Statistical Approaches for Determining Normal Limits in OCT Databases

Kouros Nouri-Mahdavi, MD MSc
Jules Stein Eye Institute
University of California Los Angeles

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Disclaimer and Acknowledgment

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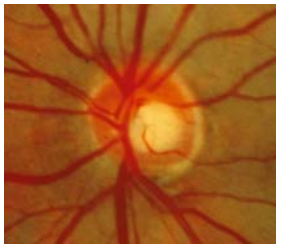
Detection of Disease

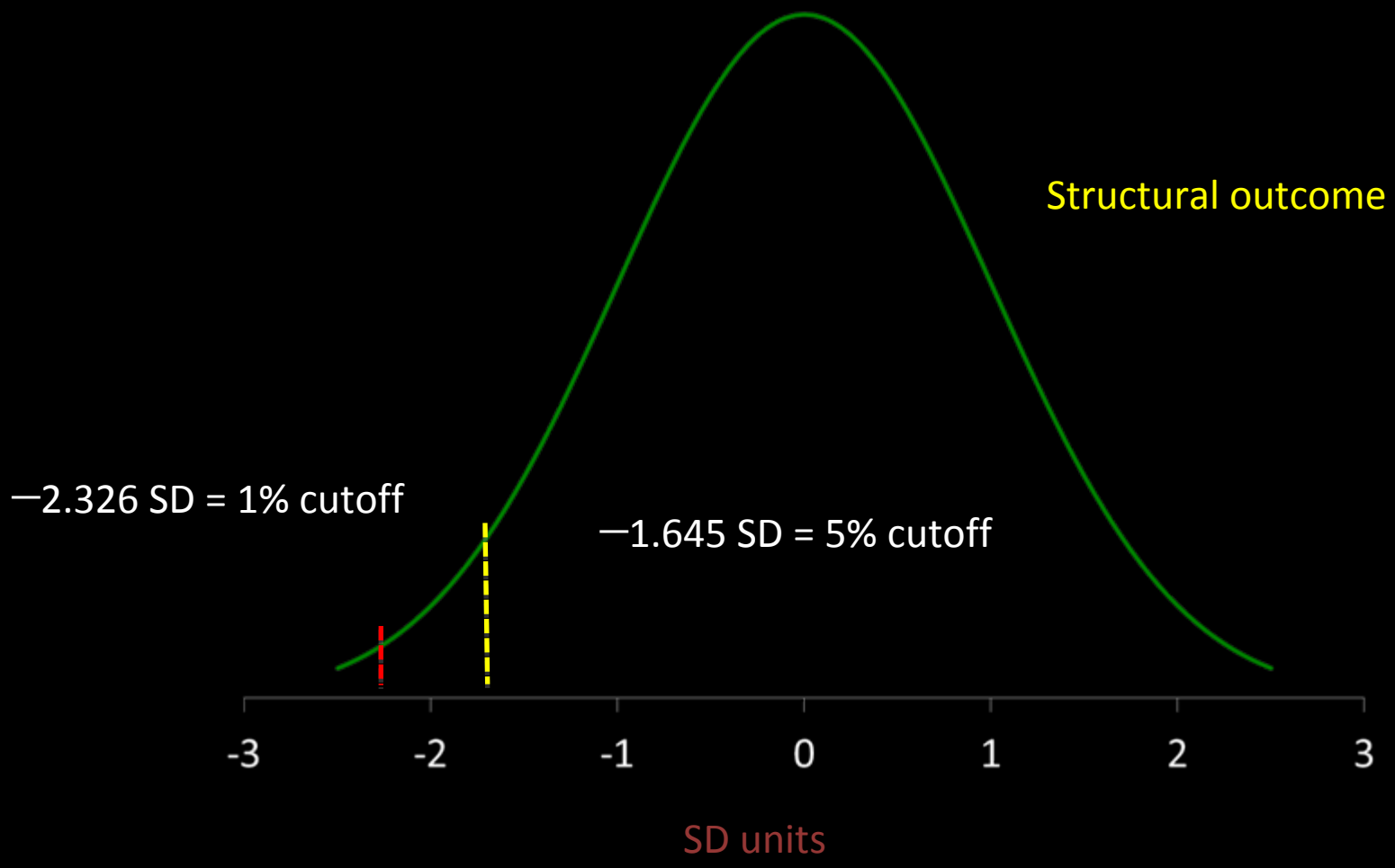
- Definition of “normal”
- Choice of the sample
- Sample size
- Composition of the normative database
- Covariates: to adjust or not to adjust

Definition of "Non-Diseased" for Inclusion in Normative Databases

- No best criteria, normal IOP and *achromatic* visual fields commonly used
- Including only eyes with normal discs leads to "supernormal" normative database
- No requirement for a 'normal' disc > lower sensitivity for "preperimetric" glaucoma, not a big issue with Gaussian assumption



Current normative databases assume *Gaussian* distribution
Nonparametric estimation methods more robust but need higher sample sizes

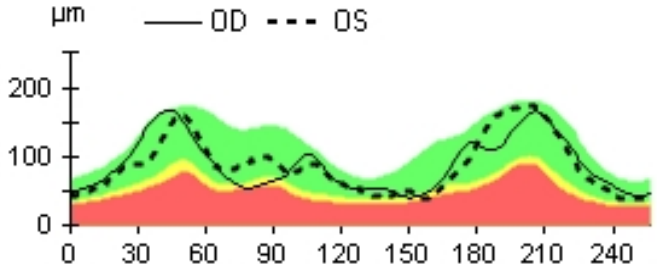


Sampling and Sample Size

- *Convenience sampling* customary
- Potential for selection bias
  - An issue for defining prediction intervals (PIs)
  - Less problematic when evaluating *correlations* or *predictors* of structural outcomes
- Distribution of predictive factors needs to be similar to ratios in the population for *PIs* but not as essential for correlations

Sampling Issues

- An effect of a small sample size is lack of precision for the 5% and 1% cutoff levels



- Does it matter clinically?
- Prediction limits generally *wider* for *regional* vs. global measures and for *1%* vs. 5% cutoff

Precision of cutoff points is a function of the sample size

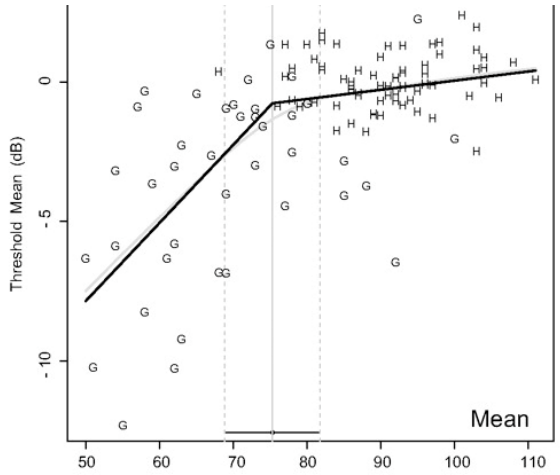
n	lower	5th ptile	upper	width of 95% CI in SD units
10	2.911	1.645	1.017	1.894
15	2.566	1.645	1.114	1.452
20	2.396	1.645	1.175	1.221
25	2.292	1.645	1.217	1.075
30	2.22	1.645	1.25	0.970
35	2.167	1.645	1.276	0.891
40	2.125	1.645	1.297	0.828
50	2.065	1.645	1.329	0.736
60	2.022	1.645	1.354	0.668
120	1.899	1.645	1.433	0.466
240	1.819	1.645	1.492	0.327
480	1.766	1.645	1.535	0.231
inf	1.645	1.645	1.645	0

5th percentile estimate = mean — 1.645 SD

Table courtesy of Jeff Gornbein DrPH

Statistical cutoff points are artificial

- Abnormality or disease defined by purely statistical means (i.e., 95% PIs, etc.) are arbitrary
  - Functional definition of abnormality?
  - Potentially limited by the high variability of SF relationship

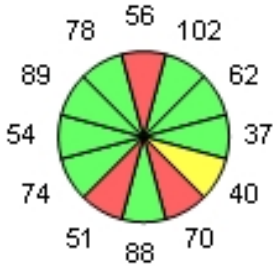


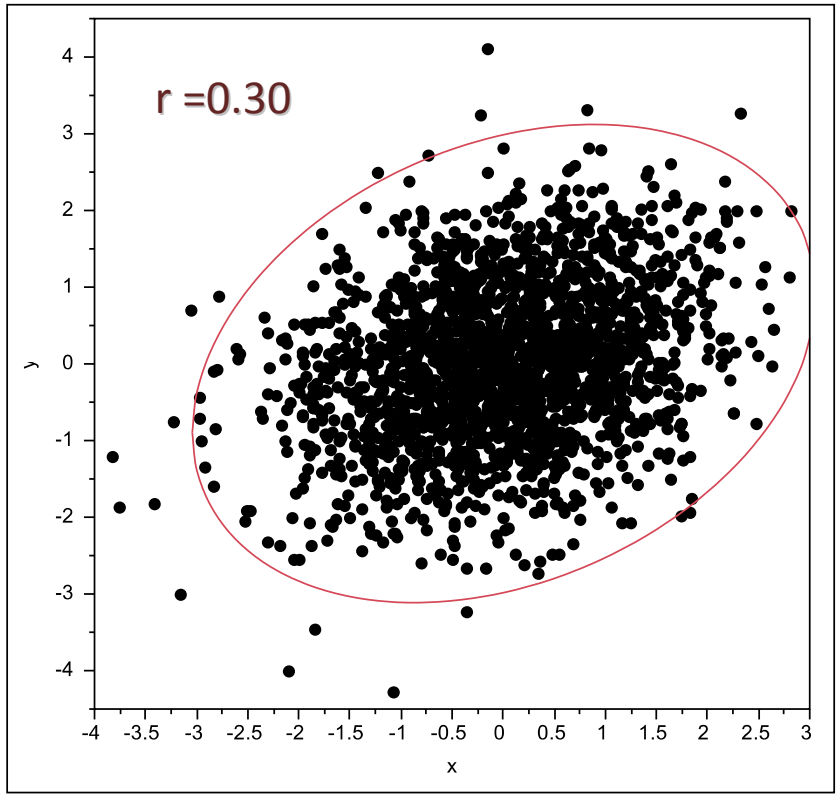
Wollstein et al. BJO 2010

Multiple comparisons can lead to false statistical 'flagging'

- More problematic with *borderline* findings and *lower* correlation

- Prediction spaces for multiple correlated variables





A bivariate normal 99% prediction ellipse

Role of Covariates

- Covariate adjustment vs. stratification
- Stratification is preferred:
  - When stratum in infrequent in the population
  - When interested in the performance of the test in particular strata
- Types of covariates
  - Affecting distribution of structural outcomes
  - Associated with potentially ‘worse’ outcomes

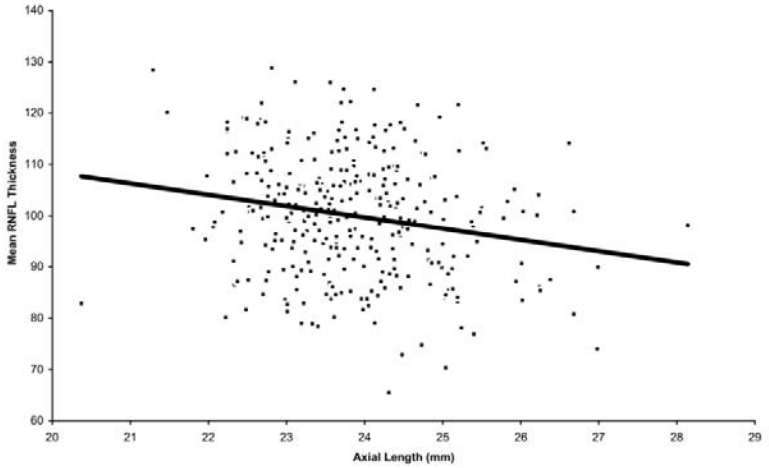
Covariates Affecting Distribution of Outcomes of Interest

- Gender?
  - GC/IPL, Mwanza et al. 2011, Koh et al. 2012; *not* with GCC, Kim et al. 2011
- Race
  - Is its influence a function of other anatomical factors?
  - Probably best to stratify for race with adequate sample size; but, assuming normal distribution, we can use mean and SD from smaller sample to adjust.
- Disc size, shape, and position in relation to fovea
- Signal strength

Covariates Potentially Associated with 'Worse' Structural Outcomes

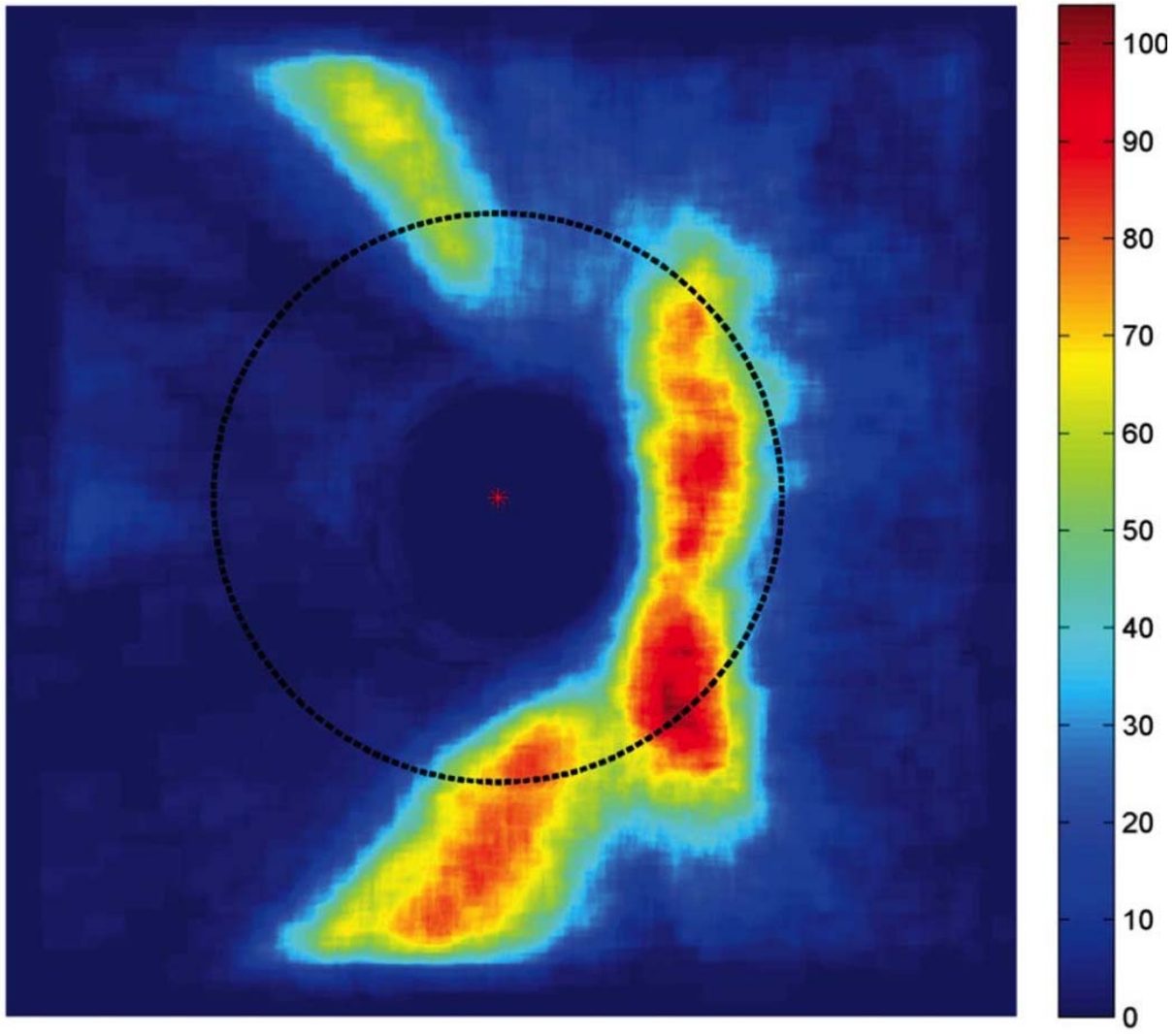
Need to adjust for? To what extent?

- Age
  - Databases limited to age ≥18
  - Commonly small number of subjects >70 yrs
  - exclude older subjects, i.e. >70-75 years?
- Refractive error?
- Axial length?



Budenz et al. Ophthalmology 2007

Distribution of RNFL Thinning in Myopia



Leung CK et al. IOVS 2012

Role of Covariates

- *Adjusted* or *stratified* prediction intervals *may* potentially improve the precision of prediction intervals
- Sliding scale significance levels?
- Use of mathematical modeling for better prediction limits?

Non-Statistical Issues Affecting Normative Databases

- Operator-related (minimal with SD-OCT)
- Anatomical
  - Disc shape and size
  - Disc location in relation to fovea (fovea-disc axis)
  - Location and angle of major vessels (10-15% of RNFL thickness)
- Image quality
  - Quality of media
  - Number of A-scans (256-1536)
  - Repetition rate (noise reduction)
  - Placement of the measurement circle
  - Tracking (reduces motion artifacts)
- Segmentation algorithms
- Optical magnification issues

THANK YOU