Robust Weighting Schemes, Longitudinal Growth Curves, and Unhealthy Subpopulations as Reference Databases

ASA Biopharmaceutical Section Statistics Workshop

Statistical Challenges for Medical Tests with Reference Databases

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Examples of Reference Databases:

- May be either prospective or retrospective
- May be cross-sectional or longitudinal

- National Health and Nutrition Examination Survey (NHANES).
  - Conducted annually since 1999
    - Data released every 2 years
  - Contains strata, clusters, sampling weights
  - Subsample will be longitudinal
    - Re-contacting some who were examined 2007-2014

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Examples (continued)

- Kid's Inpatient Database (KID).
  - Pediatric discharge data
  - Every 3 years starting 1997
    - 2015: Q1-Q3 ICD-9, Q4 ICD-10
    - 2016: ICD-10
    - Up to 15 diagnosis codes
  - All payers
  - Cost-to-Charge ratios at hospital level
- Has strata, clusters, sampling weights
- Not all states represented
- Comparing across years is an issue
- Can this be used as a reference sample?
  - Pediatric problem

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KID: Comparing across years

- Consider $\bar{X}(2003)$ and $\bar{X}(2000)$
- With respective standard errors, $se(2003)$, $se(2000)$
- Simple ~ Z-statistic:

$$\frac{\bar{X}(2003)-\bar{X}(2000)}{\sqrt{se^2(2003)+se^2(2000)}}$$

- Z is probably smaller than it should be (conservative)
  - Denominator is missing -2*Cov($\bar{X}(2003)$, $\bar{X}(2000)$)
  - Covariance is probably ≥ 0

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Examples (continued)

- Framingham Heart Study (FHS)
  - Risk factors for heart disease -1948
  - Used for “cutting-edge heart, brain, bone, and sleep research”
- Private
  - Private laboratories.
    - Urine samples from prescription drug users.
  - Individual hospitals
    - CCHMC
    - Pulmonary function tests from boys with Duchenne’s Muscular Dystrophy (DMD).
    - Lean Body Mass from DMD boys.
  - Fernald Medical Monitoring Program (FMMP)
    - Nuclear fuel processing plant, Fernald, OH
    - Uranium and radon exposure
    - Monitor health of workers and families 1990-2008
    - “Healthy” individuals could be used as a reference sample

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Reference Ranges a.k.a. Reference Intervals

- Requires database of “healthy” subjects
- Physician-determined
  - Independent of analyte measurements (FMMP)

- Convenience sample - volunteers
  - Screen for obvious exclusion factors

- Subpopulations of unhealthy
  - DMD

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Types of Reference Intervals

- Nonparametric
  - Uses order statistics
- Gaussian-based
  - Based on prediction interval
  - Uses sample mean and standard deviation

$$\bar{x} \pm t_{\alpha/2}^{(n-1)} s\sqrt{1+1/n}$$

  - Most likely requires transformation first
- Robust
  - Mimics Gaussian-based interval
  - Uses robust versions of center and spread

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Robust reference interval (continued)

Gaussian: $\bar{x} \pm t_{\alpha/2}^{(n-1)} s\sqrt{1+1/n}$

$$T_{bi}(c_1) \pm t_{\alpha/2}^{(n-1)} \sqrt{S_T^2(c_1) + s_{bi}^2(c_2)}$$

where,

$T_{bi}(c_1)$ is location estimator based on the "biweight" function. (c_1 is a tuning constant)

$S_T^2(c_1)$ is an estimator of the variance of $T_{bi}(c_1)$

$s_{bi}(c_2)$ is an estimator of spread based on the biweight. (Note the different tuning constant, c_2)

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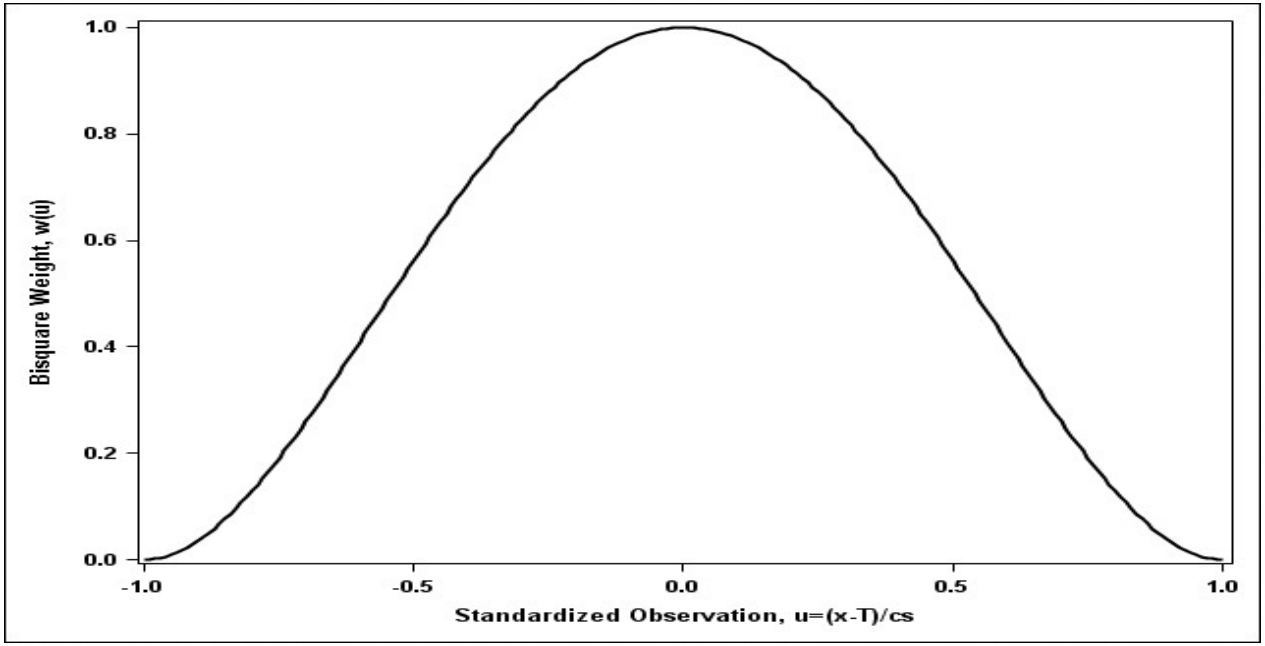
Biweight smoothly “weighs” observations.

- Values further from the center get smaller weights.
- Values very far away get zero weight.
- If weight = 1 for all values sample mean.
- If weight = 0 for all values, except middle value sample median.
- *Iterative* process starting at the sample median.



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Iteration and reweighting:

- $T_{bi}^{(j)}$ at j^{th} iteration is just a weighted average
  - The weight for x_i is $w_i = (1-u_i^2)^2$
  - Where $u_i = (x_i - T_{bi}^{(j-1)})/(c*s)$
  - and c is the tuning constant, s is robust estimator of spread, e.g., MAD.
- Straightforward for simple random samples
- Must be careful if there are sampling weights, e.g., NHANES
  - Original biweight reference interval code was written with NHANES in mind
- Strata and clusters, e.g., KID

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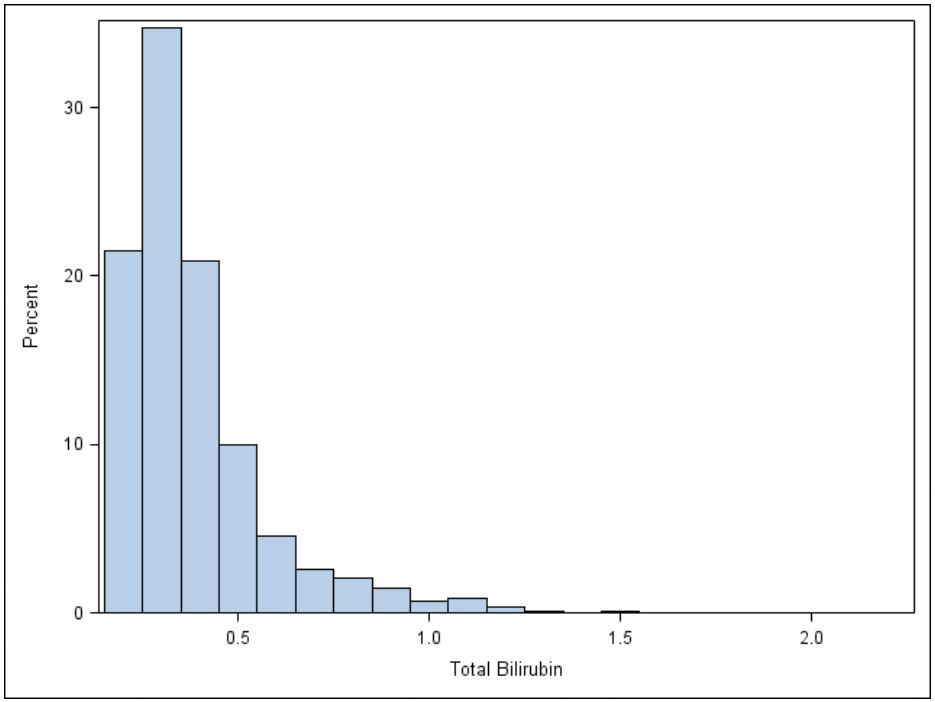
Example: Bilirubin from 3005 Boys < 12 yo



Source: Eli Lilly & Co. Clinical Trial Data, Beasley et al 2017. Manuscript under review.

95% Reference Limits	Nonparametric	90% CI	Robust	90% CI Boostrap	Bca
Lower	0.2	0.2 - 0.2	0.17	0.171-0.174	0.171-0.174
Upper	0.9	0.9 - 1.0	0.87	0.838-0.896	0.836-0.895

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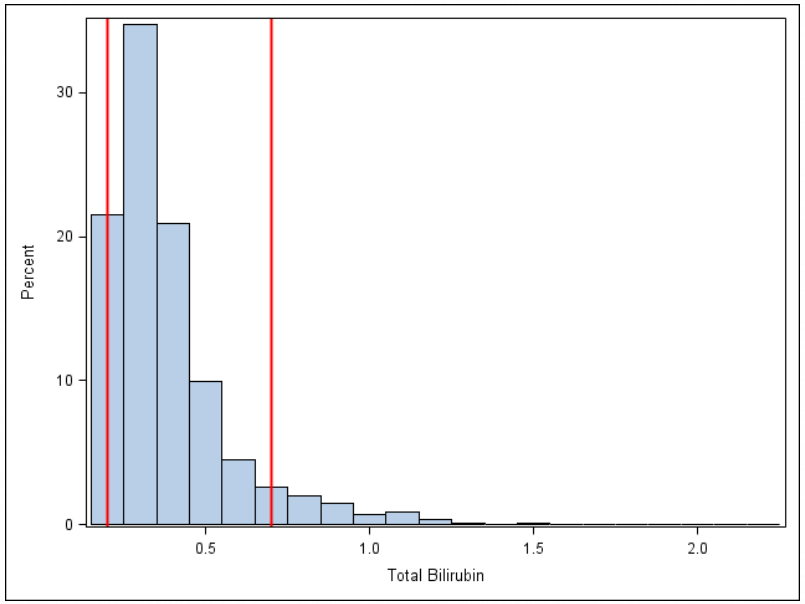
Remove Outliers:



95% Reference Limits	Outliers Removed	Nonparametric	90% CI	Robust	90% CI Boostrap	Bca
Lower	647 (= 0.2)	0.3	0.3-0.3	0.25	0.254-0.300	0.254-0.300
Upper	250 (≥ 0.7)	0.6	0.6-0.6	0.58	0.575-0.645	0.570-0.605

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However,

- All of the above reference interval approaches are based on random samples of healthy subjects
- Complicating this is the fact that it is often the case that data are collected longitudinally
  - Forced to ignore blocking variable – subject
- We are often interested in an unhealthy subpopulation as it compares to an appropriate healthy reference
- Unhealthy subpopulation as a “reference”

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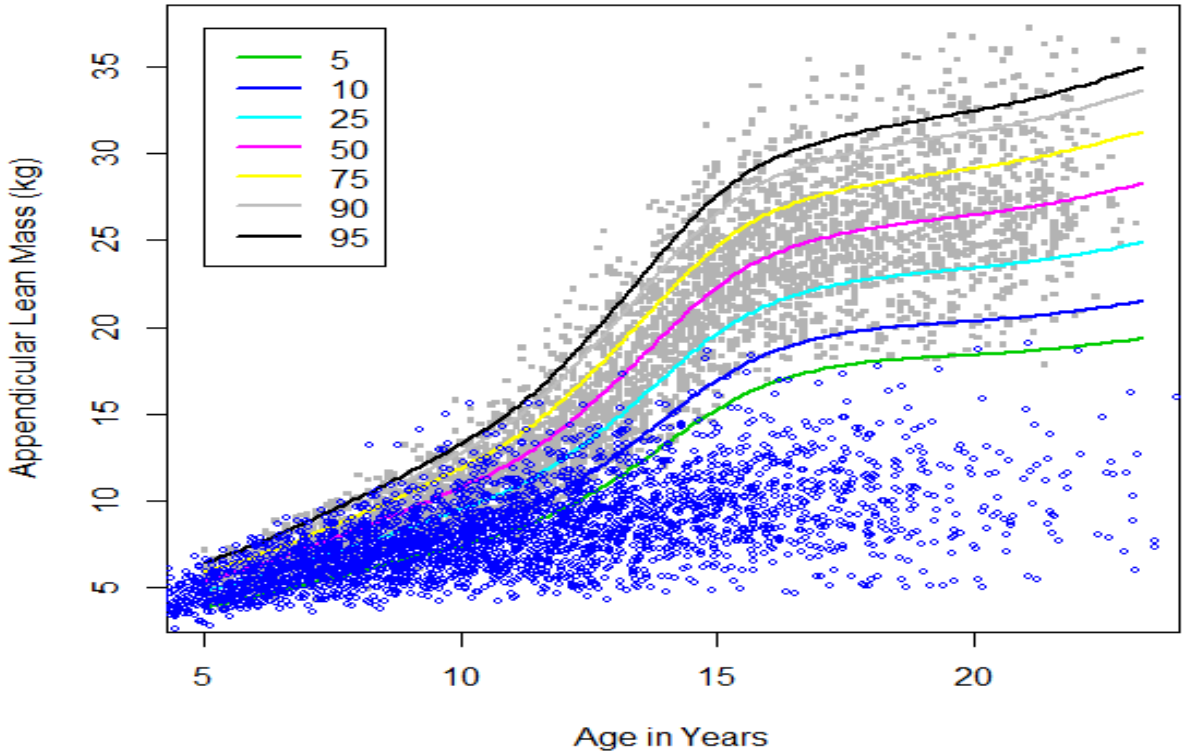
LMS Growth Curves (TJ Cole, JRSS 1988)
Generalized Additive Models for Location, Scale, and Shape
R Library gamlss



Healthy Control raw data, light grey, is longitudinal (unpublished)

Circles are DMD boys' raw data – also longitudinal

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Use Smoothing with Generalized Linear Models

- SAS Macro radial_smoothing_percentile
  - PROC GLIMMIX
- Can only have one continuous covariate – usually age
- “Nonparametric estimation of age-specific reference percentile curves with radial smoothing” X Wan, Y Qu, Y Huang, X Zhang, H Song, and H Jiang. Contemporary Clinical Trials 33 (2012): 13-22

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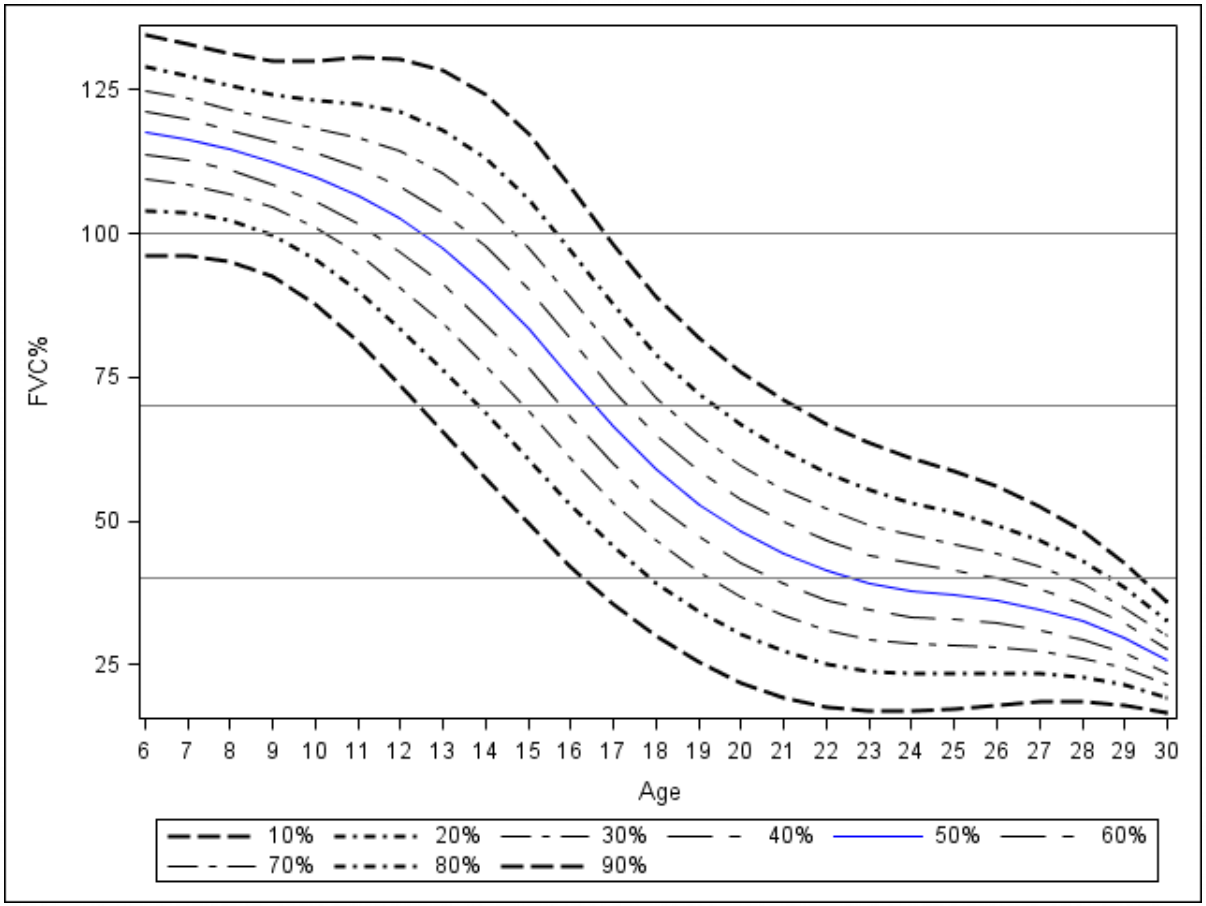
Deciles for DMD Boys: Forced Vital Capacity % (unpublished)



Longitudinal data.
Upper ages based on only a few subjects
No data available for healthy controls

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Urine Drug Testing - Provided by Amadeo Pesce

- Used to determine medication compliance
- Use of non-prescription and illicit drugs
- Most insurers prefer to pay for qualitative testing
- Quantification of the urine drugs allows for more extensive investigations
  - Data could serve as a reference sample
  - But no info within subject
- In October 2014 DEA:
  - Hydrocodone moved from Schedule III to Schedule II
  - Thus, prescriptions could no longer be called in
- Concentration of Hydrocodone should decrease over time

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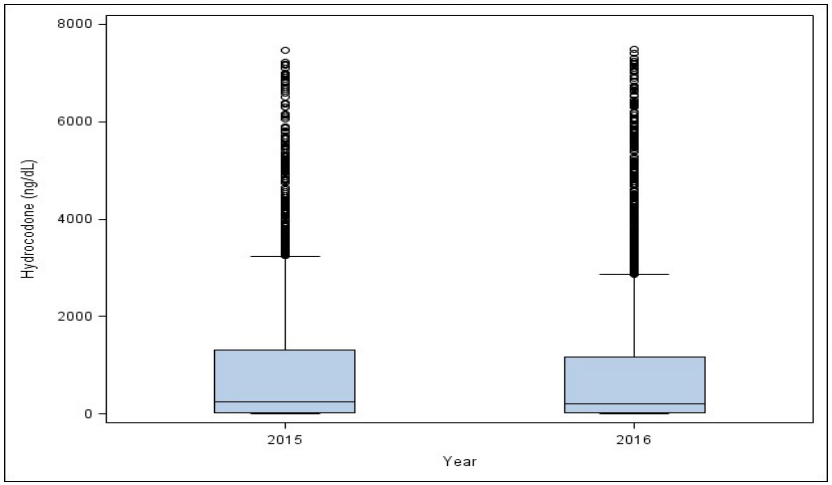
Compare October 2015 and October 2016

- Hydrocodone – Now Schedule II - Change
  - 2015: n = 2394, mean(SD) = 1206 (2449) ng/mL
  - 2016: n = 2882, mean(SD) = 1489 (4726) ng/mL
    - T-test p-value < 0.001, many outliers
    - Wilcoxon p-value = 0.03, but mean score in 2015 > 2016



- Kolmogorov-Smirnov p-value = 0.0003
  - EDF at maximum: 2016 > 2015

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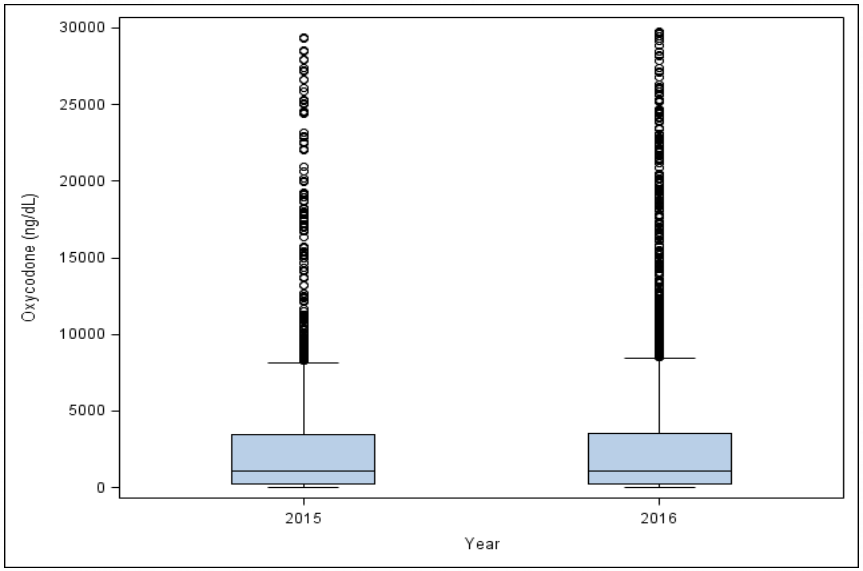
Compare October 2015 and October 2016

- Oxycodone – Still Schedule II - No change
  - 2015: n = 1822, mean(SD) = 5543 (23464) ng/mL
  - 2016: n = 3300, mean(SD) = 5344 (29642) ng/mL
    - T-test p-value = 0.80
    - Wilcoxon p-value = 0.57



- Kolmogorov-Smirnov p-value = 0.70

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Closing Remarks

- How to define “healthy” in a reference database?
- Properties of the data collection
  - Strata
  - Clusters
  - Participating hospitals, states, etc. (e.g., KID)
- How to incorporate covariance structure for age-dependent reference curves?
- Privacy, HIPAA, public policy, etc., may affect ability to do correct statistical analysis

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