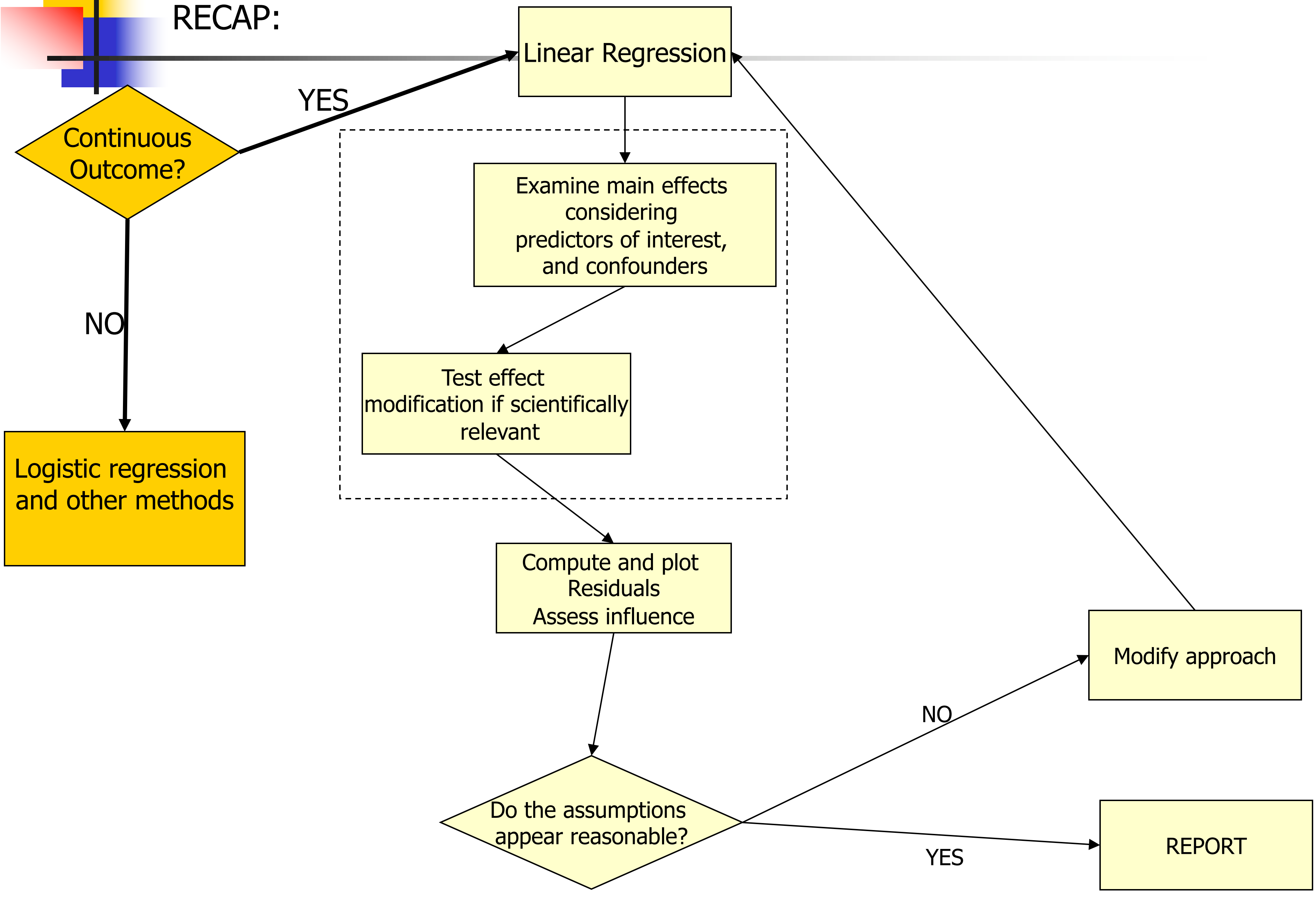
REGRESSION MODELS

ANOVA

RECAP:



Linear Regression
Continuous Outcome?
YES
NO
Examine main effects considering predictors of interest, and confounders
Test effect modification if scientifically relevant
Logistic regression and other methods
Compute and plot Residuals Assess influence
Modify approach
NO
Do the assumptions appear reasonable?
YES
REPORT

COMING UP NEXT: ANOVA – a special case of linear regression

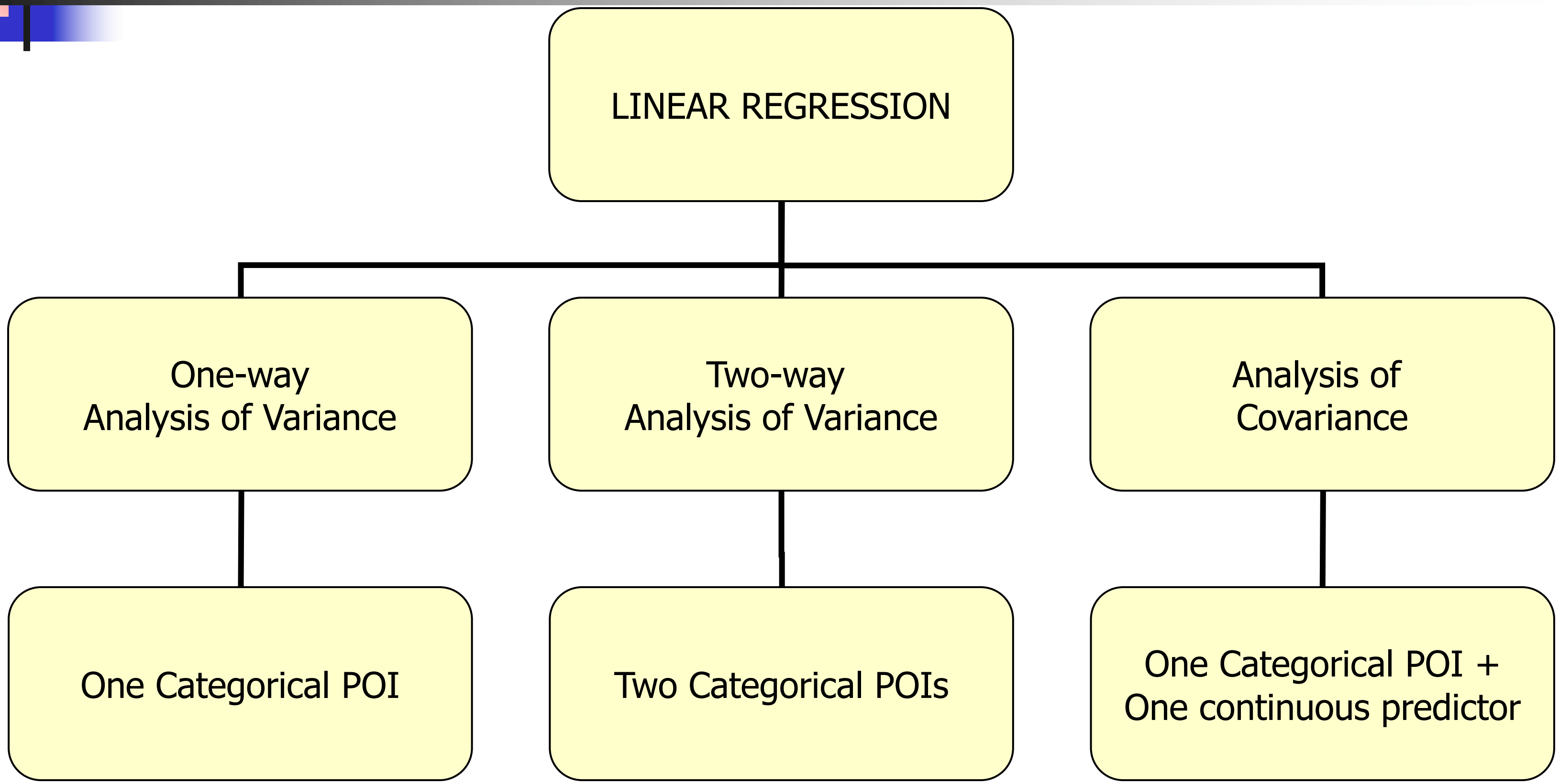
- What if the independent variables of interest are categorical?

- In this case, comparing the mean of the continuous outcome in the different categories may be of interest

- This is what is called ANalysis Of VAriance

- We will show that it is just a special case of linear regression

ANOVA – a special case of linear regression



Uses dummy variables to represent categorical variables!

Outline

- Motivation: We will consider some examples of ANOVA and show that they are special cases of linear regression
- ANOVA as a regression model
  - Dummy variables
- One-way ANOVA models
  - Contrasts
  - Multiple comparisons
- Two-way ANOVA models
  - Interactions
- ANCOVA models

ANOVA/ANCOVA: Motivation

- Let’s investigate if genetic factors are associated with cholesterol levels.
  - Ideally, you would have a confirmatory analysis of scientific hypotheses formulated prior to data collection
  - Alternatively, you could consider an exploratory analysis – hypotheses generation for future studies

ANOVA/ANCOVA: Motivation

- Scientific hypotheses of interest:
  - Assess the effect of rs174548 on cholesterol levels.
  - Assess the effect of rs174548 and sex on cholesterol levels
    - Does the effect of rs174548 on cholesterol differ between males and females?
  - Assess the effect of rs174548 and age on cholesterol levels
    - Does the effect of rs174548 on cholesterol differ depending on subject's age?

ANOVA: One-Way Model Motivation:

- Scientific question:
  - Assess the effect of rs174548 on cholesterol levels.

Motivation: Example

Here are some descriptive summaries:

```
> tapply(chol, factor(rs174548), mean)
       0        1        2 
181.0617 187.8639 186.5000 


> tapply(chol, factor(rs174548), sd)
       0        1        2 
21.13998 23.74541 17.38333 
```

Motivation: Example

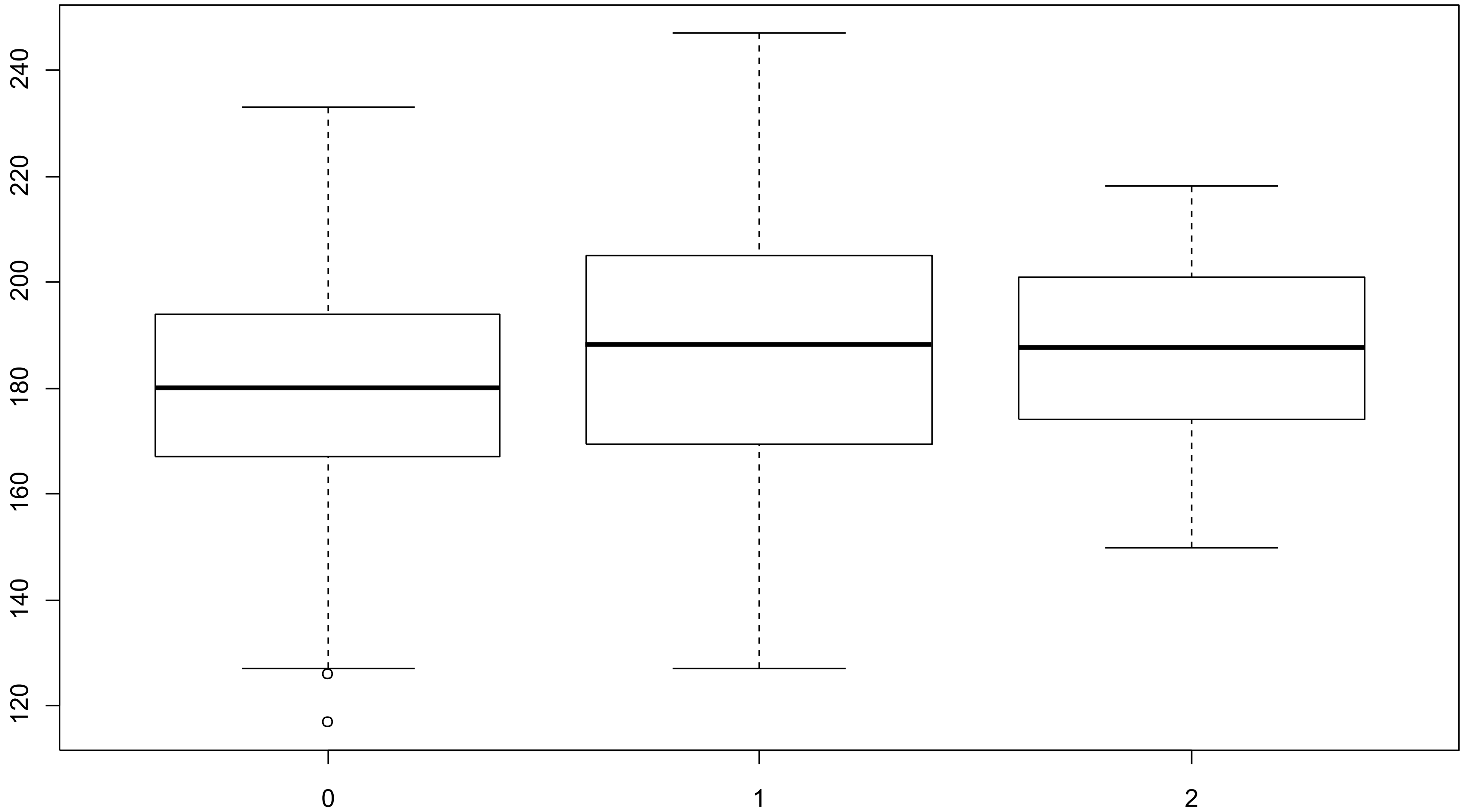
Another way of getting the same results:

```
> by(chol, factor(rs174548), mean)
   factor(rs174548): 0
[1] 181.0617
-------------------------------------------------------------------
   factor(rs174548): 1
[1] 187.8639
-------------------------------------------------------------------
   factor(rs174548): 2
[1] 186.5

> by(chol, factor(rs174548), sd)
   factor(rs174548): 0
[1] 21.13998
-------------------------------------------------------------------
   factor(rs174548): 1
[1] 23.74541
-------------------------------------------------------------------
   factor(rs174548): 2
[1] 17.38333
```

Motivation: Example

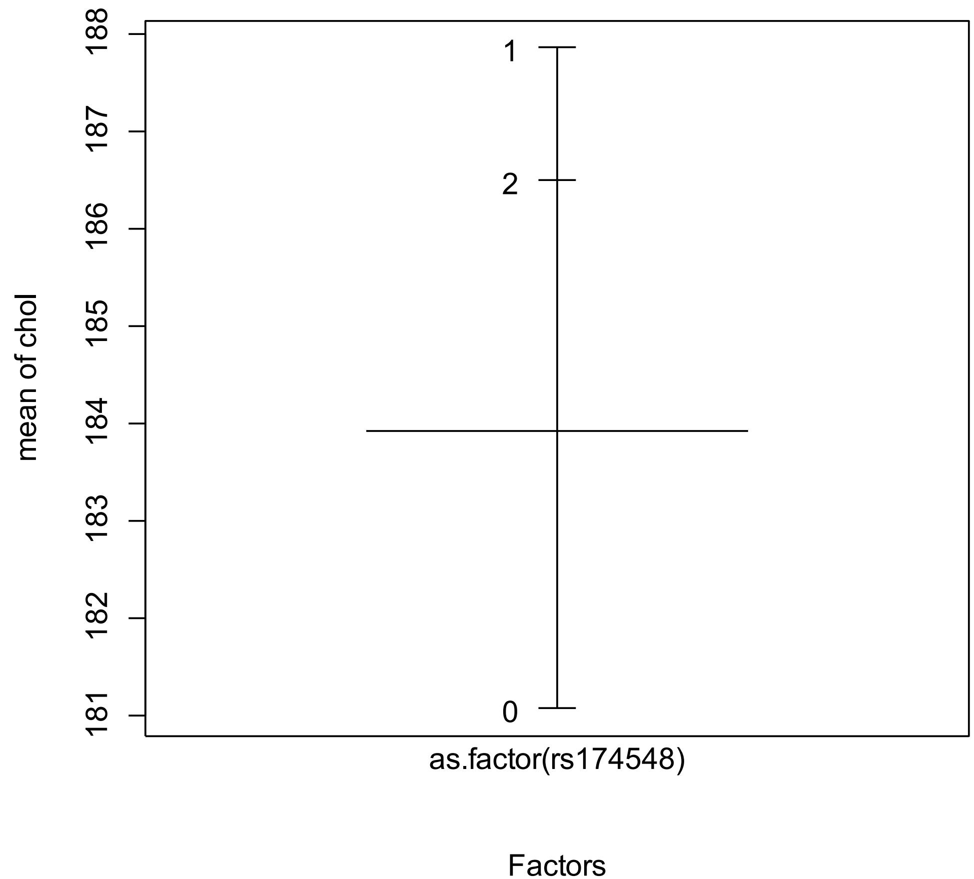
Is rs174548 associated with cholesterol?



R command: `boxplot(chol ~ factor(rs174548))`

Motivation: Example

Another graphical display:



R command:
`plot.design(chol ~ factor(rs174548))`

Motivation: Example

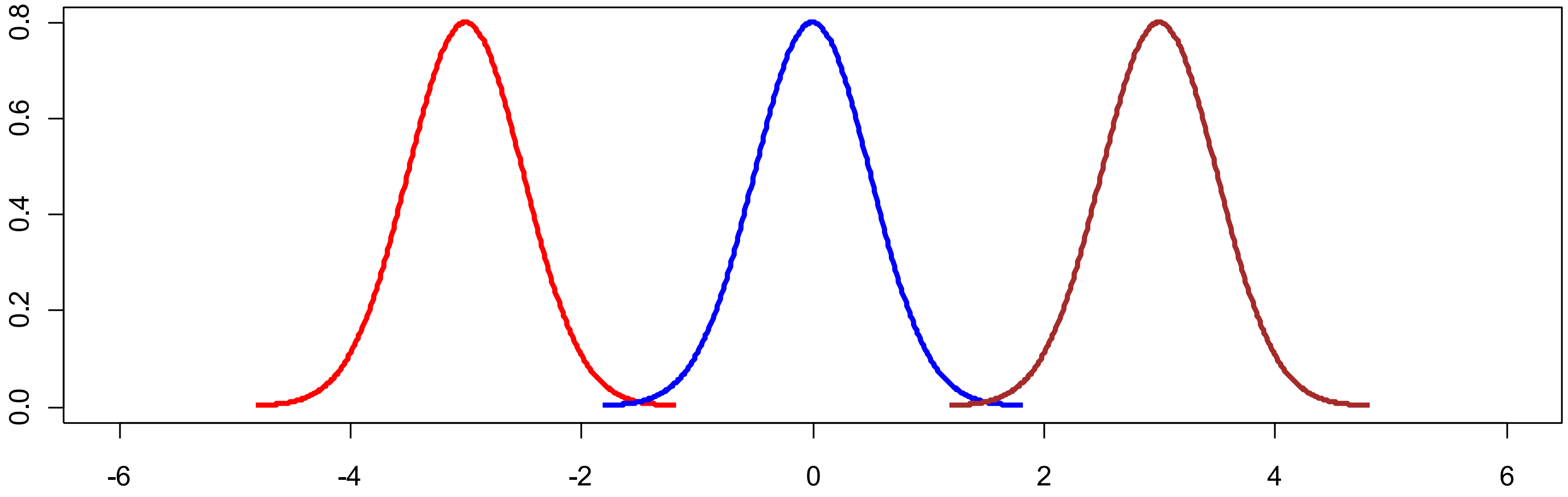
- Feature:
  - How do the mean responses compare across different groups?
    - Categorical/qualitative predictor

REGRESSION MODELS

One-way ANOVA as a regression model

ANalysis Of VAriance Models (ANOVA)

- Compares the means of several populations

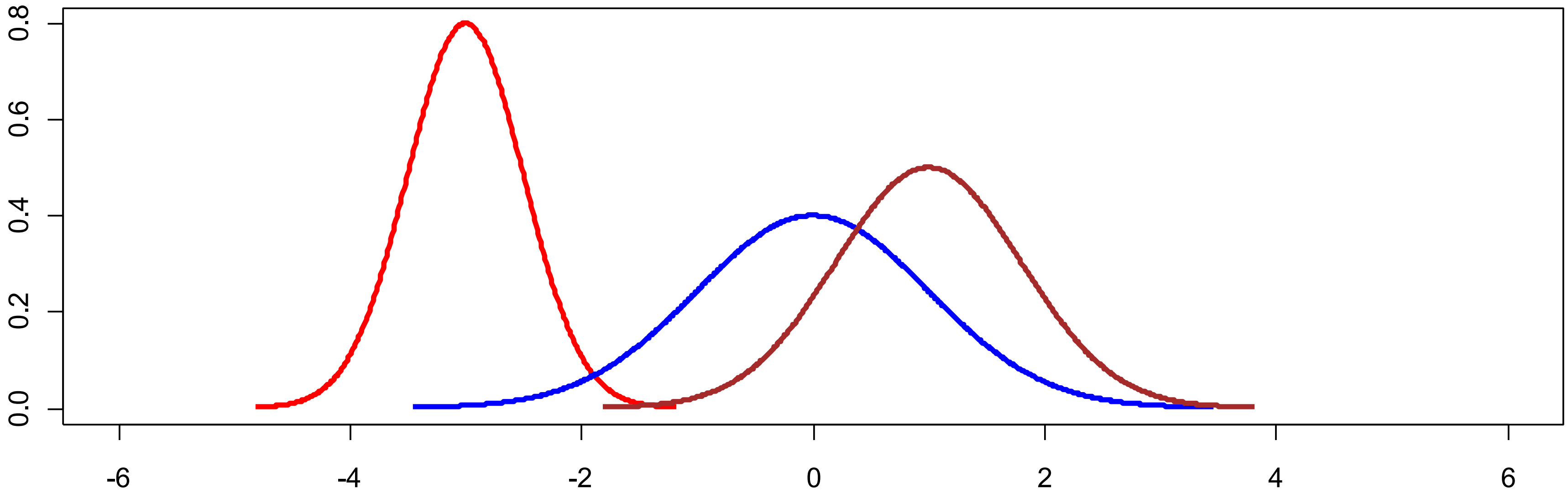


Assumptions for Classical ANOVA Framework:

Independence
Normality
Equal variances

ANalysis Of VAriance Models (ANOVA)

- Compares the means of several populations



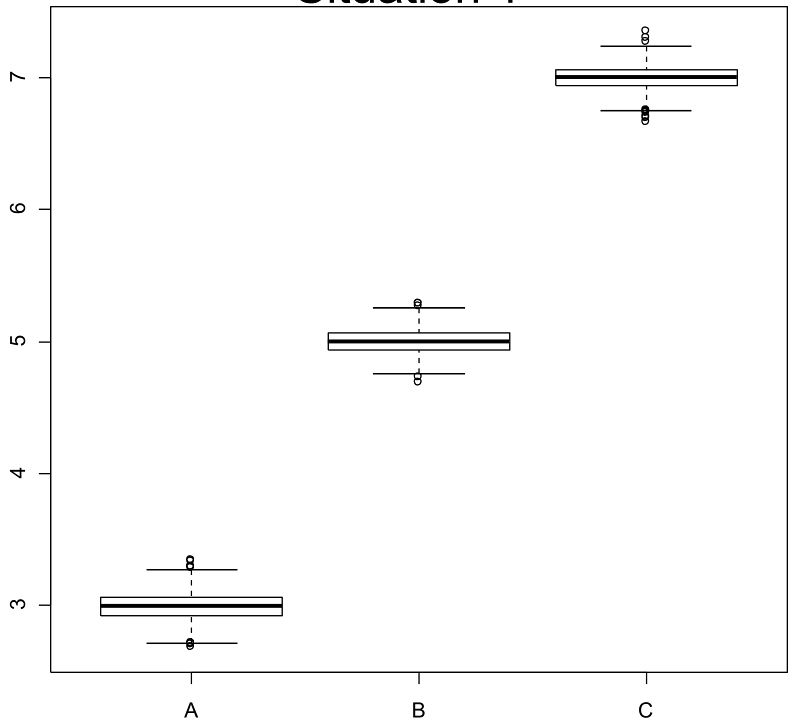
ANalysis Of VAriance Models (ANOVA)

- Compares the means of several populations
  - Counter-intuitive name!

ANalysis Of VAriance Models (ANOVA)

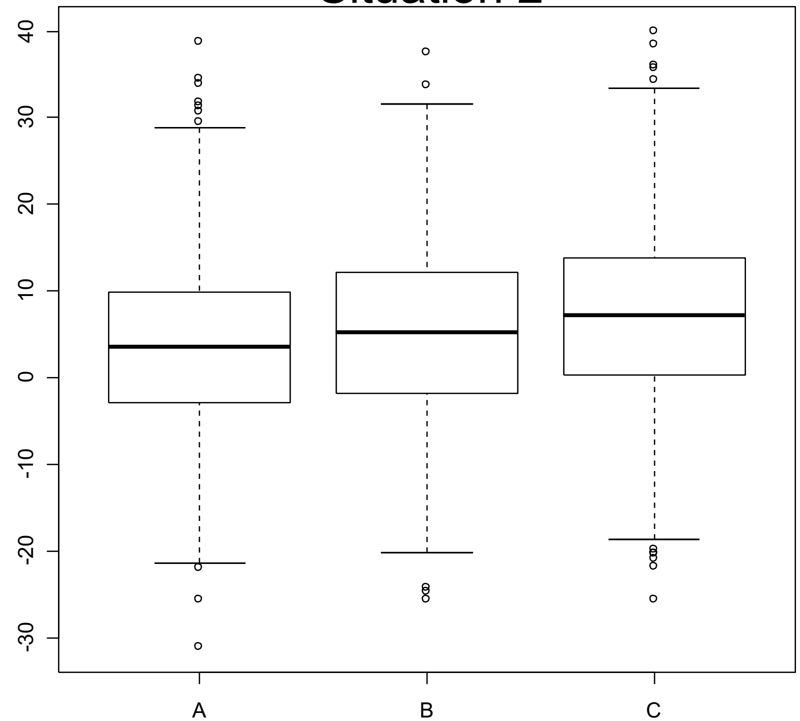
In both data sets, the true population means are: 3 (A), 5 (B), 7(C)

Situation 1



Low variance within groups

Situation 2



High variance within groups

Where do you expect to detect difference between population means?

ANalysis Of VAriance Models (ANOVA)

- Compares the means of several populations
  - Counter-intuitive name!
    - Underlying concept:
      - To assess whether the population means are equal, compares:
        - Variation between the sample means (MSR) to
        - Natural variation of the observations within the samples (MSE).
      - The larger the MSR compared to MSE the more support that there is a difference in the population means!
      - The ratio MSR/MSE is the F-statistic.

- We can make these comparisons with multiple linear regression: the different groups are represented with "dummy" variables

ANOVA as a multiple regression model

- Dummy Variables:
  - Suppose you have a categorical variable C with k categories 0,1, 2, …, k-1. To represent that variable we can construct k-1 dummy variables of the form

$$x_1 = \begin{cases} 1, & \text{if subject is in category 1} \\ 0, & \text{otherwise} \end{cases}$$

$$x_2 = \begin{cases} 1, & \text{if subject is in category 2} \\ 0, & \text{otherwise} \end{cases}$$

…

$$x_{k-1} = \begin{cases} 1, & \text{if subject is in category k-1} \\ 0, & \text{otherwise} \end{cases}$$

The omitted category (here category 0) is the **reference group**.

ANOVA as a multiple regression model

- Dummy Variables:
  - Back to our motivating example:
    - Predictor: rs174548 (coded 0=C/C, 1=C/G, 2=G/G)
    - Outcome (Y): cholesterol

Let's take C/C as the reference group.

$$x_1 = \begin{cases} 1, & \text{if code 1 (C/G)} \\ 0, & \text{otherwise} \end{cases}$$

$$x_2 = \begin{cases} 1, & \text{if code 2 (G/G)} \\ 0, & \text{otherwise} \end{cases}$$

ANOVA as a multiple regression model

rs174548	Mean cholesterol	X_1	X_2
C/C	μ_0	0	0
C/G	μ_1	1	0
G/G	μ_2	0	1

ANOVA as a multiple regression model

- Regression with Dummy Variables:
  - Example:

    Model: $E[Y|x_1, x_2] = \beta_0 + \beta_1 x_1 + \beta_2 x_2$

- Interpretation of model parameters?

ANOVA as a multiple regression model

Mean	Regression Model
μ_0	β_0
μ_1	$\beta_0 + \beta_1$
μ_2	$\beta_0 + \beta_2$

ANOVA as a multiple regression model

- Regression with Dummy Variables:
  - Example:
    Model: $E[Y|x_1, x_2] = \beta_0 + \beta_1 x_1 + \beta_2 x_2$

- Interpretation of model parameters?
  - $\mu_0 = \beta_0$: mean cholesterol when rs174548 is C/C
  - $\mu_1 = \beta_0+\beta_1$: mean cholesterol when rs174548 is C/G
  - $\mu_2 = \beta_0+\beta_2$: mean cholesterol when rs174548 is G/G

ANOVA as a multiple regression model

- Regression with Dummy Variables:
  - Example:

    Model: $E[Y|x_1, x_2] = \beta_0 + \beta_1 x_1 + \beta_2 x_2$

- Interpretation of model parameters?
  - $\mu_0 = \beta_0$: mean cholesterol when rs174548 is C/C
  - $\mu_1 = \beta_0+\beta_1$: mean cholesterol when rs174548 is C/G
  - $\mu_2 = \beta_0+\beta_2$: mean cholesterol when rs174548 is G/G
  - Alternatively
    - β_1: difference in mean cholesterol levels between groups with rs174548 equal to C/G and C/C ($\mu_1 - \mu_0$).
    - β_2: difference in mean cholesterol levels between groups with rs174548 equal to G/G and C/C ($\mu_2 - \mu_0$).

ANOVA: One-Way Model

- Goal:
  - Compare the means of K independent groups (defined by a categorical predictor)
    - Statistical Hypotheses:
      - (Global) Null Hypothesis:

        H_0: $\mu_0 = \mu_1 = \ldots = \mu_{K-1}$ or, equivalently,

        H_0: $\beta_1 = \beta_2 = \ldots = \beta_{K-1} = 0$

      - Alternative Hypothesis:

        H_1: not all means are equal

  - If the means of the groups are not all equal (i.e. you rejected the above H_0), determine which ones are different (multiple comparisons)

Estimation and Inference

- Global Hypotheses

  H_0: $\mu_1 = \mu_2 = \ldots = \mu_K$ vs. H_1: not all means are equal

  H_0: $\beta_1 = \beta_2 = \ldots = \beta_{K-1} = 0$

- Analysis of variance table

Source	df	SS	MS	F
Regression	K-1	SSR= $\sum_{i}(\bar{y}_i - \bar{y})^2$	MSR= SSR/(K-1)	MSR/ MSE
Residual	n-K	SSE= $\sum_{i,j}(y_{ij} - \bar{y}_i)^2$	MSE= SSE/n-K	
Total	n-1	SST= $\sum_{i,j}(y_{ij} - \bar{y})^2$		

ANOVA: One-Way Model

- How to fit a one-way model as a regression problem?
  - Need to use “dummy” variables
    - Create on your own (can be tedious!)
    - Most software packages will do this for you
      - R creates dummy variables in the background <u>as long as</u> you state you have a categorical variable (may need to use: factor)

ANOVA: One-Way Model

By hand:
Creating “dummy” variables:

```
> dummy1 = 1*(rs174548==1)
> dummy2 = 1*(rs174548==2)
```

Fitting the ANOVA model:

```
> fit0 = lm(chol ~ dummy1 + dummy2)
> summary(fit0)
Call:
lm(formula = chol ~ dummy1 + dummy2)

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  181.062      1.455 124.411  < 2e-16 ***
dummy1         6.802      2.321   2.930  0.00358 **
dummy2         5.438      4.540   1.198  0.23167
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221,     Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184

> anova(fit0)
Analysis of Variance Table

Response: chol
           Df Sum Sq Mean Sq F value   Pr(>F)
dummy1      1   3624    3624  7.5381 0.006315 **
dummy2      1    690     690  1.4350 0.231665
Residuals 397 190875     481
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

ANOVA: One-Way Model

Better:
Let R do it for you!

```
> fit1.1 = lm(chol ~ factor(rs174548))
> summary(fit1.1)
Call:
lm(formula = chol ~ factor(rs174548))

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
                     Estimate  Std. Error t value Pr(>|t|)
(Intercept)           181.062       1.455 124.411  < 2e-16 ***
factor(rs174548)1     6.802         2.321 2.930    0.00358 **
factor(rs174548)2     5.438         4.540 1.198    0.23167
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221,     Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184

> anova(fit1.1)
Analysis of Variance Table

Response: chol
                     Df Sum Sq Mean Sq F value  Pr(>F)
factor(rs174548)      2   4314    2157  4.4865 0.01184 *
Residuals           397 190875     481
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

ANOVA: One-Way Model

- Your turn!
  - Compare model fit results (fit0 & fit1.1)
    What do you conclude?

ANOVA: One-Way Model

```
> fit0 = lm(chol ~ dummy1 + dummy2)
> summary(fit0)
Call:
lm(formula = chol ~ dummy1 + dummy2)

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  181.062      1.455 124.411  < 2e-16 ***
dummy1         6.802      2.321   2.930  0.00358 **
dummy2         5.438      4.540   1.198  0.23167
---

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221, Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184
> anova(fit0)
Analysis of Variance Table

Response: chol
           Df Sum Sq Mean Sq F value   Pr(>F)
dummy1      1   3624    3624  7.5381 0.006315 **
dummy2      1    690     690  1.4350 0.231665
Residuals 397 190875     481
---
```

```
> fit1.1 = lm(chol ~ factor(rs174548))
> summary(fit1.1)
Call:
lm(formula = chol ~ factor(rs174548))

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
                  Estimate Std. Error t value Pr(>|t|)
(Intercept)        181.062      1.455 124.411  < 2e-16 ***
factor(rs174548)1    6.802      2.321 2.930    0.00358 **
factor(rs174548)2    5.438      4.540 1.198    0.23167
---

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221,  Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184
> anova(fit1.1)
Analysis of Variance Table

Response: chol
                  Df Sum Sq Mean Sq F value  Pr(>F)
factor(rs174548)   2   4314    2157  4.4865 0.01184 *
Residuals        397 190875     481
---
```

ANOVA: One-Way Model

```
> fit0 = lm(chol ~ dummy1 + dummy2)
> summary(fit0)
Call:
lm(formula = chol ~ dummy1 + dummy2)

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  181.062      1.455 124.411  < 2e-16 ***
dummy1         6.802      2.321   2.930  0.00358 **
dummy2         5.438      4.540   1.198  0.23167
---

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221, Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184
```

```
> anova(fit0)
Analysis of Variance Table

Response: chol
           Df Sum Sq Mean Sq F value   Pr(>F)
dummy1      1   3624    3624  7.5381 0.006315 **
dummy2      1    690     690  1.4350 0.231665
Residuals 397 190875     481
---
```

```
> fit1.1 = lm(chol ~ factor(rs174548))
> summary(fit1.1)
Call:
lm(formula = chol ~ factor(rs174548))

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
                  Estimate Std. Error t value Pr(>|t|)
(Intercept)        181.062      1.455 124.411  < 2e-16 ***
factor(rs174548)1    6.802      2.321 2.930    0.00358 **
factor(rs174548)2    5.438      4.540 1.198    0.23167
---

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221,  Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184
```

```
> anova(fit1.1)
Analysis of Variance Table

Response: chol
                  Df Sum Sq Mean Sq F value  Pr(>F)
factor(rs174548)   2   4314    2157  4.4865 0.01184 *
Residuals        397 190875     481
---
```

```
> 1-pf(4.4865,2,397)
[1] 0.01183671
> 1-pf(((3624+690)/2)/481,2,397)
[1] 0.01186096
```

ANOVA: One-Way Model

```
> fit1.1 = lm(chol ~ factor(rs174548))
> summary(fit1.1)
Call:
lm(formula = chol ~ factor(rs174548))

Residuals:
      Min        1Q    Median        3Q       Max 
-64.06167 -15.91338  -0.06167  14.93833  59.13605 

Coefficients:
                    Estimate Std. Error t value Pr(>|t|)
(Intercept)          181.062      1.455 124.411  < 2e-16
factor(rs174548)1      6.802      2.321   2.930  0.00358
factor(rs174548)2      5.438      4.540   1.198  0.23167
---

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221,  Adjusted R-squared: 0.01718 
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184

> anova(fit1.1)
Analysis of Variance Table

Response: chol
                    Df Sum Sq Mean Sq F value  Pr(>F)
factor(rs174548)     2   4314    2157  4.4865 0.01184 *
Residuals          397 190875     481
---
```

- Let's interpret the regression model results!
  - What is the interpretation of the regression model coefficients?

ANOVA: One-Way Model

```
> fit1.1 = lm(chol ~ factor(rs174548))
> summary(fit1.1)
Call:
lm(formula = chol ~ factor(rs174548))

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
                    Estimate Std. Error t value Pr(>|t|)
(Intercept)          181.062      1.455 124.411  < 2e-16
factor(rs174548)1      6.802      2.321   2.930  0.00358
factor(rs174548)2      5.438      4.540   1.198  0.23167
---

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221,  Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184

> anova(fit1.1)
Analysis of Variance Table

Response: chol
                    Df Sum Sq Mean Sq F value   Pr(>F)
factor(rs174548)     2   4314    2157  4.4865 0.01184 *
Residuals          397 190875     481
---
```

- Interpretation:
  - Estimated mean cholesterol for C/C group: 181.062 mg/dl
  - Estimated difference in mean cholesterol levels between C/G and C/C groups: 6.802 mg/dl
  - Estimated difference in mean cholesterol levels between G/G and C/C groups: 5.438 mg/dl

ANOVA: One-Way Model

```
> fit1.1 = lm(chol ~ factor(rs174548))
> summary(fit1.1)
Call:
lm(formula = chol ~ factor(rs174548))

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
                     Estimate Std. Error t value Pr(>|t|)
(Intercept)           181.062      1.455 124.411  < 2e-16
factor(rs174548)1       6.802      2.321   2.930  0.00358
factor(rs174548)2          5.438      4.540   1.198
0.23167
---

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221,  Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184

> anova(fit1.1)
Analysis of Variance Table

Response: chol
                  Df Sum Sq Mean Sq F value  Pr(>F)
factor(rs174548)   2   4314    2157  4.4865 0.01184 *
Residuals        397 190875     481
---
```

- Overall F-test shows a significant p-value. We reject the null hypothesis that the mean cholesterol levels are the same across groups defined by rs174548 (p=0.01184).
  - This does not tell us which groups are different!

    (Need to perform multiple comparisons! More soon…)

ANOVA: One-Way Model

Alternative form:
(better if you will perform multiple comparisons)

```
> fit1.2 = lm(chol ~ -1 + factor(rs174548))
> summary(fit1.2)
Call:
lm(formula = chol ~ -1 + factor(rs174548))

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
                   Estimate Std. Error t value Pr(>|t|)
factor(rs174548)0   181.062      1.455  124.41   <2e-16 ***
factor(rs174548)1   187.864      1.809  103.88   <2e-16 ***
factor(rs174548)2   186.500      4.300   43.37   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.9861,     Adjusted R-squared: 0.986
F-statistic:  9383 on 3 and 397 DF,  p-value: < 2.2e-16

> anova(fit1.2)
Analysis of Variance Table
Response: chol
                   Df   Sum Sq Mean Sq F value    Pr(>F)
factor(rs174548)    3 13534205 4511402  9383.2 < 2.2e-16 ***
Residuals         397   190875     481
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

ANOVA: One-Way Model

How about this one?
How is rs174548 being treated now?

Compare model fit results from (fit1.1 & fit2).

```
> fit2 = lm(chol ~ rs174548)
> summary(fit2)

Call:
lm(formula = chol ~ rs174548)

Residuals:
    Min      1Q  Median      3Q     Max 
-64.575 -16.278  -0.575  15.120  60.722 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept)  181.575      1.411 128.723  < 2e-16 ***
rs174548       4.703      1.781   2.641  0.00858 ** 
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1 

Residual standard error: 21.95 on 398 degrees of freedom
Multiple R-squared: 0.01723,    Adjusted R-squared: 0.01476 
F-statistic: 6.977 on 1 and 398 DF,  p-value: 0.008583 

> anova(fit2)
Analysis of Variance Table

Response: chol
           Df Sum Sq Mean Sq F value   Pr(>F)   
rs174548    1   3363    3363  6.9766 0.008583 **
Residuals 398 191827     482                    
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

ANOVA: One-Way Model

```
> fit2 = lm(chol ~ rs174548)
> summary(fit2)

Call:
lm(formula = chol ~ rs174548)

Residuals:
    Min      1Q  Median      3Q     Max 
-64.575 -16.278  -0.575  15.120  60.722 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept)  181.575      1.411 128.723  < 2e-16 ***
rs174548       4.703      1.781   2.641  0.00858 ** 

Residual standard error: 21.95 on 398 degrees of freedom
Multiple R-squared: 0.01723, Adjusted R-squared: 0.01476 
F-statistic: 6.977 on 1 and 398 DF,  p-value: 0.008583 

> anova(fit2)
Analysis of Variance Table

Response: chol
           Df Sum Sq Mean Sq F value   Pr(>F)   
rs174548    1   3363    3363  6.9766 0.008583 **
Residuals 398 191827     482                    
```

- Model: $E[Y|x] = \beta_0 + \beta_1 x$

where Y: cholesterol, x: rs174548

- Interpretation of model parameters?
  - β_0: mean cholesterol in the C/C group [estimate: 181.575 mg/dl]
  - β_1: mean cholesterol difference between C/G and C/C – or – between G/G and C/G groups [estimate: 4.703 mg/dl]
- This model presumes differences between “consecutive” groups are the same (in this example, linear dose effect of allele) – more restrictive than the ANOVA model!

Back to the ANOVA model…

ANOVA: One-Way Model

```
> fit1.1 = lm(chol ~ factor(rs174548))
> summary(fit1.1)
Call:
lm(formula = chol ~ factor(rs174548))

Residuals:
      Min        1Q    Median        3Q       Max
-64.06167 -15.91338  -0.06167  14.93833  59.13605

Coefficients:
                    Estimate Std. Error t value Pr(>|t|)
(Intercept)          181.062      1.455 124.411  < 2e-16
factor(rs174548)1      6.802      2.321   2.930  0.00358
factor(rs174548)2      5.438      4.540   1.198  0.23167
---

Residual standard error: 21.93 on 397 degrees of freedom
Multiple R-squared: 0.0221,  Adjusted R-squared: 0.01718
F-statistic: 4.487 on 2 and 397 DF,  p-value: 0.01184

> anova(fit1.1)
Analysis of Variance Table

Response: chol
                    Df Sum Sq Mean Sq F value  Pr(>F)
factor(rs174548)     2   4314    2157  4.4865 0.01184 *
Residuals          397 190875     481
---
```

- We rejected the null hypothesis that the mean cholesterol levels are the same across groups defined by rs174548 (p=0.01184).
  - What are the groups with differences in means?

MULTIPLE COMPARISONS (coming up)

One-Way ANOVA allowing for unequal variances

We can also perform one-way ANOVA allowing for unequal variances:

```
> oneway.test(chol ~ factor(rs174548))

        One-way analysis of means (not assuming equal variances)

data:  chol and factor(rs174548)
F = 4.3258, num df = 2.000, denom df = 73.284, p-value = 0.01676
```

- We reject the null hypothesis that the mean cholesterol levels are the same across groups defined by rs174548 (p=0.01676).
  - What are the groups with differences in means?

MULTIPLE COMPARISONS (coming up)

One-Way ANOVA with robust standard errors

```
> summary(gee(chol ~ factor(rs174548), id=seq(1,length(chol))))
Beginning Cgee S-function, @(#) geeformula.q 4.13 98/01/27
running glm to get initial regression estimate
         (Intercept) factor(rs174548)1    factor(rs174548)2
          181.061674            6.802272             5.438326

 GEE:  GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
 gee S-function, version 4.13 modified 98/01/27 (1998)

Model:
 Link:                      Identity
 Variance to Mean Relation: Gaussian
 Correlation Structure:     Independent

Call:
gee(formula = chol ~ factor(rs174548), id = seq(1, length(chol)))

Summary of Residuals:
         Min           1Q        Median           3Q          Max
-64.06167401 -15.91337769  -0.06167401  14.93832599  59.13605442

Coefficients:
                     Estimate Naive S.E.    Naive z Robust S.E.   Robust z
(Intercept)        181.061674   1.455346 124.411431    1.400016 129.328297
factor(rs174548)1    6.802272   2.321365   2.930290    2.402005   2.831914
factor(rs174548)2    5.438326   4.539833   1.197913    3.624271   1.500530

Estimated Scale Parameter:  480.7932
Number of Iterations:  1
```

Kruskal-Wallis Test

- Non-parametric analogue to the one-way ANOVA
  - Based on ranks

- In our example:

```
> kruskal.test(chol ~ factor(rs174548))

        Kruskal-Wallis rank sum test

data:  chol by factor(rs174548)
Kruskal-Wallis chi-squared = 7.4719, df = 2, p-value = 0.02385
```

  - Conclusion:
    - Evidence that the cholesterol distribution is not the same across all groups.
    - With the global null rejected, you can also perform pairwise comparisons [Wilcoxon rank sum], but adjust for multiplicities!