Quantitative Bias Analysis

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Disclosure: Opinions/statements in this course reflect personal opinions, not policy or opinions of Amgen, Inc. or FDA.

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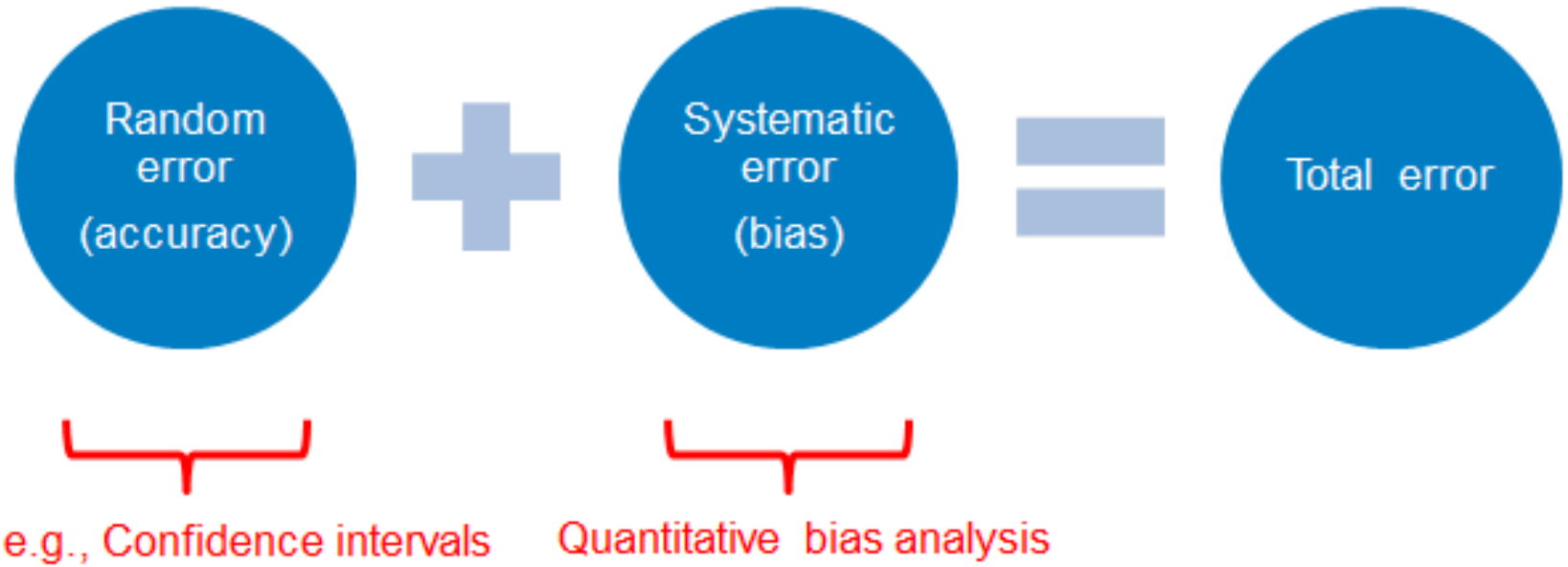
Section 1

What is a quantitative bias analysis?

What is quantitative bias analysis (QBA)?

- Make some bias assumptions and calculate bias-adjusted estimates
- Why do QBA?
  - Bias is usually addressed in the 'limitations' section qualitatively
  - With a few assumptions, we can actually show that bias does or does not affect the final results quantitatively.

Types of error



- Systematic error=bias

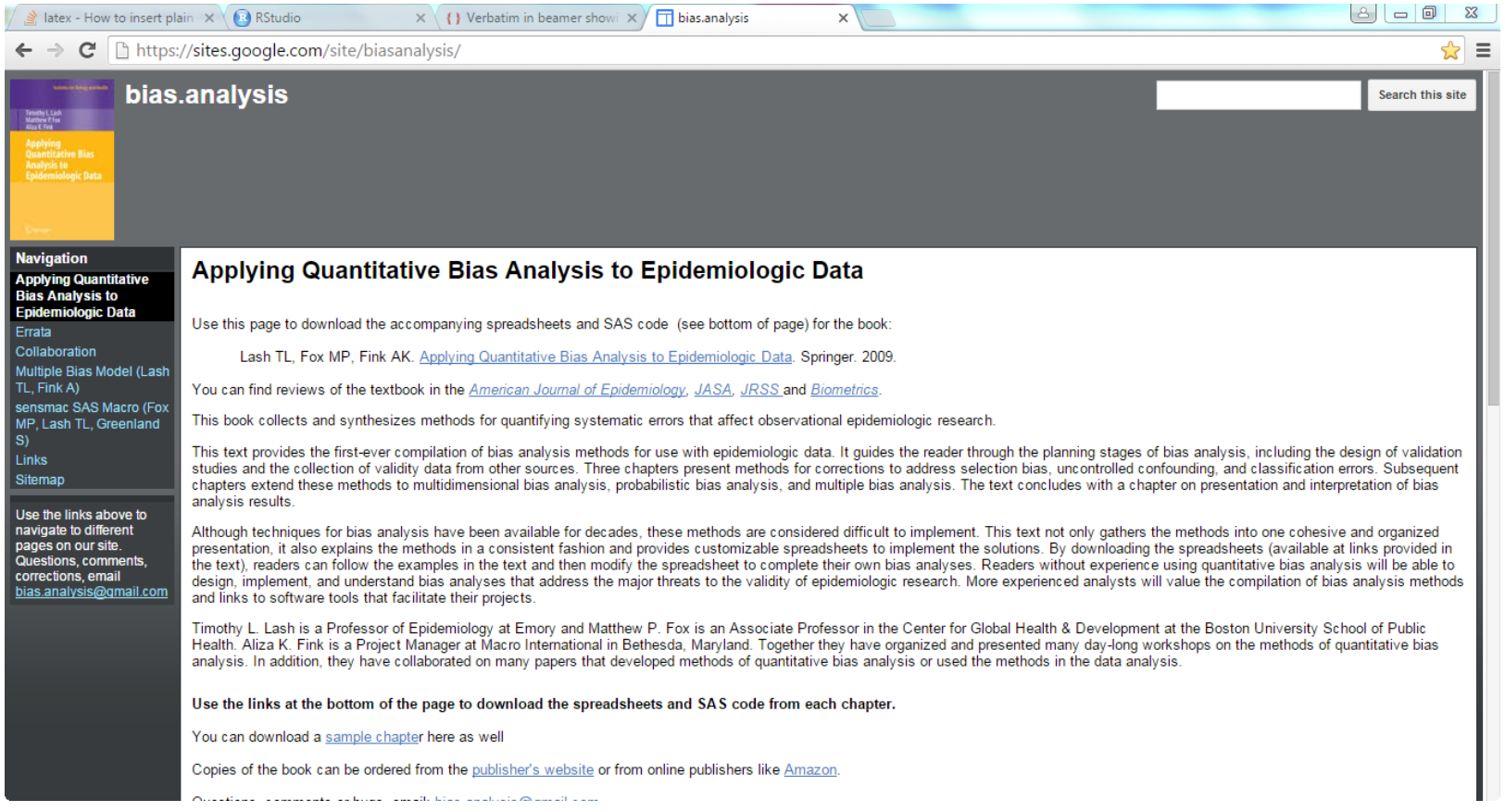
Types of QBA problems

The QBA book


Statistics for Biology and Health
Timothy L. Lash
Matthew P. Fox
Aliza K. Fink
Applying Quantitative Bias Analysis to Epidemiologic Data
Springer

The QBA book: website

https://sites.google.com/site/biasanalysis/



The QBA book: website

- Chapter 1-3 background
- Chapter 4- onwards has specific problems.
- The website has Excel spreadsheets to help with simple bias analysis
- SAS macros to help with more complex bias analysis
- There is also an R package 'episensr' that has software for all the techniques in the book

Section 2

Simple selection bias

Selection bias

- Differential initial participation bias is a kind of selection bias that occurs when both the exposure and the outcome affect the probability of initial participation in a study.
- To calculate the adjusted risk estimate you need:
  1. Observed data (counts from a 2x2 table representing the number of subjects exposed/not exposed and cases/controls: a, b, c, and d
  2. Outcome (OR or RR)
  3. Selection proportions for each of the four exposure/outcome combinations: S_a, S_b, S_c, S_d.
- For example, S_a is the proportion of all potential participants who were exposed and had the outcome, who actually participated in the study.

Selection bias: example

- Association between mobile phone use and uveal melanoma (Stang et al, 2009)
- Cases were identified during September 2002 to September 2004 from a tertiary care hospital in Germany
- 94% of cases and 55% of controls agreed to participate.
- Some non-participants agreed to answer a brief survey.

Selection bias: example

	Exposed Mobile phone +	Unexposed Mobile phone -
Uveal melanoma + /Cases	a=136	c=107
Uveal melanoma - /Controls	b=297	d=165
Total	433	272

$$\begin{aligned} \text{Observed OR} &= \frac{a \times d}{b \times c} \\ &= \frac{136 \times 165}{297 \times 107} \\ &= 0.71 \end{aligned}$$

Selection bias: example

- Evidence of selection bias
- Based on the survey of non-participants, and non-participation rates, researchers estimated participation rates in each of the four exposure/outcome categories.

	Exposed Mobile phone +	Unexposed Mobile phone -
Uveal melanoma + /Cases	S_a=0.94	S_b=0.85
Uveal melanoma - /Controls	S_c=0.64	S_d=0.25

Selection bias: example

$$
\begin{aligned}
\text{Adjusted OR} &= \frac{a/S_a \times d/S_d}{b/S_b \times c/S_c} \\
&= \frac{136/0.94 \times 165/0.25}{297/0.85 \times 107/0.64} \\
&= 1.63
\end{aligned}
$$

Section 3

FDA Sentinel QBA methods

Sentinel QBA

- Working group outlined a test case of QBA methods for mini-sentinel (Sept 2015)

MINI-SENTINEL METHODS

ANALYTICAL METHODS TO ASSESS ROBUSTNESS OF DRUG SAFETY MONITORING RESULTS

Prepared by: Joshua J. Gagne, PharmD, ScD,[1] Shirley V. Wang, PhD,[1] Matthew Fox, PhD,[2] Timothy Lash, PhD,[3] Wesley Eddings, PhD,[1] Sascha Dublin, MD, PhD,[4] Tobias Gerhard, PhD,[5] Bruce Psaty, MD, PhD,[6] Judy Maro, PhD,[7] Catherine Rogers, MPH,[7] Rita Ouellet-Hellstrom, PhD, MPH,[8] Simone Pinheiro, ScD, MSc,[8] Mark Levenson, PhD,[9] Richard Forshee,[10] Azadeh Shoaibi, PhD, MS, MHS,[11] Sebastian Schneeweiss, MD, ScD[1]

http://mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Analytical-Methods-to-Assess-Robustness-of-Drug-Safety-Monitoring-Results.pdf

Sentinel QBA: Example

- What is the risk of angioedema for new lisinopril users compared to new beta-blocker users?
- No prior use of lisinopril or ACE inhibitors or beta-blockers in prior 183 days for either group
- Single code ICD-9 995.1 recorded any position, IP or OP or ER
- Censoring: discontinuation of medication, death, disenrollment
- Database: large commercial insurer 2008-2013

	Lisinopril	Beta-blockers
Angioedema	664	276
No angioedema	230856	231244
Total	231520	231520

Sentinel QBA: Example

- Initial analyses (not corrected for bias): propensity score matching
- Propensity score adjusted for: Age, prior allergic reaction, diabetes, ischemic heart disease, prescription NSAIDs
- Unadjusted results: RR=2.4 (95%CI 2.1-2.8) and 2.3 (95%CI 1.9-2.8) from a Cox PH model

Sentinel QBA: Example, "front-end" sensitivity analyses

Table 2. Results from three "front end" sensitivity analyses varying parameters from primary analysis

Scenario	Description	HR (95% CI)
Reference	Primary analysis	2.32 (1.94 to 2.79)
1	Additional confounding adjustment with empirical variables identified hdPS	2.49 (2.05 to 3.02)
2	Extend new users washout and covariate assessment windows to 365 days	2.62 (2.13 to 3.21)
3	Change in risk window to first 30 days following initial exposure	2.98 (2.25 to 3.95)
4	1 and 2 above simultaneously	2.52 (2.06 to 3.14)
5	1 and 3 above simultaneously	3.50 (2.59 to 4.75)

hdPS, high-dimensional propensity score; HR, hazard ratio; CI, confidence interval

- QBA adjusted values range from 2.5 to 3.5 (unadjusted was 2.3)
- Note: hdPS was a method to identify "likely" confounders

Sentinel QBA: Example, "back-end" sensitivity analyses

Table 3. Results of quantitative bias analysis correcting for outcome misclassification (Reference Risk Ratio, 2.41)

Scenario	Assumed specificity	Assumed sensitivity	Corrected risk ratio
1	0.999777494	0.2	2.73
2	0.999777494	0.4	2.73
3	0.999777494	0.6	2.73
4	0.999777494	0.8	2.73
5	0.999777494	1.0	2.73
6	0.999891798	0.2	2.55
7	0.999891798	0.4	2.55
8	0.999891798	0.6	2.55
9	0.999891798	0.8	2.55
10	0.999891798	1.0	2.55
11	1.0	0.8	2.41
12	0.99	1.0	0.81

- Doesn't matter what the sensitivity is, only specificity is important
- RR generally underestimated without adjustment

Section 4

Misclassification bias

Misclassification bias

- An example of more sophisticated techniques.
- Misclassification bias occurs when some exposed subjects are labeled non-exposed and vice versa, and the misclassification is related to the outcome.
- SIMEX (simulation and extrapolation) method adjusts the odds ratio (OR) by resampling according to the estimated sensitivity and/or specificity

Cook JR, Stefanski LA (1994). Simulation-extrapolation estimation in parametric measurement error models.

Journal of American Statistical Association, 89, 1314-28

Misclassification bias: example

- In heart failure patients, what is the risk of 30-day hospitalization for patients with stroke compared to patients without stroke at baseline?
- One algorithm to identify stroke in claims data has a validated sensitivity = 82% and specificity = 93%

Tirschwell, D. L. and W. T. Longstreth (2002). "Validating Administrative Data in Stroke Research." Stroke 33(10): 2465-70.

Misclassification bias: example

- Install library
- Read in data
- Look at first 5 rows:

```
> library(simex)
> hf = read.table(file="Y:/hfdata.2011.2012.csv",sep=",", header=T)
> hf[1:5,]
  hf.ENROLID hf.comorb.STRK hf.Hosp30day.allcause
   875931501      No stroke                     1
  2060826701      No stroke                     0
 27457582701      No stroke                     0
 28419528901      No stroke                     0
 28096163501         Stroke                     0
```

Misclassification bias: example

- Build logistic regression model ("naive"/not adjusted for bias)
- OR=$\exp(0.385) = 1.5$

```
> nave = glm(Hosp30day.allcause~ comorb.STRK,family= binomial,data =hf, x=TRUE, y=TRUE)
> summary(naive)

Coefficients:
                   Estimate Std. Error z value Pr(>|z|)
(Intercept)       -2.530062   0.005359 -472.14   <2e-16 ***
comorb.STRKStroke  0.385192   0.018181   21.19   <2e-16 ***
```

Misclassification bias: example

- Enter sensitivity (82%) and specificity (93%)

```
> mc = matrix(c(0.93,0.07,0.18,0.82),nrow=2)
> mc
          No stroke Stroke
No stroke      0.93   0.18
Stroke         0.07   0.82
```

Misclassification bias: example

- Use SIMEX to correct for bias
- Corrected OR=$\exp(0.71) = 2.0$

```
> mod.strk = mcsimex(naive, mc.matrix = mc, SIMEXvariable = comorb.STRK, B=100)
> mod.strk

Jackknife variance:
                   Estimate Std. Error t value Pr(>|t|)
(Intercept)       -2.536858   0.005499 -461.36   <2e-16 ***
comorb.STRKStroke  0.712671   0.027697   25.73   <2e-16 ***
```