Bias and Misclassification in Birth Defects Epidemiology

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What is Bias?

- Definitions from Merriam-Webster:

  - ✓ a tendency to believe that some people, ideas, etc., are better than others that usually results in treating some people unfairly
  - ✓ a strong interest in something or ability to do something
  - ✓ a line diagonal to the grain of a fabric; *especially* a line at a 45 degree angle to the selvage often utilized in the cutting of garments for smoother fit
  - ✓ a peculiarity in the shape of a bowl that causes it to swerve when rolled on the green in lawn bowling

- Obviously, the editors of the Merriam-Webster dictionary are not epidemiologists.

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Epidemiologic Definitions of Bias

- But wait, Merriam-Webster does have an epidemiologic definition of a sort
  - ✓ deviation of the expected value of a statistical estimate from the quantity it estimates
  - ✓ systematic error introduced into sampling or testing by selecting or encouraging one outcome or answer over others
- Or from an epidemiology textbook
  - ✓ Bias may be defined as any systematic error in an epidemiological study that results in an incorrect estimate of the true effect of an exposure on the outcome of interest. (Hennekens and Buring 1987)

What is Misclassification?

- In epidemiology, practitioners love to call the same thing by many names.
- Information bias refers to bias due to measurement error.
- However, information bias is also referred to by some as observational basis or as misclassification.
- From *The Dictionary of Epidemiology* (5th Ed, 2008)

  Information bias: 1. A flaw in measuring exposure, covariate, or outcome variables that results in different quality (accuracy) of information between comparison groups. The occurrence of information biases may not be independent of the occurrence of selection biases 2. Bias in an estimate arising from measurement errors."

Misclassification

- Thus, misclassification refers to measurement error.
- There are two types of measurement error:
  - ✓ Nondifferential misclassification
  - ✓ Differential misclassification

Nondifferential misclassification

- Occurs when all classes, groups, etc of observations in the study have the same error rate or probability of being misclassified.
- Conventional wisdom suggests that in the case of a dichotomous outcome, nondifferential misclassification results in an underestimation of the true association between exposure and outcome.
- This assertion has recently been challenged, but most epidemiologists tend to feel that this is the case. (Jurek et al, IJE 2004)

Differential Misclassification

- This occurs when the error rate or likelihood that an observation is misclassified differs across groups of study subjects.
- This is a not uncommon situation, in fact in most cases it is best for the epidemiologist to assume it is the case unless proven otherwise.
- Effects of differential misclassification can vary from overestimation to underestimation of the true effect. This cannot be determined without some form of sensitivity analysis.

How Likely Is Measurement Error?

- Birth defects surveillance data, and the linked vital statistics data we utilize for population-based birth defects epidemiology, are subject to measurement error.
- We can have under or over ascertainment of specific birth defects, leading to outcome measurement error.
- Many variables on birth certificates are potentially affected by exposure measurement error.

Evaluating the Value of Secondary Data

- Completeness of registration of individuals
  - ✓ Comparing data set with one or more independent sources
  - ✓ Comprehensive records review
  - ✓ Aggregated methods
- **Accuracy and degree of completeness of variables**
  - ✓ Precision
  - ✓ Validity
- Size of data sources
- Registration period
- Data accessibility, availability, and cost
- Data format

Limitations of FBDR Data

- Only includes live births
- Until 2006, AHCA inpatient discharge data limited to only 10 ICD-9-CM diagnosis codes and 10 procedure codes
- Until October 2009, a single ICD-9-CM code was used to describe different malformations: (i.e. 756.79 used cover both gastroschisis/omphalocele)
- Source data sets (AHCA and CMS) must be matched to a birth certificate, relies on linkage process and accuracy of data
- **Dependent on how the condition is noted in the medical record, interpreted by the medical coder, and how it is entered into the hospital information system**

No confirmation of diagnosis

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*Data Quality Assurance**

- **Desired outcome** → Diagnoses of birth defects in FBDR
  - ✓ Think about Down syndrome…
  - ✓ False positives, false negatives (misclassification)

- The Registry has other surveillance projects in limited geographic areas on a limited # of defects
  - ✓ "Confirmation" of defects using **medical record review**
  - ✓ Is this enough? What if medical record is wrong, what if there are not **additional confirmatory elements** (i.e. karyotyping)?

- Many datasets may not offer the opportunity to evaluate data quality. May need to rely on internal validation and reliability studies, if there are any.

Understand Misclassification

- When analyzing any secondary dataset, you **must understand and be able to explain biases**, including misclassification (of exposure, outcome, etc)

- Can you assess the extent of misclassification?

- Can you assess the type of misclassification?
  - ✓ Non-differential (random)
  - ✓ Differential

- It is vital to **explain plausible alternative explanations for your findings**, not only on the possibility, but the magnitude of the effect on your measure(s) of association

Potential Impact of Misclassification

- You want to test a hypothesis stating that **foreign-born** women are at **lower** risk of having an infant with **spina bifida**…

- The **truth** (which you do not know) is as follows:

	Affected	Unaffected	TOTAL
Foreign-born	50	80	130
U.S.-born	50	20	70
TOTAL	100	100	200

OR (true) = 0.25

Non-Differential Misclassification (of disease)

- I've mentioned that a passive registry such as the FBDR may suffer from **under-ascertainment** of birth defects.
- Imagine that there is a **global** 10% under-ascertainment in infants of ***both*** foreign-born and U.S.-born women.

- What would you observe?

	Affected	Unaffected	TOTAL
Foreign-born	45 →	85	130
U.S.-born	45 →	25	70
TOTAL	90	110	200

OR (observed) = 0.29

always towards the null

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Differential Misclassification (of disease)

- However, due to the often large disparity in information available for record linkage between these groups
- The overall 10% under-ascertainment we observe is **not uniform**, rather is 40% for foreign-born and 6% for U.S.-born women.

- What would you observe this time?

	Affected	Unaffected	TOTAL
Foreign-born	30 →	100	130
U.S.-born	47 →	23	70
TOTAL	77	123	200

OR (observed) = 0.14

Overestimation

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Birth Defects Research (Part A) 85:890–896 (2009)

Maternal Nativity as a Risk Factor for Gastroschisis: A Population-Based Study

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Received 14 April 2009; Revised 3 June 2009; Accepted 5 June 2009

BACKGROUND: The prevalence of gastroschisis is increasing in many parts of the world, although the etiol-

bias that "selects" women in better health before conception (Lechner and Mielck, 1998; Wingate and Alexander, 2006). Wingate and Alexander (2006) studied an internally migrant (movement only within the borders of a single nation) population of Mexican origin, and reported that women with active mobility histories had lower risks of delivering low birth weight or small-for-gestational age infants than less mobile women.

According to the weathering hypothesis, the health of certain populations deteriorates with increasing time spent living in the U.S. and accumulating socioeconomic disadvantages. It has been suggested that U.S-born Hispanics experience more weathering than foreign-born Hispanics, likely owing to greater relative deprivation for the former (Geronimus, 1992; Wildsmith, 2002). However, because younger women have the highest risk for gastroschisis, it is unlikely that the weathering hypothesis con-

represent. We had no information on length of residence in the United States, motivation for emigrating, or generation status, thus making it difficult to further clarify the relationship between maternal nativity and gastroschisis risk. Lastly, there is some evidence of under-identification of birth defects among non–native-born women, primarily owing to the FBDR's limited success in linking vital statistics birth records to hospital discharge records (birth and postbirth hospitalizations) in this population. Although this limitation is not large enough to affect our overall findings, we anticipate that it might result in a bias away from the null, thus producing a slight overestimation of the protective effects of being foreign born. Despite these limitations, our findings are based on a large, multiethnic, population-based study, thus making the results generalizable. In addition, Florida has a diverse population with a Hispanic subgroup distribution

*Aren't you **missing** something?*

- Despite researchers' best efforts, **unplanned missing data** persists as an omnipresent obstacle
- Understand your missing data
  - ✓ Extent of missingness
  - ✓ Pattern of missingness (MCAR, MAR, MNAR)
- What is driving your missingness?
- Reasons are varied, from completely related to the exposure and/or outcome of interest to pure randomness
- Consider proactive and reactive ways to prevent missingness
  - ✓ **Proactive**: MOP, training, buy-in, pretesting (you can't control with 2° data)
  - ✓ **Reactive**: Deletion, single or multiple imputation

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