

Biost 517

Applied Biostatistics I

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

Lecture 13: Two Sample Inference About Other Measures of Location

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Lecture Outline

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- General Setting
 - Inference About Medians
 - Wilcoxon Rank Sum Test

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General Setting

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Scientific Questions

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- The scientific questions most often addressed using statistics
 - Quantifying the distribution of a random variable in a population
 - Association between two random variables
 - Perhaps adjusting for other variables
 - Difference in association between two variables across subgroups
 - Effect modification

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Detecting Associations

- “No association” = Independence between two variables

- Knowing the value of one random variable confers no knowledge about the other variable

- Mathematical definition of independence

Random variables X, Y are independent if for every choice of constants a, b

$$\Pr(X \leq a, Y \leq b) = \Pr(X \leq a)\Pr(Y \leq b)$$

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Role of Sampling Plan

- Most often we detect associations by comparing distributions across groups
 - It is often easiest to choose sample sizes within groups defined by one variable
 - Cohort studies
 - Case-control studies
 - Interventions
 - Even in cross-sectional studies it is often easier to think about comparing groups

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Comparing Conditional Distn

- Equivalent statements of statistical independence of random variables X, Y

- The distribution of X does not differ as Y varies

- The distribution of Y does not differ as X varies

Random variables X, Y are independent if for every choice of constants a, b_1, b_2

$$\Pr(X \leq a | Y = b_1) = \Pr(X \leq a | Y = b_2)$$

$$\Pr(Y \leq a | X = b_1) = \Pr(Y \leq a | X = b_2)$$

(one of these conditions implies the other)

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Differences in Distributions

- There is only one way two distributions can be the same:
 - The difference between the distribution functions must be zero at every point
- There are an infinite number of ways that two distributions can differ
 - An infinite number of places to differ
 - An infinite number of values for the difference

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Comparing Parameters

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- To make it more manageable:
 - Inference about associations is usually based on showing differences between population parameters
 - IF some summary measure (e.g., mean, median) is different for two distributions,
 - THEN the distributions must be different

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Population Parameters

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- Scientific questions are typically answered by making inference about some population parameter, e.g.
 - Mean
 - Geometric mean
 - Median
 - Proportion above threshold
 - Odds above threshold
 - Hazard

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Measures of Association

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- Most often: difference or ratio of univariate parameters
 - Difference (or ratio) of means
 - Ratio of geometric mean
 - Ratio (or difference) of medians
 - Difference (or ratio) of proportions
 - Odds ratios
 - Hazard ratio (or difference)

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Measures of Association

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- Sometimes a measure of association is based on summary of bivariate distribution
 - Mean ratio of observations
 - Median difference of observations
 - Probability that a randomly chosen observation from one group might exceed one chosen from the other group

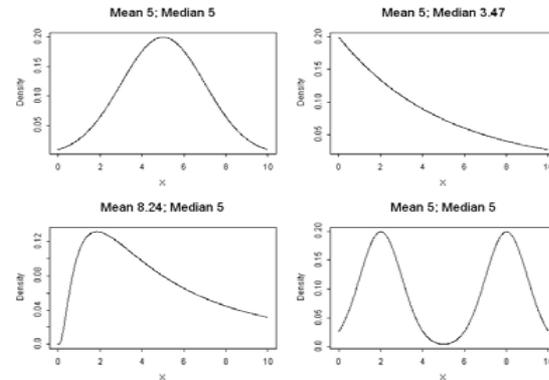
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Interpreting Comparisons

- Using summary measures to detect associations does require caution when interpreting results
 - Lack of a difference between population parameters for two distributions does not necessarily imply that the entire distributions are the same

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Comparing Distributions



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Interpreting “Negative” Results

- Differential diagnosis for failure to detect a difference between population parameters across two groups
 - Maybe the two distributions are the same
 - Maybe the two distributions are different (an association exists), but the population parameters are the same
 - Maybe the true value of the population parameters are different, but we lacked sufficient precision to detect it with high confidence

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Choice of Parameters

- It is therefore important to choose parameters that (in order of importance)
 - Capture scientifically important differences
 - Capture differences that will likely exist
 - Can be measured with statistical precision

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Inference Using the Sample Median

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Median

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- Justification for use of the median
 - Scientific relevance
 - When it is most important to show effect across all subjects
 - (The mean would detect large effects that occur only in a very small subset)
 - Statistical issues
 - The sample median tends to be more efficiently estimated than the mean when the data are distributed with heavy tails

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Median

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- Approximate inference for the sample median can use asymptotic theory
 - The sample median is asymptotically normally distributed
 - The formula for the standard error is difficult to use

$$X_m \sim N\left(mdn(X), \frac{1}{4n[f(mdn(X))]^2}\right)$$

- Bootstrapping is easiest

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Bootstrapped Standard Errors

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- Bootstrapping can be used to find sampling distributions when the formulas are too difficult
 - Based on the presumption that the sample adequately represents the true distribution of data
 - Sample size is adequate

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Basic Strategy

- We pretend that the sample is the population
 - Sample randomly (and with replacement) from the sample to generate pseudosamples
 - Each pseudosample uses same sample size
 - Each observation equally likely to be sampled at each “draw” from the “pseudopopulation”

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Bootstrapped Standard Errors

- From a large number of pseudosamples, we can estimate the sampling distribution of a wide variety of statistics
 - The statistic is calculated on each pseudosample
 - Then analyze the statistics obtained across all replications of the pseudosamples
 - Recall the standard error is just the SD of a statistic computed from replicated experiments

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Inference with Bootstrapped SE

- Providing that we know the statistic is approximately normally distributed

100(1- α)% confidence interval is (θ_L, θ_U)

$$\theta_L = \hat{\theta} - z_{1-\alpha/2} s\hat{e}(\hat{\theta})$$

$$\theta_U = \hat{\theta} + z_{1-\alpha/2} s\hat{e}(\hat{\theta})$$

Hypothesis tests based on

$$Z = \frac{\hat{\theta} - \theta_0}{s\hat{e}(\hat{\theta})} \sim N(0,1)$$

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Ex: SE of Sample Median

- Bootstrapped estimates of the standard error for sample median

| | Data | Median |
|------------------|-------------------|--------|
| Original sample: | {1, 5, 8, 3, 7} | 5 |
| Bootstrap 1 | : {1, 7, 1, 3, 7} | 3 |
| Bootstrap 2 | : {7, 3, 8, 8, 3} | 7 |
| Bootstrap 3 | : {7, 3, 8, 8, 3} | 7 |
| Bootstrap 4 | : {3, 5, 5, 1, 5} | 5 |
| Bootstrap 5 | : {1, 1, 5, 1, 8} | 1 |

etc.

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1000 Bootstrapped Samples

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- Descriptive statistics for the sample medians from 1000 bootstrapped samples

| | |
|--------------------|-------|
| n | 1000 |
| Mean | 4.964 |
| Standard Deviation | 1.914 |
| Median | 5 |
| Minimum, Maximum | 1, 8 |
| 25th, 75th %ile | 3, 7 |

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Inference for Sample Median

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- From the above bootstrapped samples:
 - Estimated SE sample median is 1.914
 - The standard deviation of the sample medians across the 1000 pseudosamples
 - A 95% asymptotic (with $n=5$?) confidence interval (using the 0.975 quantile of the standard normal distribution) is thus
$$5 \pm 1.96 * 1.914 = 1.25, 8.75$$

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Bootstrapped Standard Errors

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- There are some instances when bootstrapping does not work
 - For instance, no sample of continuous data is ever adequate to bootstrap the sampling distribution of the minimum or maximum
 - We can never mimic the chance to have observed more extreme values than were in our sample
 - But as a general rule, bootstrapping behaves remarkably well for measures of location and variability

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Median: Stata Commands

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- Stata has some capability to perform inference using the sample median
 - “centile” provides confidence intervals based on binomial distributions
 - Adequate for quantifying population median
 - Such CI could be used with standard normal critical values to get standard errors for use in two sample problems

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Stata: SE fo Sample Median

- Stata can find bootstrapped standard errors and confidence intervals
 - E.g, bootstrapped inference for median bilirubin in Primary Biliary Cirrhosis data set
 - bs “summ bili, detail” “_result(10)”, reps(1000)
 - summ bili, detail returns the median as its 10th result
 - I want 1000 bootstrapped samples (this is overkill)
 - More complicated analyses could be done with Stata command bstrap and a Stata program

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Ex: Median Bili in PBC Data

- E.g, bootstrapped inference for median bilirubin in liver data set

```
Bootstrap statistics   Number of obs   =       418
                    Replications   =       1000
```

| Vrble | Reps | Obs | Bias | StdErr | [95% Conf Int] |
|-------|------|-----|--------|--------|----------------|
| _bs_1 | 1000 | 1.4 | -.0230 | .0966 | 1.21 1.59 (N) |
| | | | | | 1.2 1.6 (P) |
| | | | | | 1.3 1.8 (BC) |

N = normal; P = percentile; BC = bias-corrected

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Two Group Comparisons

- To compare medians, we would compute SE for each group individually, then use methods for combining estimates

For independent $\hat{\theta}_1 \sim N(\theta_1, se_1^2)$, $\hat{\theta}_2 \sim N(\theta_2, se_2^2)$

$$\hat{\theta}_1 + \hat{\theta}_2 \sim N(\theta_1 + \theta_2, se_1^2 + se_2^2)$$

$$\hat{\theta}_1 - \hat{\theta}_2 \sim N(\theta_1 - \theta_2, se_1^2 + se_2^2)$$

$$\hat{\theta}_1 / \hat{\theta}_2 \sim N\left(\frac{\theta_1}{\theta_2}, \frac{1}{\theta_2^2} \left(se_1^2 + \frac{\theta_1^2}{\theta_2^2} se_2^2 \right)\right)$$

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Wilcoxon Rank Sum Test

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Motivation

- Once upon a time...
 - Computing was not as readily available
 - Finding exact distributions was more difficult
 - Taking logarithms of data was more difficult
 - (I still have a slide rule)
 - People worried about assumptions of normality

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Wilcoxon Rank Sum Test

- One idea was to downweight influence of outliers by analyzing the ranks of the data instead of the measurements themselves
 - Analogous to comparing the mean ranks

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Notation for Ranks

Data $\{X_1, X_2, \dots, X_n\}$
Order stats $\{X_{(1)}, X_{(2)}, \dots, X_{(n)}\}$

Ranks $\{R_1, R_2, \dots, R_n\}$

If $X_i = X_{(k)} = X_{(k+1)} = \dots = X_{(k+t)}$

$$\text{then } R_i = \frac{k + (k+t)}{2}$$

(untied X_i is the R_i -th smallest : $X_{(R_i)} = X_i$)

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Example of Ranks

Data $\{4, 7, 4, 2, 37, 5, 7, 4\}$

Order stats $\{2, 4, 4, 4, 5, 7, 7, 37\}$

Ranks $\{3, 6.5, 3, 1, 8, 5, 6.5, 3\}$

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Wilcoxon Rank Sum Test

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- Then compare average ranks for two groups
 - Exact distribution from permutation tests
 - What is the probability of obtaining a particular average rank for a group if we just mix up all the observations?
 - Draw n numbers from the integers from 1 to $m+n$
 - A test of the null hypothesis that the two distributions are equal
 - A central limit theorem can be used in large samples

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Mann-Whitney Formulation

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- Rank sum test considers the probability that a randomly chosen subject from one group might be larger than a randomly chosen subject from the other group
 - “Pr ($Y > X$)”
 - Intuitive null hypothesis: $\text{Pr} (Y > X) = 0.5$
 - Not consistent in large samples for just ANY difference in distributions, only for distributions that differ so that $\text{Pr} (Y > X)$ is not 0.5

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Sampling Distribution

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- We only know sampling dist under complete equality of distributions
 - We can get point estimates of $\text{Pr} (Y > X)$, but this is not often supplied
 - We can not get general confidence intervals for the $\text{Pr} (Y > X)$
 - We do not know the distribution of our test statistic under the alternative
 - We do not have power formulas for sample size computation

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Rank Sum Based CI

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- Some authors describe CI for differences in the median (or mean) based on the Wilcoxon statistic
 - However, these CI are based on the assumption that the shape of the distribution is the same for each group
 - I think this is an inappropriate assumption: It is assuming you know something that is more detailed (shape of distribution) than what you are trying to detect (general location)

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Stata Commands

- "ranksum varname, by(groupvar)"
 - Compares the groups indicated by binary variable groupvar
 - Provides two-sided P values
 - No relevant estimates, CI

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Ex: Compare Bilirubin by Sex

```
. ranksum bili, by(sex)
Two-sample Wilcoxon rank-sum (Mann-Whitney) test
      sex |      obs   rank sum   expected
      0 |      36   6623.5     5634
      1 |     276  42204.5    43194
-----
combined |     312   48828    48828
unadjusted variance  259164.00
adjustment for ties    -401.30
-----
adjusted variance   258762.70
Ho: bili(sex==0) = bili(sex==1)
      z =    1.945
      Prob > |z| =    0.0518
```

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Interpretation

- We do not have enough evidence to state with 95% confidence that the distribution of bilirubin is different between men and women who have Primary Biliary Cirrhosis
- We have no idea what precision we have to detect a meaningful difference
 - We have no point estimates or CI

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Additional Comments

- The Wilcoxon rank sum test can be shown to be "intransitive"
 - It is possible to simultaneously decide that
 - Group A tends to be higher than Group B
 - Group B tends to be higher than Group C
 - Group C tends to be higher than Group A
 - Arises because $\Pr(Y > X)$ is intransitive
- I think that this is not very useful scientifically

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