Biost 518
Applied Biostatistics II

Scott S. Emerson, M.D., Ph.D.
Professor of Biostatistics
University of Washington

Lecture 4:
Review of Simple Regression I

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Lecture Outline

- General Regression Setting
- Inference on Means
- Inference about Geometric Means
- Inference about Odds
- Inference about Rates
- Inference about Hazards

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General Regression Setting

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Two Variable Setting

- Many statistical problems consider the association between two variables
  - Response variable
    - (outcome, dependent variable)
  - Grouping variable
    - (predictor, independent variable)

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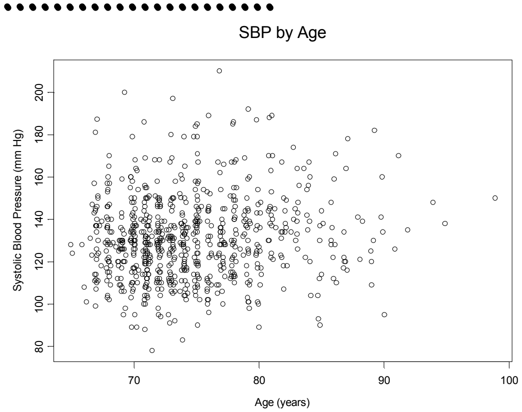
Addressing Scientific Question

- Compare the distribution of the response variable across groups that are defined by the grouping variable
  - Within each group, the value of the grouping variable is constant

Intro Course Classification

- Characterize statistical analyses by
  - Number of samples (groups), and
  - Whether subjects in groups are independent
- Correspondence with two variable setting
  - By characterization of grouping variable
    - Constant: One sample problem
    - Binary: Two sample problem
    - Categorical: k sample problem (e.g., ANOVA)
    - Continuous: Infinite sample problem
      - Regression

Example: SBP and Age



Regression Methods

- Regression extends one and two sample statistics (e.g., the t test) to the infinite sample problem
  - While we don't really ever have (or care) about an infinite number of samples, it is easiest to use models that would allow that in order to handle
    - Continuous predictors of interest
    - Adjustment for other variables

Regression vs Two Samples

- When used with a binary grouping variable common regression models reduce to the corresponding two variable methods
  - Linear regression with a binary predictor
    - Classical: t test with equal variance
    - Robust SE: t test with unequal variance (approx)
  - Logistic regression with a binary predictor
    - Score test: Chi squared test for association
  - Cox regression with a binary predictor
    - Score test: Logrank test

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Guiding Principle

"Everything is regression."

- Scott Emerson

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Uses of Regression

- Two major uses of regression
  - Borrow information to address "sparse data" in some groups
    - E.g., 68 and 70 year olds provide information about 69 year olds
    - Question: How far away do you want to go?
  - Provide a statistical "contrast" to compare distribution of response across groups
    - Think of a "slope" as an average comparison of summary measures per unit difference in the grouping variable

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Regression Inference

- Estimates
  - Slope: (average) contrasts across groups
  - Fitted values: estimated summary measure in a group
- Standard errors
- Confidence intervals
- P values testing for
  - Intercept of zero (who cares?)
  - Slope of zero (test for linear trend in summary measures)

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Robust Standard Errors

- I have recommended the use of robust standard errors
  - Relaxes assumptions about variance of data within groups
  - Allows tests of weak null hypotheses
    - Statements about equality of summary measures rather than equality of entire distributions
  - Soon: Allows regression with correlated data

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Simple Linear Regression

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Interpretation

- Interpretation of "regression parameters"
  - Intercept β_0: Mean Y for a group with X=0
    - Quite often not of scientific interest
      - Often outside range of data, sometimes impossible
  - Slope β_1: Difference in mean Y across groups differing in X by 1 unit
    - Usually measures association between Y and X

$$E(Y \mid X) = \beta_0 + \beta_1 \times X$$

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Derivation of Interpretation

- Simple linear regression of response Y on predictor X
    - Mean for an arbitrary group derived from model
    - Interpretation of parameters by considering special cases

Model	$E[Y_i \mid X_i] = \beta_0 + \beta_1 \times X_i$
$X_i = 0$	$E[Y_i \mid X_i = 0] = \beta_0$
$X_i = x$	$E[Y_i \mid X_i = x] = \beta_0 + \beta_1 \times x$
$X_i = x+1$	$E[Y_i \mid X_i = x+1] = \beta_0 + \beta_1 \times x + \beta_1$

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Example: Mental Function by Age

- Cardiovascular Health Study
  - A cohort of ~5,000 elderly subjects in four communities followed with annual visits
    - A subset of 735 subjects
  - Mental function measured at baseline by Digit Symbol Substitution Test (DSST)
  - Question: How does performance on DSST differ across age groups

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Example: Scatterplot

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Statistical Validity of Inference

- Inference (CI, P vals) about <u>associations</u> requires three general assumptions
  - Approximate normal distribution for estimates
    - Normal data or large N
  - Assumptions about independence of observations
    - Independence or identified clusters
  - Assumptions about variance of observations within groups
    - Robust SE: relaxes requirement for equal variance

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Prediction of Group Means

- Additional ssumption about adequacy of linear model for prediction of group means with linear regression
  - Classically OR robust standard error estimates:
    - The mean response in groups is linear in the modeled predictor
      - (We can model transformations of the measured predictor)

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Prediction Intervals

- Inference (prediction intervals) about individual observations in specific groups has still another assumption
  - Assumption about distribution of errors within each group
    - Normally distributed errors

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Regression in Stata

- Inference based on either classical linear regression or robust standard errors
  - Classical linear regression
    - "`regress respvar predictor`"
      - E.g., `regress dsst age`
  - Robust standard error estimates
    - "`regress respvar predictor, robust`"
      - E.g., `regress dsst age, robust`
  - The two approaches differ in CI and P values, not estimates

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Ex: Robust Standard Errors

```
. regress dsst age, robust
Linear regression
                                Number of obs =     723
                                F(  1,    721) =  130.72
                                Prob > F      =  0.0000
                                R-squared     =  0.1319
                                Root MSE      =  11.847

      |        Robust
 dsst |  Coef  StdErr       t   P>|t|   [95% Conf  Int]
  age | -.863  .0755   -11.43  0.000    -1.01   -.715
_cons |   105   5.71    18.45  0.000     94.1     117
```

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Interpretation of Intercept

$$E[DSST_i \mid Age_i] = 105 - 0.863 \times Age_i$$

- Estimated mean DSST for newborns is 105
  - Pretty ridiculous estimate
    - We never sampled anyone less than 67
    - Maximum value for DSST is 100
    - Newborns would in fact (rather deterministically) score 0
- In this problem, the intercept is just a mathematical construct to fit a line over the range of our data

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Interpretation of Slope

$$E\left[DSST_i \mid Age_i\right] = 105 - 0.863 \times Age_i$$

- Estimated difference in mean DSST for two groups differing by one year in age is -0.863, with older group averaging a lower score
  - For 5 year age difference: 5 x -0.863 = - 4.32
  - For 10 year age difference: - 8.63
- (If a straight line relationship is not true, we interpret the slope as an average difference in mean DSST per one year difference in age)

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Robust Standard Errors

- Inference for association based on slope
  - Weak null based inference
    - Estimated trend in mean DSST by age is an average difference of -.863 per one year differences in age (DSST lower in older)
    - CI for trend: -1.01, -0.715
    - P value < .0001 suggests mean DSST differs across age groups
      - T statistic: -11.43 (Who cares?)

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Inference for Correlation

- Hypothesis tests for a nonzero correlation are EXACTLY the same as a test for a nonzero slope in classical linear regression
  - Interestingly:
    - The statistical significance of a given value of r depends only on the sample size
      - Correlation is far more of a statistical than a scientific measure

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Regression and t Tests

- Linear regression with a binary predictor (two groups) corresponds to familiar t tests
  - Classical linear regression: Two sample t test which presumes equal variances (exactly the same)
  - Robust standard error estimates: Two sample t test which allows unequal variances (nearly the same)
  - Identified clusters with robust standard error estimates: Paired t test (nearly the same)

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Inference for the Geometric Mean

Simple Linear Regression on Log Transformed Data

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Regression on Geometric Means

- Geometric means of distributions are typically analyzed by using linear regression on log transformed data
  - Common choice for inference when a positive response variable is continuous, and
    - we are interested in multiplicative models,
    - we desire to downweight outliers, and/or
    - the standard deviation of response in a group is proportional to the mean
      - "Error is +/- 10%" instead of "Error is +/- 10"

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Interpretation of Parameters

- Linear regression on log transformed Y
  - (I am using natural log)

Model $E[\log Y_i \mid X_i] = \beta_0 + \beta_1 \times X_i$

$X_i = 0$ $E[\log Y_i \mid X_i = 0] = \beta_0$

$X_i = x$ $E[\log Y_i \mid X_i = x] = \beta_0 + \beta_1 \times x$

$X_i = x+1$ $E[\log Y_i \mid X_i = x+1] = \beta_0 + \beta_1 \times x + \beta_1$

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Interpretation of Parameters

- Restated model as log link for geometric mean

Model $\log \mathrm{GM}[Y_i \mid X_i] = \beta_0 + \beta_1 \times X_i$

$X_i = 0$ $\log GM[Y_i \mid X_i = 0] = \beta_0$

$X_i = x$ $\log GM[Y_i \mid X_i = x] = \beta_0 + \beta_1 \times x$

$X_i = x+1$ $\log GM[Y_i \mid X_i = x+1] = \beta_0 + \beta_1 \times x + \beta_1$

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Interpretation of Parameters

- Interpretation of regression parameters by back-transforming model
  - Exponentiation is inverse of log

Model $\quad \text{GM}\left[Y_i \mid X_i\right] = e^{\beta_0} \times e^{\beta_1 \times X_i}$

$$X_i = 0 \qquad GM\left[Y_i \mid X_i = 0\right] = e^{\beta_0}$$
$$X_i = x \qquad GM\left[Y_i \mid X_i = x\right] = e^{\beta_0} \times e^{\beta_1 \times x}$$
$$X_i = x+1 \qquad GM\left[Y_i \mid X_i = x+1\right] = e^{\beta_0} \times e^{\beta_1 \times x} \times e^{\beta_1}$$

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Interpretation of Parameters

- Geometric mean when predictor is 0
  - Found by exponentiation of the intercept from the linear regression on log transformed data: exp(β0)
- Ratio of geometric means between groups differing in the value of the predictor by 1 unit
  - Found by exponentiation of the slope from the linear regression on log transformed data: exp(β1)
- Confidence intervals for geometric mean and ratios found by exponentiating the CI for regression parameters

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Example

- Trends in FEV with height
  - FEV data set
    - A sample of 654 healthy children
    - Lung function measured by forced expiratory volume (FEV)
      - maximal amount of air expired in 1 second
    - Question: How does FEV differ across height groups

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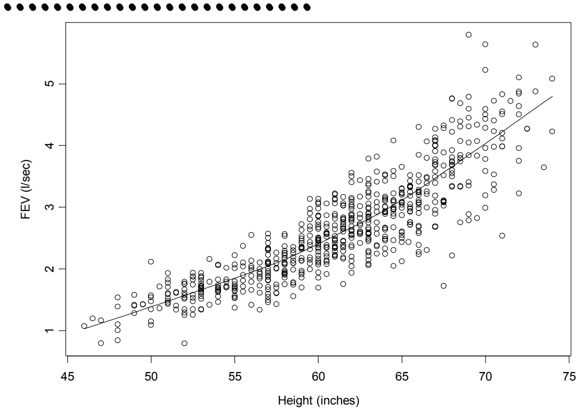
FEV versus Height



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Choice of Summary Measure

- Scientific justification for geometric mean
  - FEV is a volume
  - Height is a linear dimension
    - Each dimension of lung size is proportional to height
  - Standard deviation likely proportional to height

Science $FEV \propto Height^3$

$\sqrt[3]{FEV} \propto Height$

Statistics $\log(FEV) \propto 3\log(Height)$

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Model Geometric Mean

- Science dictates any of the models
  - Statistical preference for transformation of response
    - May transform to equal variance across groups
    - “Homoscedasticity” allows easier inference
  - Statistical preference for log transformation
    - Easier interpretation: multiplicative model
    - Compare groups using ratios

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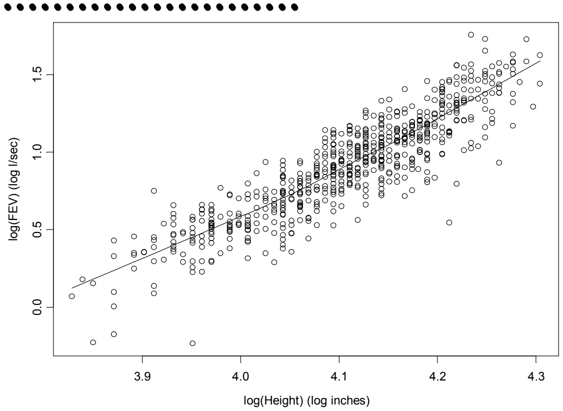
log(FEV) versus log(Height)



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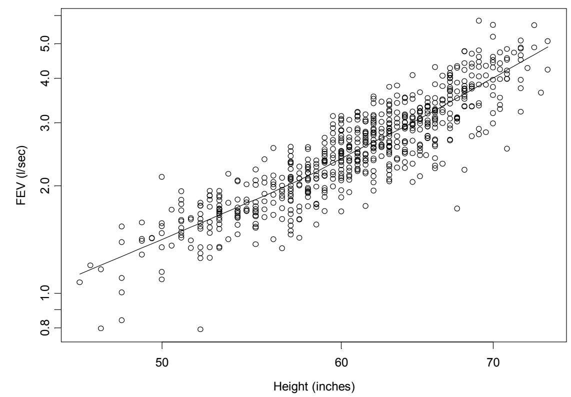
log-log Plot of FEV vs Height



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Estimation of Regression Model

```
. regress logfev loght, robust
Regression with robust standard errors

                                    Number of obs =     654
                                    F(  1,   652) = 2130.18
                                    Prob > F      =  0.0000
                                    R-squared     =  0.7945
                                    Root MSE      =   .1512
       |         Robust
logfev |  Coef. StErr      t   P>|t|       [95% CI]
 loght |   3.12  .068  46.15  0.000    2.99     3.26
 _cons | -11.92  .278 -42.90  0.000 -12.47   -11.38
```

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Log Transformed Predictors

- Interpretation of log transformed predictors with log link function
  - Log link used to model the geometric mean
    - Exponentiated slope estimates ratio of geometric means across groups
  - Compare groups with a k-fold difference in their measured predictors
    - Estimated ratio of geometric means

$$\exp\left(\log(k)\times\beta_1\right)=k^{\beta_1}$$

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Interpretation of Stata Output

- Scientific interpretation of the slope

$$\log \mathrm{GM}\left[FEV_i \,\middle|\, loght_i\right]=-11.9+3.12\times loght_i$$

  - Estimated ratio of geometric mean FEV for two groups differing by 10% in height (1.1-fold difference in height)
    - Exponentiate 1.1 to the slope: $1.1^{3.12}$ =1.35
      - Group that is 10% taller is estimated to have a geometric mean FEV that is 1.35 times higher (35% higher)

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Why Transform Predictor?

- Typically chosen according to whether the data likely follow a straight line relationship
  - Linearity (“model fit”) necessary to predict the value of the parameter in individual groups
    - Linearity is not necessary to estimate existence of association
    - Linearity is not necessary to estimate a “first order trend” in the parameter across groups having the sampled distribution of the predictor
    - (Inference about these two questions will tend to be conservative if linearity does not hold)

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Choice of Transformation

- Rarely do we know which transformation of the predictor provides best "linear" fit
  - As always, there is a danger in using the data to estimate the best transformation to use
    - If there is no association of any kind between the response and the predictor, a "linear" fit (with a zero slope) is the correct one
    - Trying to detect a transformation is thus an informal test for an association
      - Multiple testing procedures inflate the type I error

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Sometimes Does Not Matter

- It is best to choose the transformation of the predictor on scientific grounds
  - However, it is often the case that many functions are well approximated by a straight line over a small range of the data
    - Example: In the modeling of FEV as a function of height, the logarithm of height is approximately linear over the range of heights sampled

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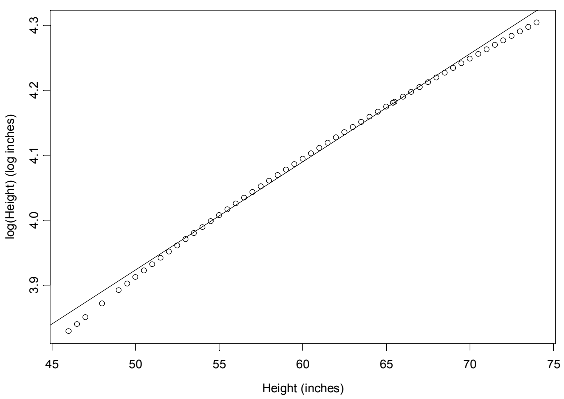
log(Height) versus Height



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Untransformed Predictors

- It is thus often the case that we can choose to use an untransformed predictor even when science would suggest a nonlinear association
  - This can have advantages when interpreting the results of the analysis
    - E.g., it is far more natural to compare heights by differences than by ratios
      - Chances are we would characterize two children as differing by 4 inches in height rather than as the 44 inch child as being 10% taller than the 40 inch child

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Statistical Role of Variables

- Looking ahead to multiple regression: The relative importance of having the “true” transformation for a predictor depends on the statistical role
  - Predictor of Interest
  - Effect Modifiers
  - Confounders
  - Precision variables

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Predictor of Interest

- In general, don’t worry about modeling the exact relationship before you have even established that there is an association (binary search)
  - Searching for the best fit can inflate the type I error
  - Make most accurate, precise inference about the presence of an association first
    - Exploratory analyses can suggest models for future analyses

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Effect Modifiers

- Modeling of effect modifiers is invariably just to test for existence of the interaction
  - We rarely have a lot of precision to answer questions in subgroups of the data
  - Patterns of interaction can be so complex that it is unlikely that we will really capture the interactions across all subgroups in a single model
    - Typically we restrict future studies to analyses treating subgroups separately

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Confounders

- It is important to have an appropriate model of the association between the confounder and the response
  - Failure to accurately model the confounder means that some residual confounding will exist
  - However, searching for the best model may inflate the type I error for inference about the predictor of interest by overstating the precision of the study
    - Luckily, we rarely care about inference for the confounder, so we are free to use inefficient means of adjustment, e.g., stratified analyses

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Precision Variables

- When modeling precision variables, it is rarely worth the effort to use the “best” transformation
  - We usually capture the largest part of the added precision with crude models
  - We generally do not care about estimating associations between the response and the precision variable
    - Most often, precision variables represent known effects on response

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