# BMEG 802 – Advanced Biomedical Experimental Design and Analysis

Regression

Joshua G. A. Cashaback, PhD

# Recap

- Effect Size
- Power
  - Parametric
  - Numerical

#### **Learning Objectives**

- Regression
  - Bivariate
    - Linear (Derivation)
    - Nonlinear
  - Multiple Regression
- Correlation
  - Pearson's r
  - lacksquare Spearman's ho

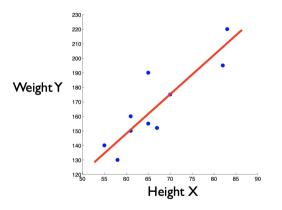
#### **BIVARIATE LINEAR REGRESSION**

# **Regression** - Bivariate

$$\hat{y}_i = B_0 + B_1 \cdot x_i$$

- want to predict  $\hat{y_i}$  (e.g., height) based on  $x_i$  (e.g., weight).
  - equation of a line
    - B<sub>1</sub> (slope), B<sub>1</sub> (intercept)
  - X,Y continuous
  - relationship between X and Y

# **Regression - Bivariate**



Height (X)	Weight (Y)
55	140
61	150
67	152
83	220
65	190
82	195
70	175
58	130
65	155
61	160

Line of best fit:  $B_0 = -7.2$ ,  $B_1 = 2.6$ 

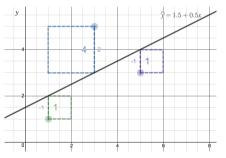
- least squares
- what do squares have to do with this???

#### **Bivariate Regression - Least Squares**

Optimization problem:

$$min(y_i - \hat{y}_i)^2$$

where  $\hat{y}_i$  and  $y_i$  are respectively the predicted and actual y values.



We find  $B_1$  (slope),  $B_0$  (intercept) that minimize the squared differences!

#### **Least Squares Derivation**

remember,  $\hat{y_i} = B_0 + B_1 \cdot x_i$  and we want to  $min(y_i - \hat{y}_i)^2$ 

$$(y_i - \hat{y}_i)^2 = (y_i - (B_0 + B_1 \cdot x_i))^2$$
  
$$(y_i - \hat{y}_i)^2 = (y_i - B_0 - B_1 \cdot x_i)^2$$

In particular, we minimum the sum of squares

$$\sum_{i=1}^{n} (y_i - \hat{y}_i)^2 = \sum_{i=1}^{n} (y_i - B_0 - B_1 \cdot x_i)^2$$

$$SS = \sum_{i=1}^{n} (y_i - B_0 - B_1 \cdot x_i)^2$$

$$\frac{\partial SS}{\partial B_0} = 0$$

$$\frac{\partial SS}{\partial B_1} = 0$$

Results in two equations with two unknowns.

#### **Least Squares Derivation - Intercept**

$$\frac{\partial}{\partial B_0} \sum_{i=1}^n (y_i - B_0 - B_1 \cdot x_i)^2 = 0$$

We can move the sum outside:

$$\sum_{i=1}^{n} \frac{\partial}{\partial B_0} (y_i - B_0 - B_1 \cdot x_i)^2 = 0$$

Taking the derivative (note the chain rule):

$$\sum_{i=1}^{n} 2(y_i - B_0 - B_1 \cdot x_i)(-1) = 0$$

Rearranging,

$$-2\sum_{i=1}^{n}(y_{i}-B_{0}-B_{1}\cdot x_{i})=0$$

#### **Least Squares Derivation - Slope**

$$\frac{\partial}{\partial B_1} \sum_{i=1}^n (y_i - B_0 - B_1 \cdot x_i)^2 = 0$$

$$\sum_{i=1}^n \frac{\partial}{\partial B_0} (y_i - B_0 - B_1 \cdot x_i)^2 = 0$$

$$\sum_{i=1}^n 2(y_i - B_0 - B_1 \cdot x_i)(-x_i) = 0$$

$$-2 \sum_{i=1}^n (y_i - B_0 - B_1 \cdot x_i)(x_i) = 0$$

Two equations and two unknowns

#### **Least Squares Derivation - Tip Interlude**

$$\bar{x} = \frac{1}{n} \sum_{i=1}^{n} x_i;$$

Thus,

$$\sum_{i=1}^{n} x_i = n\bar{x}$$

Similarly,

$$\sum_{i=1}^n y_i = n\bar{y}$$

When summing a constant you can multiply by n. For example,

$$\sum_{i=1}^{n} \bar{x} = n\bar{x}$$

#### **Least Squares Derivation - Tip Interlude Cont'd**

$$\sum_{i=1}^{n} (x_{i} - \bar{x})(y_{i} - \bar{y}) = \sum_{i=1}^{n} x_{i} \cdot y_{i} - \sum_{i=1}^{n} x_{i} \cdot \bar{y} - \sum_{i=1}^{n} y_{i} \cdot \bar{x} + \sum_{i=1}^{n} \bar{x} \cdot \bar{y}$$

$$= \sum_{i=1}^{n} x_{i} \cdot y_{i} - \sum_{i=1}^{n} x_{i} \cdot \bar{y} - \sum_{i=1}^{n} y_{i} \cdot \bar{x} + \sum_{i=1}^{n} \bar{x} \cdot \bar{y}$$

$$= \sum_{i=1}^{n} x_{i} \cdot y_{i} - n \cdot \bar{x} \cdot \bar{y} - n \cdot \bar{x} \cdot \bar{y} + n \cdot \bar{x} \cdot \bar{y}$$

$$= \sum_{i=1}^{n} x_{i} \cdot y_{i} - n \cdot \bar{x} \cdot \bar{y}$$

$$(1)$$

$$= \sum_{i=1}^{n} x_{i} \cdot y_{i} - n \cdot \bar{x} \cdot \bar{y} - n \cdot \bar{x} \cdot \bar{y}$$

$$= \sum_{i=1}^{n} x_{i} \cdot y_{i} - n \cdot \bar{x} \cdot \bar{y}$$

$$(2)$$

#### **Least Squares Derivation - Tip Interlude Cont'd**

$$\sum_{i=1}^{n} (x_i - \bar{x})^2 = \sum_{i=1}^{n} (x_i^2 - 2 \cdot x_i \cdot \bar{x} + \bar{x}^2)$$

$$= \sum_{i=1}^{n} x_i^2 - 2 \cdot \bar{x} \sum_{i=1}^{n} \cdot x_i + \sum_{i=1}^{n} \bar{x}^2$$

$$= \sum_{i=1}^{n} x_i^2 - 2 \cdot \bar{x} \cdot n \cdot \bar{x} + n\bar{x}^2$$

$$= \sum_{i=1}^{n} x_i^2 - n\bar{x}^2$$
(8)

#### **Least Squares Derivation - Intercept**

Let's do some algebra on our previous equation:

$$-2\sum_{i=1}^{n}(y_i-B_0-B_1\cdot x_i)=0$$

Divide both sides by -2,

$$\sum_{i=1}^{n} (y_i - B_0 - B_1 \cdot x_i) = 0$$

$$\sum_{i=1}^{n} y_i - \sum_{i=1}^{n} B_0 - B_1 \cdot \sum_{i=1}^{n} x_i = 0$$

$$n \cdot \bar{y} - n \cdot B_0 - B_1 \cdot n \cdot \bar{x} = 0$$

$$\bar{y} - B_0 - B_1 \cdot \bar{x} = 0$$

$$B_0 = \bar{y} - B_1 \cdot \bar{x}$$

#### **Least Squares Derivation - Slope**

$$-2\sum_{i=1}^{n} (y_i - B_0 - B_1 \cdot x_i)(x_i) = 0$$

$$\sum_{i=1}^{n} (x_i \cdot y_i - B_0 \cdot x_i - B_1 \cdot x_i^2) = 0$$

$$\sum_{i=1}^{n} x_i \cdot y_i - B_0 \sum_{i=1}^{n} x_i - B_1 \sum_{i=1}^{n} x_i^2 = 0$$

$$\sum_{i=1}^{n} x_i \cdot y_i - B_0 \sum_{i=1}^{n} x_i - B_1 \sum_{i=1}^{n} x_i^2 = 0$$

Substitute in  $B_0$ 

$$\sum_{i=1}^{n} x_i \cdot y_i - (\overline{y} - B_1 \cdot \overline{x}) n \cdot \overline{x} - B_1 \sum_{i=1}^{n} x_i^2 = 0$$

#### **Least Squares Derivation - Slope Cont'd**

$$\sum_{i=1}^{n} x_{i} \cdot y_{i} - (\bar{y} - B_{1} \cdot \bar{x}) n \cdot \bar{x} - B_{1} \sum_{i=1}^{n} x_{i}^{2} = 0$$

$$\sum_{i=1}^{n} x_{i} \cdot y_{i} - n \cdot \bar{x} \cdot \bar{y} + n \cdot B_{1} \cdot \bar{x}^{2} - B_{1} \sum_{i=1}^{n} x_{i}^{2} = 0$$

$$\sum_{i=1}^{n} x_{i} \cdot y_{i} - n \cdot \bar{x} \cdot \bar{y} = B_{1} \sum_{i=1}^{n} x_{i}^{2} - n \cdot B_{1} \cdot \bar{x}^{2}$$

$$\sum_{i=1}^{n} (x_{i} - \bar{x})(y_{i} - \bar{y}) = B_{1} \sum_{i=1}^{n} (x_{i} - \bar{x})^{2}$$

$$B_{1} = \frac{\sum_{i=1}^{n} (x_{i} - \bar{x})(y_{i} - \bar{y})}{\sum_{i=1}^{n} (x_{i} - \bar{x})^{2}}$$

#### **Derivation Summary**

$$B_{1} = \frac{\sum_{i=1}^{n} (x_{i} - \bar{x})(y_{i} - \bar{y})}{\sum_{i=1}^{n} (x_{i} - \bar{x})^{2}}$$
$$B_{0} = \bar{y} - B_{1} \cdot \bar{x}$$

#### Calculate B's

Height weight example.

```
weight = c(55,61,67,83,65,82,70,58,65,61)
height = c(140,150,152,220,190,195,175,130,155,160)
B1 = sum((weight - mean(weight)) * (height - mean(height))) / sum((weight
B0 = mean(height) - B1 * mean(weight)
BO
## [1] -7.17693
B1
## [1] 2.606851
```

#### **Bivariate Prediction**

We can now predict height based on weight

```
weight_bob = 80
height_bob = B0 + B1 * weight_bob
height_bob
```

```
## [1] 201.3711
```

- Assumes residuals are normally distributed (plot residuals  $(y_i \hat{y_i})$ 
  - flat line with equal noise throughout range of x-values
- Cannot extrapolate
- Least squares sensitive to outliers (robust = absolute deviations)
- Make sure to plot data to see if linear relationship holds

#### **Bivariate - Standard Error of Estimate**

$$SE = \sqrt{\frac{\sum_{i}^{n}(y_i - \hat{y})^2}{N - 2}}$$

- Quality of the fit
- N = number of pairs of data
  - N-2 = degrees of freedom (lose two because we have two parameters,  $B_1, B_0$ )

```
SE = sqrt(sum((height - (B0 + B1 * weight))^2) / (length(weight) - 2))
SE
```

## [1] 14.11408

# **Correlation Coefficent (r)**

Pearson correlation coefficient (r) is the covariance of the two variables divided by the product of their standard deviations.

metric for goodness of fit

$$r_{xy} = \frac{\sum_{i=1}^{n} (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n} (x_i - \bar{x})^2} \sqrt{\sum_{i=1}^{n} (y_i - \bar{y})^2}}$$

- range [-1,1]
  - 0 = no relationship
  - 1 = perfect positive correlation
  - -1 = perfect negative correlation

#### **Correlation Coefficent (r)**

```
r = sum((weight - mean(weight)) * (height - mean(height))) / (sqrt(sum((weight - mean(meight))) / (sqrt(sum((weight - mean(meight)))) / (sqrt(sum((weight - mean(meight)))))
r
## [1] 0.8786421
OR
cor(height, weight)
## [1] 0.8786421
```

#### Coefficent of Determination (r)

```
r^2 (square correlation coefficient)
```

- amount of variance explained
- another way to measure quality of fit
- range [0,1]
  - 0 = no relationship
  - 1 = perfect correlation (explains 100% of the relationship)

```
rsquared = cor(weight,height)^2
rsquared
```

```
## [1] 0.772012
```

#### **Bivariate Regression - Significance Test**

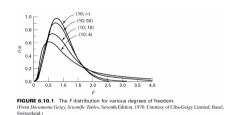
```
H0: (population) r=0;
H1: (population) r not equal to 0 (two-tailed)
H1: (population) r<0 (or >0): one-tailed
Sampling distribution of r
```

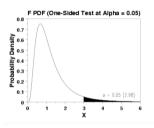
- IF we were to randomly draw two samples from two populations that were not correlated at all, what proportion of the time would we get a value of r as as extreme as we observe?
- if p < .05 we reject H0

NOTE: Correlation DOES NOT equal Causation

#### Bivariate Regression - Significance Test Cont'd

#### F-Distribution (Fisher-Snedecor):





- Compare if regression explains significantly more data with  $B_1$
- $p(df_{k-1}, df_{N-k})$  probability of F-statistic
  - $k = number of parameters (e.g., k = 2 since B_1, B_0)$
  - N = number of pairs

# Bivariate Regression - Significance Test Cont'd

F-statistic for Bivariate regression:

## [1] 0.0008176335

$$F = \frac{r^2(N-2)}{1-r^2}$$

```
N = length(weight)
Fstat0 <- (r*r*(N-2)) / (1-(r*r))
# Area under F-Distribution, using pf() function
pval0 \leftarrow 1 - pf(Fstat0, 1, N-2) # Fstat, parameters (k-1), df (N-k)
Fstat0
## [1] 27.08957
pval0
```

#### Bivariate Regression in R

#### Linear

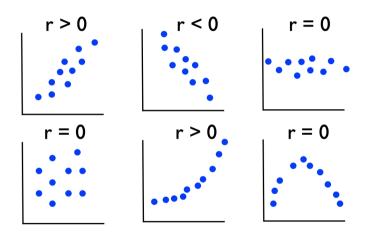
```
m1 <- lm(weight ~ height) # Linear model function!
```

```
## Call:
## lm(formula = weight ~ height)
## Residuals:
      Min
              10 Median
                                    Max
## -8.6002 -2.9754 0.6787 2.0677 6.9190
##
## Coefficients:
             Estimate Std. Error t value Pr(>|t|)
## (Intercept) 17.3322 9.6037 1.805 0.108760
## height 0.2962 0.0569 5.205 0.000818 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
## Residual standard error: 4.757 on 8 degrees of freedom
## Multiple R-squared: 0.772, Adjusted R-squared: 0.7435
## F-statistic: 27.09 on 1 and 8 DF. p-value: 0.0008176
```

#### **Bivariate Regression in R**

```
summary(m1)$coefficients[1] # B 0, coefficient
## [1] 17.33223
summary(m1)$coefficients[2] # B_1, coefficient
## [1] 0.2961474
summarv(m1)$coefficients[2,4] # p-value
## [1] 0.0008176335
summary(m1)$r.squared # r^2 of model
## [1] 0.772012
```

#### **BIVARIATE NONLINEAR REGRESSION**

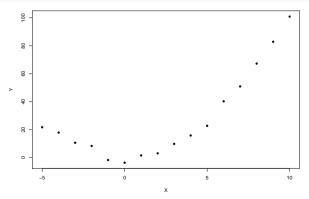


remember: r measures linear correlation

```
X <- c(-5,-4,-3,-2,-1,0,1,2,3,4,5,6,7,8,9,10)

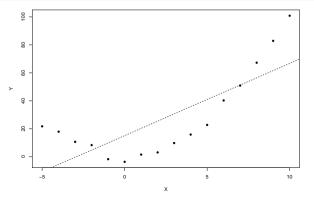
Y <- X^2 + rnorm(16,0,3)

plot(X,Y,pch=16)
```



Linear regression would produce:

```
m2 <- lm(Y ~ X)
plot(X,Y,pch=16)
abline(m2, lty=2)</pre>
```

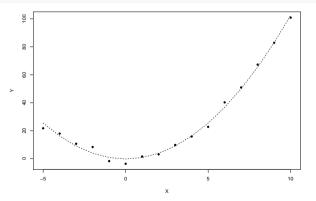


We can include nonlinear terms:  $\hat{y}_i = B_0 + B_1 \cdot x_i^2$ 

```
Xsquared <- X*X # make a nonlinear variable in R
m0 <- lm(Y ~ Xsquared)
summary(m0)
##
## Call:
## lm(formula = Y ~ Xsquared)
##
## Residuals:
      Min
               10 Median
                                     Max
## -3.7168 -1.8619 0.3192 1.6358 4.4240
##
## Coefficients:
              Estimate Std. Error t value Pr(>|t|)
## (Intercept) -0.18797
                       0.83779 -0.224
                                          0.826
## Xsquared 1.02608 0.02066 49.666 <2e-16 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
## Residual standard error: 2.463 on 14 degrees of freedom
## Multiple R-squared: 0.9944, Adjusted R-squared: 0.994
## F-statistic: 2467 on 1 and 14 DF, p-value: < 2.2e-16
```

#### Plotting the result:

```
Xsquared <- X*X # make a nonlinear variable in R
yfit <- predict(m0,data.frame(X=Xsquared)) # predicted y-values from linear model
plot(X,Y,pch=16)
lines(X,Yfit,lty=2)</pre>
```



Note: In practice you typically assume linearity a priori (unless you have theoretical reason)

#### **MULTIPLE REGRESSION**

#### **Multiple Regression**

Same idea as bivariate, but just adding more terms

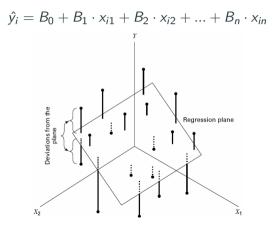


TABLE 10.6.1 Bone Toughness and Collagen Network Properties for 29 Femurs

w	P	s
193.6	6.24	30.1
137.5	8.03	22.2
145.4	11.62	25.7
117.0	7.68	28.9
105.4	10.72	27.3
99.9	9.28	33.4
74.0	6.23	26.4
74.4	8.67	17.2
112.8	6.91	15.9
125.4	7.51	12.2
126.5	10.01	30.0
115.9	8.70	24.0
98.8	5.87	22.€
94.3	7.96	18.2
99.9	12.27	11.5
83.3	7.33	23.9
72.8	11.17	11.2
83.5	6.03	15.€
59.0	7.90	10.€

s 87.2 8.27 24.7 84.4 11.05 25.6 78.1 7.61 18.4 51.9 6.21 13.5 57.1 7.24 12.2 54.7 8.11 149 78.6 10.05 8.9 53.7 8.79 14.9 96.0 10.40 10.3 89.0 11.72 15.4

W (Bone Toughness: Force required to fracture bone)

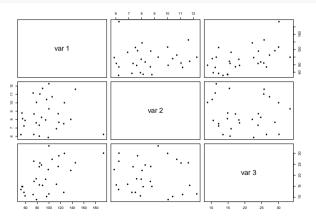
P (Porosity)

S (Tensile Strength)

Inputting data (note, you can also have R read in files)

Take a look at the data

pairs(data0, pch=16)



Look at individual correlations between variables

```
cor(data0)
```

```
## [,1] [,2] [,3]
## [1,] 1.00000000 0.04331177 0.53547194
## [2,] 0.04331177 1.00000000 -0.08015793
## [3,] 0.53547194 -0.08015793 1.00000000
```

#### Multiple Regression in R

```
m2 < -1m(W \sim S + P)
summary(m2)
##
## Call:
## lm(formula = W ~ S + P)
##
## Residuals:
      Min
            1Q Median
                                   Max
## -33.907 -19.594 -0.517 10.159 76.813
##
## Coefficients:
             Estimate Std. Error t value Pr(>|t|)
## (Intercept) 35.6138 29.1296 1.223 0.23245
## S
          2.3960 0.7301
                                 3.282 0.00294 **
          1.4509 2.7632
## P
                                 0.525 0.60397
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 27.42 on 26 degrees of freedom
## Multiple R-squared: 0.2942, Adjusted R-squared: 0.2399
## F-statistic: 5.419 on 2 and 26 DF, p-value: 0.01078
```

### Bivariate Regression in R

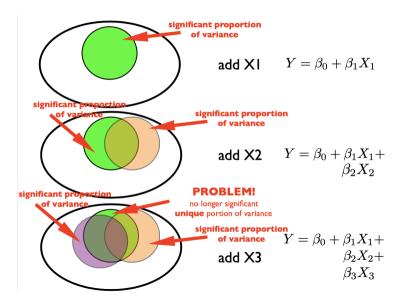
```
summary(m2)$coefficients[1] # intercept coefficient
## [1] 35.61383
summary(m2)$coefficients[2] # S coefficient
## [1] 2.395993
summary(m2)$coefficients[3] # P coefficient
## [1] 1.450938
summary(m2)$coefficients[2,4] # S p-value
## [1] 0.002940326
summarv(m2)$coefficients[3,4] # P p-value
## [1] 0.6039738
summary(m2)$r.squared # r^2 of model
## [1] 0.2942146
```

- Overall, we find that this multiple regression is significant (p = 0.01078).
- BUT, Bone Toughness is not significantly explained by Porosity (p = 0.604).
- More terms in our model reduces residuals BUT WE MAY BE JUST FITTING NOISE!
  - We want to choose the model the best explains the data with the least amount of parameters: to prevent over-fitting
    - Model comparison (e.g., F-tests, AIC https://en.wikipedia.org/wiki/Akaike\_information\_criterion)

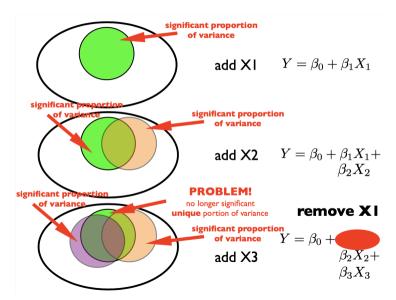
#### Other considerations

- sometimes several independent variables explain the same data (covariance)
- What is the best procedure to determine which variables to use?
  - one solution: step-wise regression

#### **Multiple Regression - Covariates**



#### **Multiple Regression - Covariates**



#### STEPS:

- 1. start with no IVs in the equation
- 2. check to see if any IVs significantly predict the DV
- 3. if no, STOP. if yes, add best IV (largest  $r^2$ ) and go to step 4
- 4. check to see if any IVs add significantly to the equation
- 5. if no, stop. if yes, add best IV (largest r^2), go to step 6
- 6. check each IV currently in the equation to make sure they contribute unique portions of variance
- 7. remove any that don't
- 8. go to step 4

Define Minimal Model (no IVs) and Full Model (all IVs)

```
m_min <- lm(W ~ 1) # minimal model
m_all <- lm(W ~ S + P) # define full model</pre>
```

Run Step-wise regression (this is a big output)

```
# perform stepwise regression
mbest <- step(m min, list(lower=m min, upper=m all), direction="both")</pre>
## Start: ATC=201
## W ~ 1
##
##
         Df Sum of Sq RSS AIC
## + S 1 7943.8 19761 193.20
                      27705 201.00
## <none>
## + P 1 52.0 27653 202.94
##
## Step: AIC=193.2
## W ~ S
```

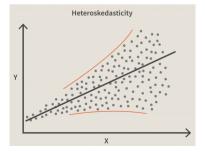
The best model uses just tensile strength (S) to explain bone toughness (W).

```
summary(mbest) # Summary of best model
##
## Call:
## lm(formula = W ~ S)
##
## Residuals:
      Min
               10 Median
                                     Max
## -37.143 -20.456 -2.391 10.433 73.705
##
## Coefficients:
##
              Estimate Std. Error t value Pr(>|t|)
## (Intercept) 48.7003 14.8762 3.274 0.00291 **
## 5
                2 3653
                        0.7179
                                   3.295 0.00276 **
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 27.05 on 27 degrees of freedom
## Multiple R-squared: 0.2867, Adjusted R-squared: 0.2603
## F-statistic: 10.85 on 1 and 27 DF, p-value: 0.002759
```

#### **BIVARIATE NONPARAMETRIC**

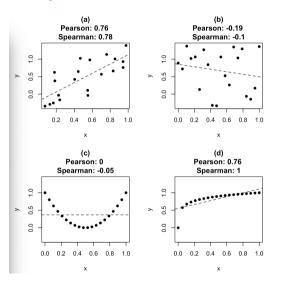
# Nonparametric - Spearman's rank correlation coefficient

- violations of normality
  - e.g., heteroskedastic
- nonlinear (monotonic functions)
  - do not have to fiddle with different powers on IVs (squaring, cubing, etc) etc.
- less sensitive to outliers



Spearman's rank correlation coefficient  $(\rho)$ 

- It assesses how well the relationship between two variables can be described using a monotonic (increasing or decreasing) function
- rank order method
- range [-1,+1]



IQ, $X_i$ $\spadesuit$	Hours of TV per week, $Y_i   \   \   \  $	$rank\; x_i \; \blacklozenge \;$	rank $y_i$ $\spadesuit$	$d_i$ $\blacklozenge$	$d_i^2$ $ullet$
86	2	1	1	0	0
97	20	2	6	-4	16
99	28	3	8	-5	25
100	27	4	7	-3	9
101	50	5	10	-5	25
103	29	6	9	-3	9
106	7	7	3	4	16
110	17	8	5	3	9
112	6	9	2	7	49
113	12	10	4	6	36

$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)}$$

$$F = \frac{r^2(N - 2)}{1 - r^2}$$

IQ and TV hours are not correlated

```
IQ = c(86, 97, 99, 100, 101, 103, 106, 110, 112, 113)
TVhours = c(2, 20, 28, 27, 50, 29, 7, 17, 6, 12)
dsquared = c(0, 16, 25, 9, 25, 9, 16, 9, 49, 36)
N = length(IQ)
rho = 1 - (6 * sum(dsquared)) / (N*(N^2-1))
Fstat1 <- (rho^2*(N-2)) / (1-(rho^2))
# Area under F-Distribution, using pf() function
pval1 \leftarrow 1 - pf(Fstat1, 1, N-2) # Fstat, parameters (k-1), df (N-k)
rho
## [1] -0.1757576
pval1
## [1] 0.6271883
```

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```
Using the Built in R function
```

```
cor.test(IQ, TVhours, method = "spearman")$estimate # rho

## rho

## -0.1757576

cor.test(IQ, TVhours, method = "spearman")$p.value #p-value

## [1] 0.6319674
```

note: p-value calculated with a nonparametric approximation method.

#### **Next Week**

Analysis of Variance (ANOVA) - between (one-way)