effect modifier, we could go on to consider it as a potential confounder of the association between X_1 and Y .

Steps

- ▶ Suppose we're primarily interested in the association between Y and X_1 .
- ▶ Have also collected data on an extraneous variable, X_2 .
- ▶ Suggested steps are:
 1. First consider whether X_2 **modifies** the effect of X_1 on Y
 - ▶ Called statistical interaction between X_1 and X_2 .
 2. If there is no statistical interaction, we can consider X_2 as a potential confounding variable.
 - ▶ X_2 could change the association between Y and X_1 when it is included in our MLR model.

- We'll be using the data on low birthweight babies to illustrate ideas.

```
uu <- url("http://people.stat.sfu.ca/~jgraham/Teaching/S305_17/Data/lbwt.csv")
lbwt <- read.csv(uu)
head(lbwt)
```

##	headcirc	length	gestage	birthwt	momage	toxemia
## 1	27	41	29	1360	37	0
## 2	29	40	31	1490	34	0
## 3	30	38	33	1490	32	0
## 4	28	38	31	1180	37	0
## 5	29	38	30	1200	29	1
## 6	23	32	25	680	19	0

Statistical Interaction

- ▶ Easiest when X_2 is binary; i.e., takes values of 0 or 1.
- ▶ X_2 *modifies* the effect of X_1 on Y if the slope of the regression line of Y on X_1 differs in the $X_2 = 0$ and $X_2 = 1$ subgroups.
- ▶ Illustrate with the variable `toxemia` in the low birthweight babies dataset.
 - ▶ `toxemia=1` if the mother is toxic during pregnancy and 0 otherwise
 - ▶ If we stratify the analysis by `toxemia` and find different slopes for gestational age in the two `toxemia` groups, there is statistical interaction between gestational age and `toxemia`.

MLR Model with Statistical Interaction

- ▶ Consider the MLR model with *linear predictor*:

$$\mu_{Y|X_1, X_2} = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2, \text{ where}$$

- ▶ Y is head circumference, headcirc.
- ▶ X_1 is gestational age, gestage.
- ▶ X_2 is toxemia (1 is toxic, 0 is not)
- ▶ $X_1 \times X_2$ is the statistical interaction between gestational age and toxemia.
- ▶ β_1 , β_2 , and β_3 are the corresponding regression coefficients:
 - ▶ β_1 is the gestational-age **main effect**
 - ▶ β_2 is the toxemia **main effect**
 - ▶ β_3 is the gestational-age-by-toxemia **interaction effect**

Separate Lines

- ▶ Our linear predictor is

$$\mu_{Y|X_1, X_2} = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2,$$

- ▶ This model allows separate lines for the two toxemia groups.
 - ▶ Line for no-toxemia group ($X_2 = 0$): $\alpha + \beta_1 X_1$
 - ▶ intercept α and slope β_1 for gestage.
 - ▶ Line for toxemia group ($X_2 = 1$): $\alpha + \beta_1 X_1 + \beta_2 + \beta_3 X_1$
 - ▶ intercept $\alpha + \beta_2$ and slope $\beta_1 + \beta_3$ for gestage.
- ▶ Focusing on the slopes, we see that the difference between gestage slopes for the two toxemia groups is β_3 .
 - ▶ $\beta_3 = 0$ implies that the slopes are the **same** in the two groups;
 - ▶ i.e., toxemia does **not** modify the effect of gestational age on head circumference.

- ▶ To assess the evidence for statistical interaction between toxemia and gestational age, we test the hypotheses

$$H_0 : \beta_3 = 0 \text{ vs. } H_a : \beta_3 \neq 0.$$

- ▶ If H_0 is retained, we conclude that there is insufficient statistical evidence that toxemia modifies the effect of gestational age on head circumference.

- ▶ If we retain the no-interaction hypothesis $H_0 : \beta_3 = 0$, our linear predictor becomes

$$\mu_{Y|X_1, X_2} = \alpha + \beta_1 X_1 + \beta_2 X_2$$

- ▶ This model allows separate lines for the two toxemia groups but with the same slope for gestage:
 - ▶ Line for no-toxemia group ($X_2 = 0$): $\alpha + \beta_1 X_1$
 - ▶ intercept α and slope β_1 for gestage.
 - ▶ Line for toxemia group ($X_2 = 1$): $\alpha + \beta_1 X_1 + \beta_2$.
 - ▶ intercept $\alpha + \beta_2$ and slope β_1 for gestage.
- ▶ No interaction between gestage and toxemia means that each toxemia group has its own line with different intercepts, but with the same slope for gestage

Fitted Model

- ▶ Let's fit the MLR model with interaction between gestational age and toxemia:

```
lfit <- lm(headcirc ~ gestage+toxemia+gestage:toxemia,data=lbwt)
summary(lfit)$coefficients
```

##	Estimate	Std. Error	t value	Pr(> t)
## (Intercept)	1.7629121	2.10225478	0.8385815	4.037874e-01
## gestage	0.8646116	0.07389805	11.7000601	3.529066e-20
## toxemia	-2.8150322	4.98514735	-0.5646839	5.736059e-01
## gestage:toxemia	0.0461658	0.16352127	0.2823229	7.783037e-01

- ▶ From the row of output for gestage:toxemia, we see that the t -test of $H_0 : \beta_3 = 0$ vs. $H_a : \beta_3 \neq 0$ retains H_0 at the 5% level ($p = 0.78$).
- ▶ No statistical evidence that toxemia modifies the effect of gestational age on head circumference.
- ▶ However, toxemia may still be a confounding variable.

Software Notes

- ▶ In the model formula

`headcirc ~ gestage + toxemia + gestage:toxemia`

- ▶ The **interaction** term between gestage and toxemia is indicated by `gestage:toxemia`.
 - ▶ The **main-effect** terms are indicated by `gestage` and `toxemia`.
- ▶ In the model summary:
 - ▶ Information about the slope β_3 for the interaction term is in the row labelled `gestage:toxemia`.
 - ▶ Information about the slopes β_1 and β_2 for the main effect terms are in the rows labelled `gestage` and `toxemia`, respectively.

Statistical Interaction More Generally

- ▶ Interaction terms appear as products of main-effect terms.
 - ▶ E.G. in the MLR with linear predictor
$$\mu_{Y|X_1, X_2} = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2,$$
the interaction term $X_1 X_2$ is a product of the main-effect terms X_1 and X_2 .
- ▶ Interaction means that the slopes for X_1 can depend on the value of the modifying variable X_2 .
- ▶ E.G. Say X_2 is a quantitative variable taking on values between 5 and 10.
- ▶ Focus on two values $X_2 = 5$ and $X_2 = 6$ one unit apart:
 - ▶ Line for $X_2 = 5$ group is $\alpha + \beta_1 X_1 + \beta_2 5 + \beta_3 X_1 5$
 - ▶ intercept: $\alpha + \beta_2 x_2 = \alpha + \beta_2 5$, and
 - ▶ slope for X_1 : $\beta_1 + \beta_3 x_2 = \beta_1 + \beta_3 5$
 - ▶ Line for $X_2 = 6$ group is $\alpha + \beta_1 X_1 + \beta_2 6 + \beta_3 X_1 6$
 - ▶ intercept: $\alpha + \beta_2 x_2 = \alpha + \beta_2 6$, and
 - ▶ slope for X_1 : $\beta_1 + \beta_3 x_2 = \beta_1 + \beta_3 6$
- ▶ Difference in slopes for X_1 for the two groups is
$$\beta_3 6 - \beta_3 5 = \beta_3.$$

- ▶ In general, we interpret the slope β_3 for the interaction term X_1X_2 as the difference between the slopes for X_1 in two groups that are defined by a one-unit change in X_2 .
- ▶ If $\beta_3 = 0$, the slopes for X_1 are the same.
 - ▶ Therefore, X_2 does **not** modify the effect of X_1 on Y .
- ▶ To assess the statistical interaction of X_1 and X_2 , test the hypotheses that $H_0 : \beta_3 = 0$ vs. $H_a : \beta_3 \neq 0$.
- ▶ This is equivalent to testing whether or not X_2 modifies the effect of X_1 on Y .

Example: Interaction of Gestational Age and Birthweight

```
lfit <- lm(headcirc ~ gestage+birthwt+gestage:birthwt,data=lbwt)
summary(lfit)$coefficients
```

##	Estimate	Std. Error	t value	Pr(> t)
## (Intercept)	-1.2584719300	5.8038051183	-0.2168357	0.8287965594
## gestage	0.7873236476	0.2087286735	3.7719956	0.0002800541
## birthwt	0.0137084745	0.0052930812	2.5898856	0.0110948349
## gestage:birthwt	-0.0003137616	0.0001833162	-1.7115869	0.0902018614

- ▶ $\hat{\beta}_3 = -.000314$ is the estimated difference between the slopes for gestage, in 2 groups defined by a one-unit change in birthwt.
- ▶ E.G. Define two groups: one for babies with the median birthwt of 1155g and another for babies with birthwt 1156g.
 - ▶ In babies with birthwt 1156g, the slope for gestage is estimated to be 0.000314 **less** than in babies with birthwt 1155g (since $\hat{\beta}_3$ is negative).

What is the effect of gestage on headcirc in babies with a birthwt of 1156g?

- ▶ The linear predictor or population mean is

$$\mu_{Y|X_1, X_2} = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2.$$

- ▶ In babies with birthwt of $x_2 = 1156$ g this simplifies to

$$\begin{aligned}\mu_{Y|X_1, 1156} &= \alpha + \beta_1 X_1 + \beta_2 1156 + \beta_3 X_1 1156 \\ &= \alpha + \beta_2 1156 + \beta_1 X_1 + \beta_3 X_1 1156 \\ &= \alpha + \beta_2 1156 + (\beta_1 + \beta_3 1156) X_1\end{aligned}$$

- ▶ The slope for gestage (X_1) in babies with a birthwt of $x_2 = 1156$ g is therefore $\beta_1 + \beta_3 1156$
- ▶ **In babies with a birthwt of 1156g**, we estimate that the effect of gestage on headcirc is

$$\hat{\beta}_1 + \hat{\beta}_3 1156 = 0.787 - 0.000314 \times 1156 = 0.424;$$

i.e., a one-week increase in gestage is associated with an estimated 0.424cm increase in headcirc

Does birthwt modify the effect of gestage on headcirc?

- ▶ To address this question, let's test for statistical interaction between birthwt and gestage at the 5% level.

```
summary(lfit)$coefficients
```

##	Estimate	Std. Error	t value	Pr(> t)
## (Intercept)	-1.2584719300	5.8038051183	-0.2168357	0.8287965594
## gestage	0.7873236476	0.2087286735	3.7719956	0.0002800541
## birthwt	0.0137084745	0.0052930812	2.5898856	0.0110948349
## gestage:birthwt	-0.0003137616	0.0001833162	-1.7115869	0.0902018614

- ▶ Compare the p -value for the interaction term to the level 0.05.
 - ▶ Since the p -value is 0.09, we retain the null hypothesis of no interaction.
- ▶ Conclude that there is insufficient statistical evidence to claim that birthwt modifies the effect of gestage on headcirc.
- ▶ Though birthwt is not declared an effect modifier, it could still confound the association between gestage and headcirc

...

Confounding Variables

Changing the role of birthwt

- ▶ Having declared birthwt not to be an effect modifier, we may now consider it as a potential **confounder** of the association between gestage and headcirc.
- ▶ Look at the relationship between head circumference, Y , and gestational age, X_1 , both adjusting for and ignoring birth weight, X_2 .
- ▶ If analyses of an association between Y and X_1 with and without X_2 give “meaningfully different” estimates of the slope for X_1 , then X_2 is declared to be a confounder.
- ▶ Definition of “meaningfully different” depends on context.
- ▶ One rule-of-thumb: If the estimated slope $\hat{\beta}_1$ changes by more than 10% when X_2 is excluded, then X_2 is a confounder (Budtz-Jorgensen et al. 2007, Annals of Epidemiology).
 - ▶ **Note:** No statistical test for confounding is involved.

Example: birthwt as confounder

```
coefficients(lm(headcirc ~ gestage + birthwt, data=lbwt))
```

```
## (Intercept)      gestage      birthwt  
## 8.308015388 0.448732848 0.004712283
```

```
coefficients(lm(headcirc ~ gestage, data=lbwt))
```

```
## (Intercept)      gestage  
## 3.9142641 0.7800532
```

- ▶ Measure change in the estimate of β_1 relative to the fitted model that *includes the confounding variable*, as this is considered the safer estimate of the true effect.
 - ▶ Specifically, look at change as % of this estimate.
- ▶ The percent change in $\hat{\beta}_1$ is $|0.445 - 0.780|/|0.445| \times 100\% = 75\%$.
 - ▶ As this is larger than 10%, birthwt would be considered a confounder by the rule-of-thumb.

Interpreting slope for gestage when birthwt is a confounder

```
coefficients(lm(headcirc ~ gestage + birthwt,data=lbwt))
```

```
## (Intercept)      gestage      birthwt  
## 8.308015388 0.448732848 0.004712283
```

- ▶ Interpretations of the slope for gestage:
 - ▶ “For a given birth weight, a one-week increase in gestational age is associated with an estimated 0.449cm increase in head circumference.”
 - ▶ Or, “A one-week increase in gestational age is associated with an estimated 0.449cm increase in head circumference, after adjusting for the effect of birth weight.”