Statistical Test Selection in Epidemiologic Research

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CPeRT Center for Pharmacoepidemiology Research and Training

ISPE

"I was told there would be no math!"

- Chevy Chase
'Spies Like Us'

Learning Objectives

- Understand variable characteristics to guide statistical test selection
- Learn to use, interpret correlation coefficients
- Understand variables influencing sample size
- Gain familiarity with use, interpretation of linear and logistic regression

Outline

- Constructing a research project
- Correlation / regression
- Linear regression
- Logistic regression

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Constructing a Research Project

- Research question
- Variable characteristics
- Study design, sample size
- Statistical methods

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3 Types of Questions: Different Analyses

Research Question Type #1

- How much or common?
  - Design: Cross-sectional, cohort studies
    - Descriptive statistics:
      - Percentages, frequencies
      - Means (standard deviations)
      - Medians (interquartile ranges)
      - Prevalence (95% CIs)
      - Incidence (95% CIs)

Potential Analyses

Research Question Type #2

- Are these groups different?
  - Design: Case-control, cohort, RCTs
    - T-test: difference in means
    - Wilcoxon rank-sum: difference in medians
    - Chi square, Fisher's exact: diff. in frequencies
    - ANOVA, Kruskal-Wallis: diff. in means, medians among ≥3 groups
    - Odds ratios, hazard ratios, relative risks

Potential Analyses

Research Question Type #3

- Can certain variables predict outcome?
  - Design: Cohort study
    - Linear regression
    - Logistic regression
    - Survival analysis (Cox regression)

Potential Analyses

Constructing a Research Project

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Variable Characteristics to Consider

- Categorical or continuous?
  - Continuous: Normal or not?
- How many independent variables?
- How many groups?

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Categorical or Continuous?

- Continuous: *Any value within a range*
  - Age (years)
  - Blood pressure (mm Hg)
  - Height (m)
  - Weight (kg)
  - CD4 cell count (cells/mm^3)

Categorical or Continuous?

- Categorical: *Discrete categories*

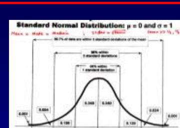
Nominal
Named categories with no order
- Blood type
- Medical specialty

Ordinal
Ordered categories, differences unequal
- NY Heart Class

Variable Characteristics to Consider

- Categorical or continuous?
  - Continuous: Normal or not?
- How many independent variables?
- How many groups?

Normal Distribution



- Continuous data
- Symmetrical, bell shaped
- Mean, median, mode all the same and located at the center
- Allows use of parametric tests (e.g., t-tests)
- If not, must use non-parametric tests

Variable Characteristics to Consider

- Categorical or continuous?
  - Continuous: Normal or not?
- How many independent variables?
- How many groups?

Depends on Clinical Question!

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Hypothesis Testing

- Develop hypothesis
- Test hypothesis:
  - Collect data, observe effect
    H_0 = No effect or difference
    H_a = Effect or difference
- How likely is it that effect occurs by chance
  - If very unlikely ($p < 0.05$), reject H_0

Effect Size, Significance, Power,

- Effect Size: Magnitude of effect being studied
  - Should represent clinically significant difference
- Significance: Probability of Type I error (α=0.05)
- Power: Probability of detecting difference (80%)
- Sample Size: n required to show a difference at set values of effect size, power, and significance

Determination of Sample Size

- Why is this necessary?
  - To detect effect size (OR, RR, HR) as significant
  - Avoid false-positive, false-negative conclusions
  - Avoid enrolling too many patients
- When to determine sample size?
  - During preparation of all protocols (perform early!)
- How to calculate?
  - Stata
  - Other programs: PS - Power / Sample Size, nQuery

Variables Used to Calculate Sample Size

- Detectable (clinically meaningful) difference (d*):
  - Magnitude of difference in proportions, means
- r: ratio of unexposed:exposed, controls:cases
- Power ($1 - \beta$):
  - Type II error (β) = prob. that there is no difference when one does exist (false-negative; set at 0.1, 0.2)
- Type I error (α):
  - Prob. of concluding that there is difference when one does not exist (false-positive; usually set at 0.05)

Variables Used to Calculate Sample Size

- p_1 (for proportions):
  - Proportion exposed who develop disease (cohort/ cross-sectional)
  - Proportion of cases exposed (case-control)
- p_0 (for proportions):
  - Proportion unexposed who develop disease (cohort/ cross-sectional)
  - Proportion of controls exposed (case-control)
- Standard deviation (σ) of continuous outcome

Calculation of Sample Size

- Primary outcome is variable for which you perform sample size calculation
  - If secondary outcomes important, ensure sample size is sufficient
- Typically, have more power to detect differences in continuous outcomes

Sample Size Calculation: Difference in Means

- Sample size for difference in means:

$$n = \frac{(Z_\beta + Z_{\alpha/2})^2 \, \sigma^2 \, (r + 1)}{(d^*)^2 r}$$

- Variables:
  - σ = standard deviation of outcome (σ^2=variance)
  - $Z_{\alpha/2}$ = type I error of 0.05; value=1.96
  - Z_β = type II error; for 0.2 [80% power], value=0.84
  - $(Z_\beta + Z_{\alpha/2})^2$ = 7.85 for 80% power
  - $(Z_\beta + Z_{\alpha/2})^2$ = 10.5 for 90% power
  - r = ratio; d* = detectable difference

Sample Size Calculation: Difference in Proportions

- Sample size for difference in proportions:

$$n = \frac{(Z_\beta + Z_{\alpha/2})^2 \, p_w (1 - p_w)(r + 1)}{(d^*)^2 r}$$

- Note: p_w = weighted average of p_1 and p_0

$$p_w = (p_1 + rp_0) / (1+r)$$

Variables Affecting Sample Size

- Detectable difference:
  - Smaller difference (effect size): ↑ sample size
- Power:
  - ↑ power (e.g., 80 → 90%): ↑ sample size
- Standard deviation of outcome (σ):
  - Smaller σ: ↓ sample size
- P_0:
  - Smaller p_0: ↑ sample size
- Significance level (α):
  - ↑ α → ↓ sample size

Sample Size Calculations

- You must increase sample size to reflect:
  - Loss to follow up
  - Expected response rate
  - Lack of adherence, etc.

  } ↓ Effective sample size
- Example:
  - Targeted number of exposed = 1,200 subjects
  - But only 70% expected to consent (30% refusal rate)
  - Adjust targeted number of exposed as follows:
    - 1,200 / 0.7 = 1,714 exposed
  - So if 1:1 ratio, need 1,714*2 = 3,428 total subjects

Constructing a Research Project

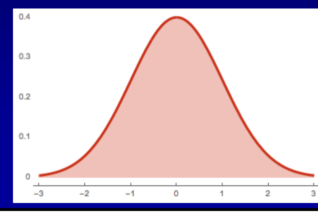
- Research question
- Variable characteristics
- Study design, sample size
- Statistical methods

Select Appropriate Statistical Test for Continuous Data

Purpose of Test	Normal Theory Test (Parametric)	Corresponding Non-Parametric Test
Compare paired data	Paired t-test	Wilcoxon signed-rank test
Compare 2 independent samples	Two-sample t-test	Wilcoxon rank-sum test (Mann-Whitney U test)
Compare ≥3 groups	One-way ANOVA	Kruskal-Wallis

Parametric Tests

- Continuous data
- Normally distributed



Non-Parametric Tests

- Not normally distributed continuous data
  - Small samples

    OR
  - Categorical data
    - Nominal, ordinal
    - Dichotomous (Outcome vs. no outcome)

Select Appropriate Statistical Test for Each Question

Purpose of Test	Normal Theory Test (Parametric)	Corresponding Non-Parametric Test
Compare paired data	Paired t-test	Wilcoxon signed-rank test
Compare 2 independent samples	Two-sample t-test	Wilcoxon rank-sum test (Mann-Whitney U test)
Compare ≥3 groups	One-way ANOVA	Kruskal-Wallis

Categorical Data Analysis: Chi Square Analysis

- Answers: “Are these groups different?”
- Contingency tables evaluate relation between values of ≥2 categorical variables
  - Rows, columns are independent

Categorical Data Analysis: Fisher’s and McNemar’s Tests

- Fisher’s Exact Test: Use if any value in a cell of table is <5
- McNemar’s Test: Use if data are from paired samples

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Correlation / Regression

- Examine relation between variables
- Correlation:
  - Tests significance of relation
- Regression:
  - Quantifies relationship, controlling for confounders

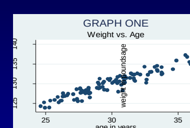
Correlation Coefficient

- Quantifies relationship between two variables
  - Correlation coefficient ("r") ranges -1 to +1

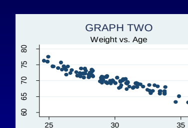
Value of r	Interpretation
r = 0	Two variables do not vary together at all
0 > r > 1	Two variables increase or decrease together
r = 1.0	Perfect correlation
-1 > r > 0	One variable increases as the other decreases
r = -1.0	Perfect negative or inverse correlation

- Often useful to graph data

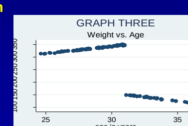
Correlations



Positive Correlation



Negative Correlation



Relation between weight and age is different for younger vs. older

Correlation Statistics

- Pearson's correlation (most widely used):
  - Assumes normally distributed data
  - Compute pairwise correlation ("r"), p values
- Spearman's rank-correlation coefficient:
  - One or more variables → not normally distributed
  - Less sensitive to effects of outlier data
  - Compute correlation ("r"), p values

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Linear Regression

- Allows you to relate <u>continuous</u> outcome (y) to one or more predictor variables (x_1, …, x_k)
  - Mean value of y is expressed as linear combination of x's (x's may be <u>continuous</u> or <u>categorical</u>)
  - Useful when have many potential confounders
- Have equation in the form:

$$y = \alpha + \beta * x$$

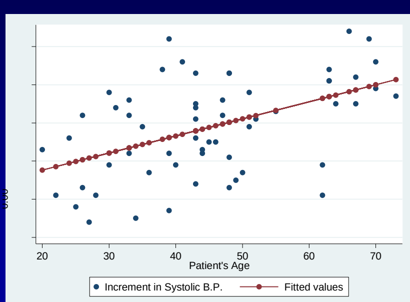
- Typically written as:

$$E(y) = \beta_0 + \beta_1 * x \rightarrow \text{fitted values}$$

Linear Regression

- Perform ordinary least squares regression of dependent variable y on independent variable x
- Estimates minimize squared distance between observed data and fitted values from model

Linear Regression: Determine Best Fit Line in Data



For every 1 unit (cm) ↑ in height, the pulmonary deadspace ↑ by 1.03 mL.

```
. regress deadspace height

      Source |       SS       df       MS              Number of obs =      15
-------------+------------------------------           F(  1,    13) =   32.81
       Model |  5607.43156     1  5607.43156           Prob > F      =  0.0001
    Residual |  2221.50178    13  170.884752           R-squared     =  0.7162
-------------+------------------------------           Adj R-squared =  0.6944
       Total |  7828.93333    14  559.209524           Root MSE      =  13.072

------------------------------------------------------------------------------
   deadspace |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      height |   1.033323   .1803872     5.73   0.000     .6436202    1.423026
       _cons |   -82.4852   26.30147    -3.14   0.008    -139.3061   -25.66433
------------------------------------------------------------------------------
```

The constant is mean deadspace for a child without asthma.

Mean deadspace for child without asthma = 83 mL
Mean deadspace for child with asthma = 52.9 mL

```
.
. regress deadspace asthma

      Source |       SS       df       MS              Number of obs =      15
-------------+------------------------------           F(  1,    13) =    9.92
       Model |  3388.05833     1  3388.05833           Prob > F      =  0.0077
    Residual |    4440.875    13  341.605769           R-squared     =  0.4328
-------------+------------------------------           Adj R-squared =  0.3891
       Total |  7828.93333    14  559.209524           Root MSE      =  18.483

------------------------------------------------------------------------------
   deadspace |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      asthma |    -30.125   9.565644    -3.15   0.008    -50.79032   -9.459683
       _cons |         83   6.985759    11.88   0.000     67.90819    98.09181
------------------------------------------------------------------------------
```

Multivariable Linear Regression

- Evaluate continuous outcome by linear relationship with independent variables
- Have >1 independent variable

Use of Multivariable Linear Regression

- Multiple factors may predict outcome
  - Blood pressure may be affected by weight, hormones, age, other factors
- Control for factors that can vary, but may confound, statistical analysis
  - E.g., age, sex, race, comorbidities
- Improve prediction

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Logistic Regression

- Alternate form of regression
  - Use when outcome is binary
    - Death versus survive
    - Acute MI versus no acute MI
  - One or more predictor variables

Logistic Regression

- Regression method for <u>binary</u> outcomes
- Useful for:
  - Continuous or discrete covariates
  - Adjusting for potential confounders
  - Evaluation of effect modifiers
- Provides OR (95% CI) of outcome for those with vs. without exposure of interest
-

Logistic Regression

- Determination of odds ratios (ORs) is based on maximum likelihood methods
  - Find coefficient values that maximize likelihood of obtaining observed data
- Output requested: β coefficients or ORs

Logistic Regression

```
. logit status admit_type

Iteration 0:   log likelihood = -100.08048
Iteration 1:   log likelihood = -93.176936
Iteration 2:   log likelihood = -92.528575
Iteration 3:   log likelihood = -92.524467
Iteration 4:   log likelihood = -92.524467

Logistic regression                               Number of obs   =        200
                                                  LR chi2(1)      =      15.11
                                                  Prob > chi2     =     0.0001
Log likelihood = -92.524467                       Pseudo R2       =     0.0755

------------------------------------------------------------------------------
      status |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  admit_type |   2.184917   .7450489     2.93   0.003     .7246476    3.645186
       _cons |  -3.238678   .7208382    -4.49   0.000    -4.651495   -1.825861
------------------------------------------------------------------------------

. logistic status admit_type

Logistic regression                               Number of obs   =        200
                                                  LR chi2(1)      =      15.11
                                                  Prob > chi2     =     0.0001
Log likelihood = -92.524467                       Pseudo R2       =     0.0755

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  admit_type |   8.889907   6.623415     2.93   0.003     2.064004    38.28988
       _cons |   .0392157   .0282682    -4.49   0.000     .0095473    .1610788
------------------------------------------------------------------------------
```

Issues to Consider with Logistic Regression

- Which variables to include
- Which fitting method to use
- Collinearity
- Effect modifiers:
  - Does alcohol use level alter relation between drugs and acute liver injury?

Final Important Consideratons

- Know your data before analysis!
  - Look for missing data, develop plan to address
  - Graph variables, relationships between variables
- Collaboration with biostatistician is useful