

Extracting Real-World Evidence from Real-World Data

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Course Materials

All course materials can be downloaded from

https://rhubb.github.io/Deming_short_course/

This includes:

- Schedule for the tutorial
- Slides
- Reference list
- Exercises
- Data sets used in R tutorial
- R code for tutorial solutions

Tutorial Schedule

- 15:30 - 15:45 Intro to Real-World Data
- 15:45 - 16:30 Overview of EHR and claims data structure
- 16:30 - 17:00 Extracting data elements from the EHR
- 17:00 - 17:10 Break
- 17:10 - 17:40 Missing data issues
- 17:40 - 18:00 Correcting for bias due to EHR data errors
- 18:00 - 18:25 R Tutorial
- 18:25 - 18:30 Conclusions & Wrap-up

Meet the Instructors

Rebecca Hubbard

- Began my career at Kaiser Permanente Washington Health Research Institute (formerly Group Health RI), a public interest research group in an integrated health care system
- This gave me a lot of exposure to the opportunities of using EHR data for research but also the messiness and limitations of the data
- Since then I have worked with many administrative healthcare databases including
 - ▶ Medicare (public payer claims)
 - ▶ Optum Insight (private payer claims)
 - ▶ Kaiser Permanente (integrated health system and health plan)
 - ▶ U Penn (health system, tertiary care)
 - ▶ Flatiron Health (pooled data from community cancer care)
 - ▶ PEDSnet (multi-site network of children's hospitals)

Meet the Instructors

Xu Shi

- I was first exposed to research on EHR data when I was a research assistant at Kaiser Permanente Washington Health Research Institute. I worked on a post-market safety surveillance project for the FDA's Sentinel Initiative.
- Currently I develop statistical methods for EHR data quality control and harmonization, and comparative effectiveness and safety research. I also co-lead the Causal Inference Core of the FDA's Sentinel Initiative Innovation Center to develop innovative statistical methods to monitor the safety of FDA-regulated medical products and explore novel ways to utilize information from distributed EHR data partners.
- I also taught a graduate-level course on analysis of EHR data (slides are available at <http://www.xuritashi.com/teaching.html>)

EHR and the Real World

- EHR are one of the first “Real World Data” sources statisticians have gotten their hands dirty with
- The size of these data sets suggests enormous potential for learning about health and healthcare in real world settings.
 - ▶ Worldwide digital healthcare data is expected to reach 25 exabytes (10^{18} bytes) in 2020.
- But... with big data comes big responsibility
- That is, more data, more problems

Electronic Health Records

Definition

“An *Electronic Health Record (EHR)* is an electronic version of a patient’s medical history, that is maintained by the provider over time, and may include all of the **key administrative clinical data** relevant to that persons care under a particular provider, including **demographics, progress notes, problems, medications, vital signs, past medical history, immunizations, laboratory data and radiology reports.**”

– Centers for Medicare and Medicaid Services

Where do EHR data come from?

- Records from a single medical practice
- Records from a healthcare system including multiple practices
- Records from an integrated healthcare system including clinical data and claims
- Pooled data from multiple healthcare systems
- Regional or national databases in areas with a unified health system
- Claims data?
 - ▶ Medicare and Medicaid claims
 - ▶ Multi-payer claims databases

Objectives

- The objective of this short course is to present an overview of some of the practical challenges that arise in the analysis of EHR data and some methods to address them
- Focus is on **data structure and quality** particularly as they impact validity of research results
- Describe **strengths and limitations** of EHR data for research purposes
- Present **alternative statistical methods** to address challenges encountered in EHR data

Outline

FDA Framework for Real World Evidence

Overview of the structure of EHR data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Conclusions

- The 21st Century Cures Act was designed to accelerate medical product development
- This included identifying ways to use RWE to approve a new indication for a drug or satisfy post-approval study requirements
- RWD (principally EHR and medical claims data) can be used in many ways in medical product development
 - ▶ Hypothesis generation
 - ▶ Identifying novel risk factors
 - ▶ Assessing trial feasibility
 - ▶ Defining inclusion/exclusion criteria and baseline characteristics
 - ▶ Informing prior probability distributions for Bayesian models
 - ▶ Assembling geographically distributed research cohorts for rare diseases
 - ▶ Generating evidence on product safety
 - ▶ **Generating evidence on product effectiveness**

Using RWD for post-marketing safety surveillance

- EHR data have been used for some time to support post-marketing safety surveillance
- FDA's Sentinel System consist of 18 data partners (integrated healthcare systems and claims databases) including over 100 million patients
- Sentinel is a distributed network
 - ▶ Data are held locally by each partner using a common data model
 - ▶ Queries are developed to investigate safety signals
 - ▶ Query is run locally against each site's data
 - ▶ Results are pooled at a central coordinating center

Using RWD to generate evidence on effectiveness

- Establishing evidence of effectiveness using EHR data is more challenging
- Observational studies typically have too many sources of potential bias to be relied upon in the regulatory process, confounding by indication particularly problematic
- Pragmatic clinical trials embedded in healthcare systems can be used
- In rare cases, FDA has approved a new product based on historical control arm data from EHR
 - ▶ Only applies in oncology or rare disease settings where randomization is considered unethical or infeasible

Potential uses of RWD in effectiveness studies

- Facilitate pragmatic trials/large simple trials embedded in healthcare systems
- External control arm for a single arm trial
- Additional control data (hybrid control arm) for an RCT
- Observational comparative effectiveness analyses

Challenges to validity of RWE from a regulatory perspective

- Lack of alignment of trial and RWD inclusions/exclusion criteria
- Lack of alignment of trial and RWD definitions for key data elements (treatments, outcomes, confounders, etc)
- Lack of capture of endpoints
- Missing data
- Channeling bias and confounding

FDA considerations for use of RWD

- Are the data fit for use?
 - ▶ Consideration of data quality issues
 - ▶ Missing data due to porosity of EHR
- Is the study design adequate to provide evidence?
 - ▶ Sources of bias
- Does the study conduct meet FDA regulatory requirements?
 - ▶ Study monitoring
 - ▶ Data integrity

Framework for FDA's Real-World Evidence Program

<https://www.fda.gov/media/120060/download>

FDA Draft Guidance on Considerations for Using Real-World Data

<https://www.fda.gov/media/152503/download>

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What are the advantages of using EHR data for research?

- No need for patient recruitment or data collection
- Large sample size
- Diverse population
- Generalizability
- Potential for multi-site studies
- Cheap and “easy” access

What are the disadvantages of using EHR data for research?

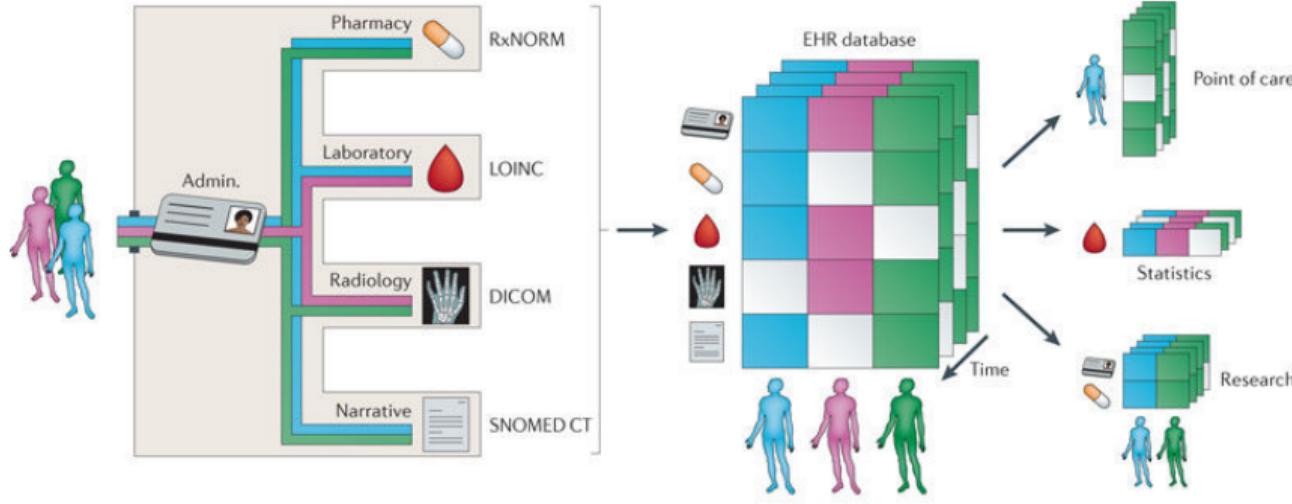
- Data quality may be poor (quantity vs quality tradeoff)
- Data collection is not systematic leading to complex missing data patterns
- Extracting data from text notes is challenging and error-prone
- Privacy protections (HIPAA) limit what data can be accessed and by whom

Dimensions of data quality

- **Completeness:** Is a truth about a patient present in the EHR?
- **Correctness:** Is an element that is present in the EHR true?
- **Concordance:** Is there agreement between elements in the EHR, or between the EHR and another data source?
- **Plausibility:** Does an element in the EHR make sense in light of other knowledge about what that element is measuring?
- **Currency:** Is an element in the EHR a relevant representation of the patient state at a given point in time?

Weiskopf NG, Weng C. Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research. *Journal of the American Medical Informatics Association*. 2013;20(1):144-51.

Schematic of EHR data structure



Nature Reviews | Genetics

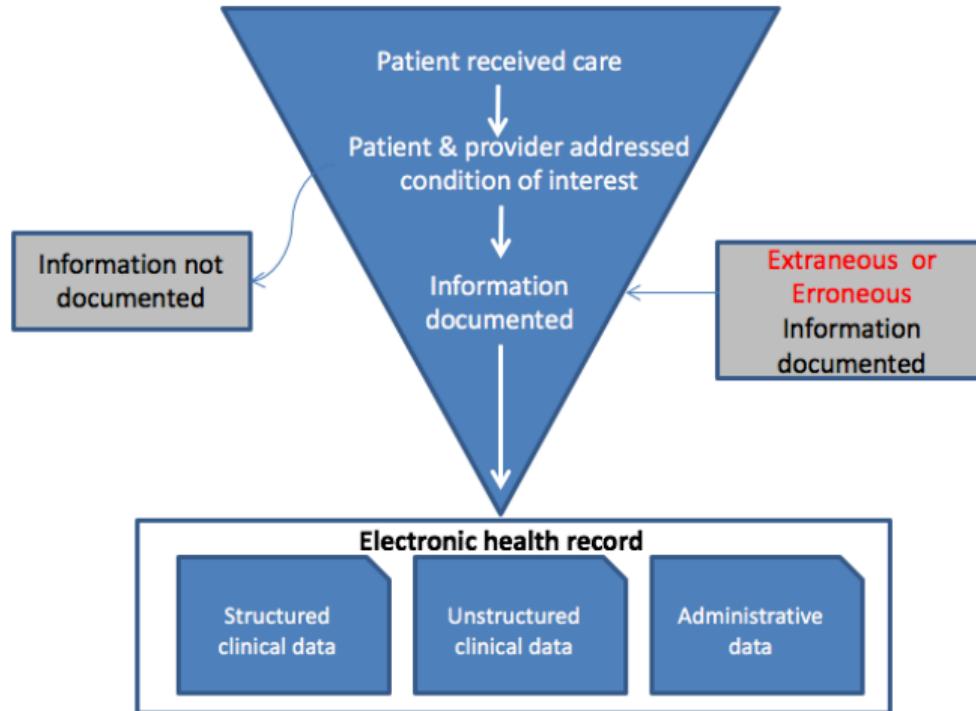
Jensen PB, Jensen LJ, Brunak S. Mining electronic health records: towards better research applications and clinical care. *Nature Reviews Genetics*. 2012;13(6):395-405.

From healthcare data to research data



- Conversion from raw healthcare data to raw research format is critical prior to analysis
- Typically need to work with a programmer or analyst with rights to access raw data, usually embedded in healthcare operations
- Refining research data prior to analysis limits volume of data, applies standardization to data elements, and reduces risks to privacy and confidentiality
- Adhere to “minimum necessary” rule
- When possible use de-identified data (no direct identifiers or HIPAA identifiers)

EHR data provenance



Structured data

- Many types of EHR data are available in *structured* form
- Structured data are standardized, pre-defined, computer readable data elements coded using a closed vocabulary
- For instance, procedure codes provide information on the specific health care procedures a patient has undergone
- Structured data are particularly useful for research because they can be readily manipulated and analyzed using statistical software
- They can also be combined across multiple healthcare systems using the same coding conventions.

Some common data formats

- **Diagnosis codes** - ICD-9/10, SNOMED, issues with rule-outs, ICD-9 to ICD-10 conversion issues (many-to-many mapping, discontinuity in temporal trends spanning switch-over date of 10/1/2015)
- **Procedure codes** - CPT/HCPCS (outpatient), DRG (inpatient), date of administration vs discharge vs test performed vs results
- **Medication codes** - NDC, RxNorm, “homegrown codes”, data for prescriptions (may not be filled or taken) vs dispensings (may not be taken), does not capture OTC use

U.S. Core Data for Interoperability (USCDI)

- Recently adopted (June 2020) standards requiring all EHR systems to adopt common, core data elements
- USCDI incorporates existing standard formats such as RxNorm, SNOMED, and LOINC
- NIH encourages researchers to leverage USCDI standard data elements
- Should lead to greater consistency and easier pooling of data from multiple EHRs

Unstructured data

- Unstructured data consists of health care providers' narrative clinical notes
- Takes the form of text which typically requires a human reader to understand and interpret
- The Health Story Project estimates that 1.2 billion clinical documents are produced in the US each year, of which 60% are in the form of unstructured notes
- Many data elements potentially of interest for research such as family history and patient behavioral risk factors may be embedded in text notes
- Extracting these data for research use is a challenge

Natural Language Processing

- Manually abstracting data from clinical notes is typically too labor intensive for large EHR-based studies which may include millions of patients
- Natural Language Processing (NLP) uses computerized algorithms to identify data elements of interest embedded in text notes
- NLP processes unstructured data (e.g., text notes) to identify “concepts” related to the factor of interest
- Standardized databases of health terminology such as the Unified Medical Language System link individual terms to unique biomedical concepts

Natural Language Processing in R

- *Text Mining with R* available online at tidytextmining.com
- tm package includes more advanced tools for processing and manipulating text
 - ▶ Meyer D, Hornik K, Feinerer I. 2008. Text mining infrastructure in R. *Journal of Statistical Software*. 25(5):1-54.
 - ▶ Vignette available in package

Summary of EHR data

| | ICD codes | CPT codes | Laboratory Data | Medication records | Clinical Documentation |
|------------------------------------|--|--|--|--|--|
| Availability in EHR systems | Near-universal | Near-universal | Near-universal | Variable | Variable |
| Recall | Medium | Poor | Medium | Inpatient: High Outpatient: Variable | Medium |
| Precision | Medium | High | High | Inpatient: High Outpatient: Variable | Medium-High |
| Fragmentation effect | Medium | High | Medium-High | Medium | Low-Medium |
| Query method | Structured | Structured | Mostly structured | Structured, text queries, and NLP | NLP, text queries, and rarely structured |
| Strengths | -Easy to query -Serves as a good first pass of disease status | -Easy to query -High precision | -Value depends on test -High data validity | Can have high validity | Best record of what providers thought |
| Weaknesses | -Disease codes often used for screening when disease not actually present -Accuracy hindered by billing realities and clinic workflow | -Most susceptible to missing data errors (e.g., performed at another hospital) -Procedure receipt influenced by patient and payer factors external to disease process | -May need to aggregate different variations of the same data elements -Normal ranges and units may change over time | -Often need to interface inpatient and outpatient records -Medication records from outside providers not present -Medications prescribed not necessarily taken | -Difficult to process automatically -Interpretation accuracy depends on assessment method -May suffer from significant "cut and paste" -Not universally available in EHRs -May be self-contradictory |
| Summary | Essential first element for electronic phenotyping | Helpful addition if relevant | Helpful addition if relevant | Useful for confirmation and a marker of severity | Useful for confirming common diagnoses or for finding rare ones |

doi:10.1371/journal.pcbi.1002823.t001

Denny JC. Mining electronic health records in the genomics era. *PLoS Computational Biology*. 2012;8(12):e1002823.

PEDSnet: A multi-site network example

- PEDSnet: A PCORI-funded consortium of 8 children's hospitals
 - ▶ Includes data collected in routine clinical encounters for ~5 million children
- Investigated pediatric Type 2 Diabetes Mellitus (T2DM) in a high risk cohort:
 - ▶ Children age 10-18 years, at least two clinical encounters between 2001-2017
 - ▶ On at least one occasion BMI z-score in excess of the 95th percentile for age and sex
 - ▶ Cohort consisted of 68,265 children

PEDSnet T2DM cohort

| | Total N = 68,265 | T2DM Codes or Biomarkers | |
|-------------------------|---------------------|--------------------------|------------------|
| | | Yes N = 804 | No N = 67,461 |
| | | N (%) | N (%) |
| Male | 36836 (53.96) | 221 (27.49) | 36615 (54.28) |
| White | 35740 (52.35) | 371 (46.14) | 35369 (52.43) |
| Endocrinologist | 5338 (7.82) | 510 (63.43) | 4828 (7.16) |
| Metformin | 764 (1.12) | 675 (83.96) | 89 (0.13) |
| Insulin | 727 (1.06) | 154 (19.15) | 573 (0.85) |
| T2DM Codes | 275 (0.4) | 221 (27.49) | 54 (0.08) |
| Any glucose measurement | 11325 (16.59) | 355 (44.15) | 10970 (16.26) |
| Any HbA1c measurement | 6031 (8.83) | 397 (49.38) | 5634 (8.35) |
| | Mean (SD) | Mean (SD) | Mean (SD) |
| Age | 11.90 (2.50) | 13.79 (2.58) | 11.87 (2.49) |
| BMI z-score | 2.02 (0.30) | 2.27 (0.36) | 2.012 (0.30) |
| Glucose | 94.309 (32.51) | 141.39 (104.47) | 92.79 (27.44) |
| Hemoglobin A1c | 5.79 (1.25) | 6.93 (1.94) | 5.71 (1.15) |

Fit for Use

- “Fit for use” means that the data should be of appropriate quality for the use we intend to put them to.
- Almost all data sources are imperfect in one respect or another.
- The relevant question is whether they are good enough for the purposes we intend to use them for.
- For example, if we are interested in studying the association between practicing yoga and blood pressure, EHR data are probably not fit for this use.
 - ▶ No structured data elements capture practice of yoga
 - ▶ Text notes are unlikely to systematically records yoga

- On the other hand, if we want to study rates of uptake of HPV testing for cervical cancer screening EHR data may be fit for this use.
 - ▶ Procedure codes capture HPV testing
 - ▶ Since a procedure code must be recorded in order for the provider to be reimbursed capture is likely to be relatively complete
- As we discuss EHR data and its analysis it is important to keep in mind that the relevance of a given issue will depend on the specific research question and the data needed to answer that question.

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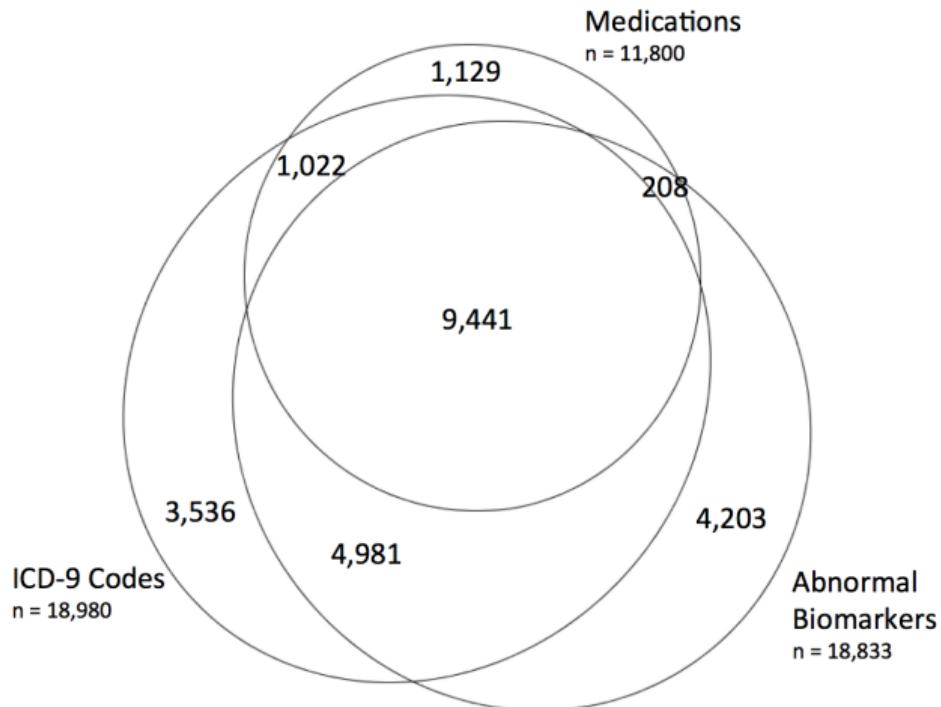
Rule-based Phenotyping

- Most of the existing literature on EHR-derived phenotyping relies on “clinical decision rules”
 - ▶ Simple or complex
 - ▶ Including one data element or many
 - ▶ May include a time component
- Algorithm based on clinical knowledge of the disease and coding practices
- May incorporate structured data as well as unstructured data, often via NLP
- Sometimes validated against gold-standard diagnosis data

Example: Rule-based Phenotyping for T2DM

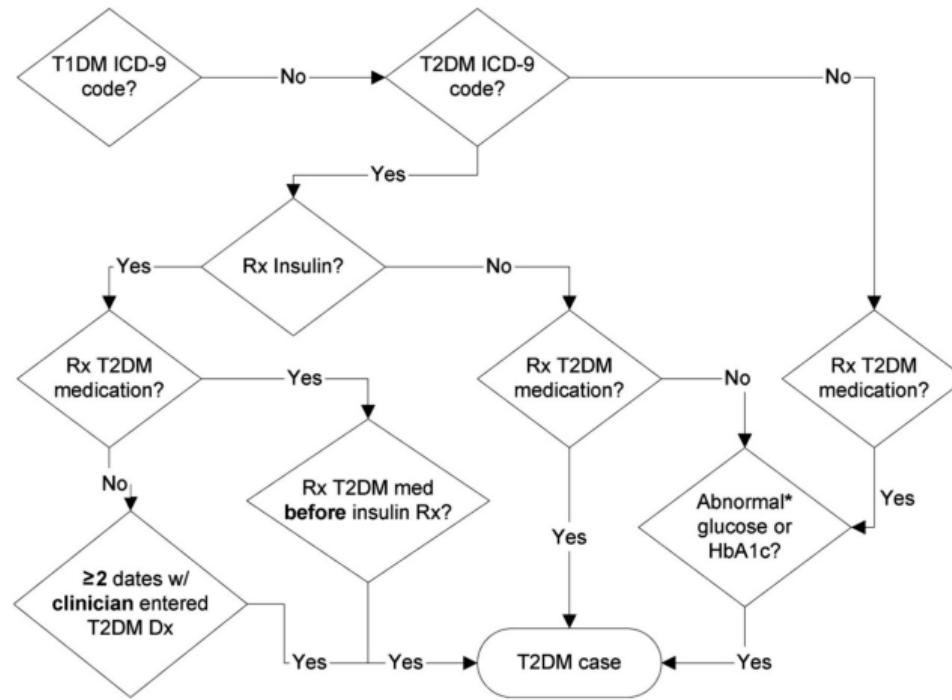
| Variable type | Examples | Format |
|--------------------|--|--|
| Diabetes diagnosis | <ul style="list-style-type: none">• T2DM• T1DM• DM NOS | ICD-9/10 codes |
| Medications | <ul style="list-style-type: none">• Insulin• Metformin | Prescribing data |
| Co-morbidities | <ul style="list-style-type: none">• PCOS• Obesity | ICD-9/10 codes |
| Biomarkers | <ul style="list-style-type: none">• Glucose• HbA1c | Procedure codes for test administration; numerical results |

Agreement among T2DM variables



Adapted from Richesson et al. *J Am Med Inform Assoc* 2013;20:e319-e326.

Example: T2DM Rule



Kho et al. J Am Med Inform Assoc 2012;19:212-218

Typical process for EHR-based phenotype development

- Clinical experts develop a list of potential variables
 - ▶ May include condition of interest, symptoms, co-morbidities, common treatments
- Translate list into corresponding structured codes (e.g., ICD-9/10, CPT)
- NLP experts map terms to UMLS concepts
- Extract all occurrences of demographics, codes of interest, biometric data, and laboratory test results from structured data
- Apply NLP to unstructured (narrative text) data

PEDSnet Example

| age | race | zBMI | HbA1c | Glucose | T2DM | FamHx | Endo |
|-----|------|----------|----------|-----------|------|-------|------|
| 11 | 0 | 1.658355 | NA | NA | 0 | 0 | 0 |
| 12 | 0 | 1.996588 | NA | 119.54555 | 0 | 0 | 0 |
| 14 | 1 | 2.057993 | 5.949531 | 98.69711 | 0 | 0 | 0 |
| 18 | 0 | 2.508225 | 5.137229 | 82.54253 | 0 | 0 | 0 |
| 11 | 1 | 1.820784 | NA | NA | 1 | 0 | 0 |
| 17 | 1 | 2.547955 | 5.622635 | 85.22707 | 0 | 0 | 0 |

Classification

- Once data have been extracted from the EHR a classification algorithm can be applied to the individual data elements to create a construct of interest
- Gold standard information for supervised learning approaches extracted via manual chart abstraction
- Classification approaches applied to EHR data range from the very simple to the very complex
 - Dichotomous classification based on presence/absence of data elements based on clinical judgment
 - Prediction modeling, e.g. CART, LASSO
 - Machine learning algorithms, e.g. random forests, neural networks
- Performance is typically evaluated based on PPV and NPV relative to gold standard
- Implications of low prevalence for PPV/NPV

Using validated phenotypes

- Ideally, only validated phenotypes should be used
- Validation requires manual chart abstraction and hence can be costly and slow
- Many validated phenotypes are available, for instance, via PheKb (<https://phekb.org>)
- However, be cautious about assuming that operating characteristics will be the same in your data set as they were in the derivation data set (i.e., lack of portability)

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Missing data in EHR

- Because EHR data are not collected according to a research protocol they will often be missing variables of interest
- While missing data are virtually ubiquitous in EHR-based studies, a critical first step to dealing with missingness is consideration of what constitutes a “complete” record
- Unlike a designed observational study, there is no prior specification of which data elements should be collected for a patient or when they should be collected
- Before we can quantify the magnitude of the missing data problem for a given study we need to define the data we wish to have
- Often useful to consider the data that we would have collected had we designed a study protocol and collected the data ourselves

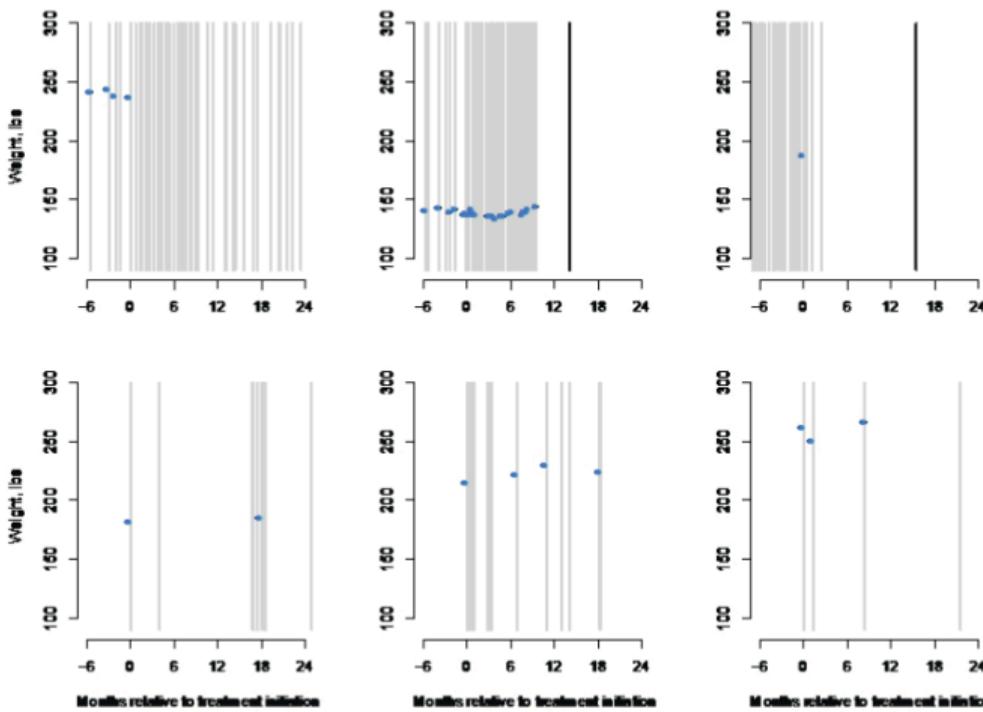
PEDSnet Example

- Objective: Study risk factors for T2DM in children
- Longitudinal study of time to T2DM diagnosis
- Covariates:
 - ▶ Time-varying measures of BMI, physical activity, diet, co-morbidities
 - ▶ Age at diagnosis of T2DM
- If this is our desired study objective and design, which of these data elements can be derived from the EHR and how much missingness will they have?

PEDSnet Example

- Patients assessed irregularly; must decide on a frequency of observation for BMI that is “good enough”
- Behavioral risk factors rarely collected, not in structured data; may be able to extract from notes with NLP but will be frequently missing
- Age at diagnosis determined based on application of a phenotyping algorithm; depending on algorithm may be missing for patients with missing biomarker data or infrequent clinical assessment

BMI data collection

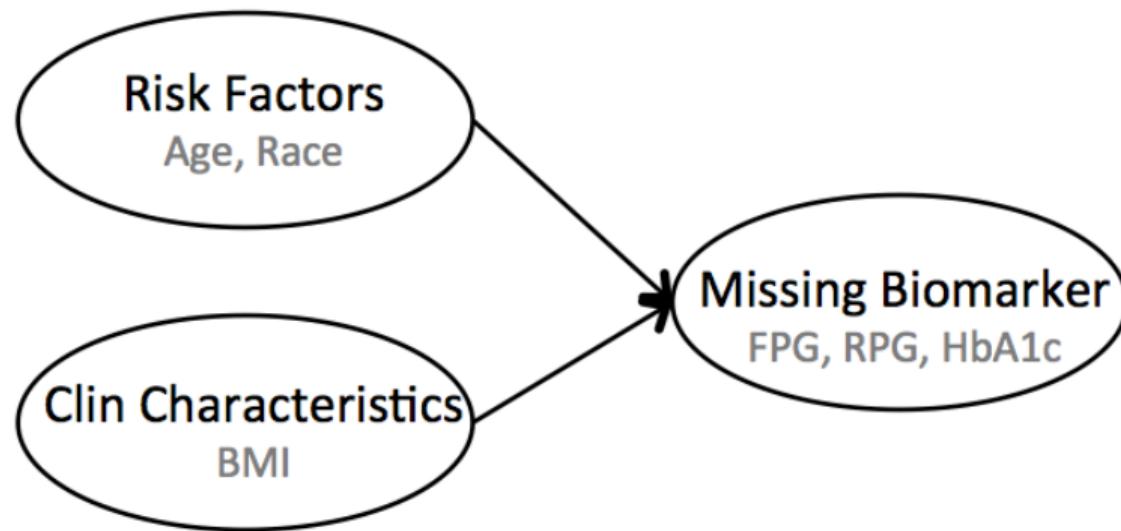


Haneuse and Daniels. 2016. eGEMS 4(1):16.

Missingness mechanisms

- Once we have decided on which data we need for our study we can evaluate missingness
- Next step is to consider causes of missing data
- Haneuse and Daniels recommend thinking about why data are *observed* rather than why data are missing
- Missingness mechanism will likely reflect interplay of patient risk factors and disease conditions, patient behavior, provider clinical practices, and healthcare system administrative practices (**data provenance**)

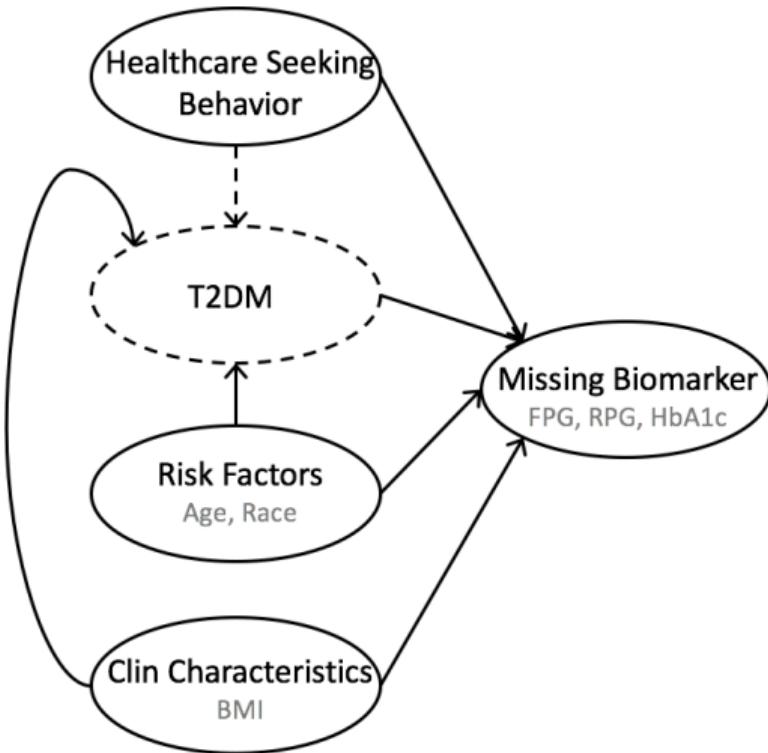
MAR missingness mechanism



- Patients with risk factors for T2DM more likely to be screened
- Risk factors more strongly associated with missingness for more definitive biomarkers (FPG, HbA1c)

MNAR missingness mechanism

- Missingness likely depends on underlying T2DM status directly
- Risk factors may influence missingness through T2DM (symptoms) or directly (screening)
- Patients' interaction with the healthcare system also affects observation process

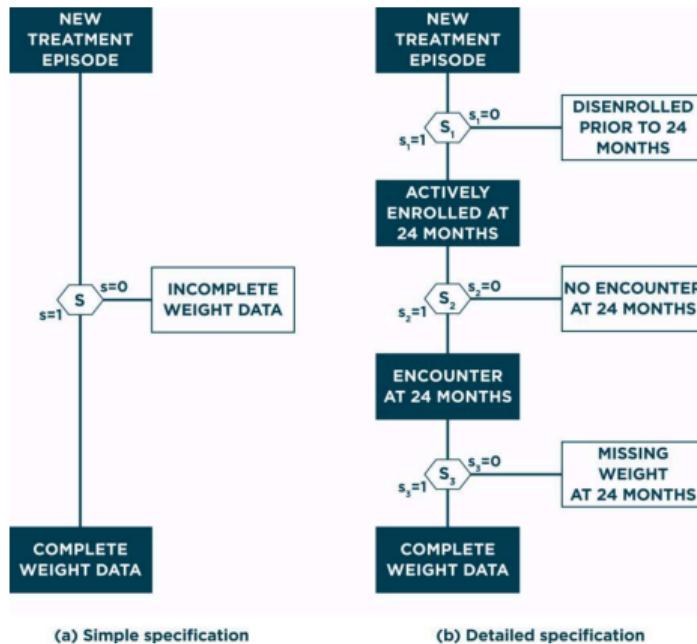


PEDSnet example: Missingness in glucose

| | OR | 95% CI | p |
|-------------------------|------|--------------|--------|
| Age at baseline (years) | 0.89 | (0.88, 0.90) | <0.001 |
| Baseline year | 1.02 | (1.02, 1.03) | <0.001 |
| Male | 1.14 | (1.09, 1.19) | <0.001 |
| Race | | | |
| Black | 0.83 | (0.79, 0.87) | <0.001 |
| Native American | 0.60 | (0.33, 1.11) | 0.106 |
| Asian | 0.90 | (0.75, 1.08) | 0.280 |
| Other | 0.57 | (0.52, 0.62) | <0.001 |
| Unknown | 1.39 | (1.25, 1.54) | <0.001 |
| Ethnicity | | | |
| Hispanic | 0.81 | (0.75, 0.88) | <0.001 |
| Endocrinologist visit | 0.23 | (0.21, 0.24) | <0.001 |
| Metformin | 0.30 | (0.26, 0.35) | <0.001 |
| Insulin | 1.10 | (0.86, 1.40) | 0.454 |
| BMI | 0.69 | (0.66, 0.73) | <0.001 |
| T1D codes | 0.91 | (0.73, 1.14) | 0.404 |
| T2D codes | 0.59 | (0.45, 0.77) | <0.001 |

Missingness modules

- Considering missingness mechanism as a series of conditional steps may help in assessment of MAR assumption (Haneuse & Daniels, 2016)



Analysis strategies in the presence of missingness

- Under MAR mechanisms can use multiple imputation (MI) or inverse probability weighting (IPW)
- Many software packages available for implementation
- In Multivariate Imputation via Chained Equations (MICE) a separate regression model is specified for each variable with missing observations
- Missing data in each variable are sequentially filled in and subsequently used in regression models for other variables
- This process is iterated until parameter estimates are stable
- Predictions are then generated from the final set of models for all missing observations

- MICE is convenient for use with EHR data because regression models for each variable can allow for different variable types and can include different predictors
- However, the process of model specification can be quite laborious
- Additionally, MICE is somewhat ad hoc in that the set of conditional models for each variable may not correspond to a joint model for all variables
- Computationally intensive for large EHR samples
- Available in many software packages including the `mice` package for R

Loss to follow-up in EHR

- A challenging aspect of longitudinal studies using EHR is that we may not know when patients have left the healthcare system
- Claims databases provide an indicator of enrollment that can be used to censor patients who disenroll
- A variety of ad hoc approaches have been proposed including
 - ▶ Censoring patients at a fixed timepoint (e.g. 1 year) after last clinical encounter
 - ▶ Restrict cohort to patients with some level of interaction with healthcare system (Lin KJ, et al. Identifying patients with high data completeness to improve validity of comparative effectiveness research in electronic health records data. *Clinical Pharmacology & Therapeutics*. 2018;103(5):899-905.)
- Care must be taken to avoid immortal time bias

A case study of missing outcome data

Carrigan G, et al. 2019. An evaluation of the impact of missing deaths on overall survival analyses of advanced non–small cell lung cancer patients conducted in an electronic health records database. *Pharmacoepidemiology and drug safety*. doi:10.1002/pds.4758

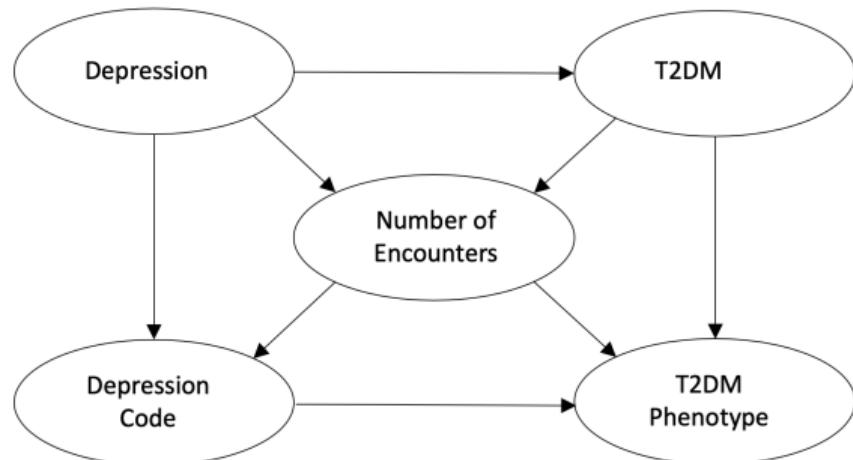
- Used data from the Flatiron Health database of community oncology centers and gold-standard death data from National Death Index to investigate effect of missing information on mortality on hazard ratio estimates
- Missing outcomes substantially inflated estimates of median survival time but had little effect on hazard ratios
- However, using EHR data as external control arm resulted in significant bias
- Implications for between-site comparisons if loss to follow-up patterns differ

Biased sampling in EHR data

- Complex observation patterns also arise in terms of the number of observations per subject in EHR data
- In EHR data, some members of the target population are more frequently observed than others
 - ▶ Co-morbidity and health outcomes: patients with co-morbidities that require regular monitoring (e.g. diabetes, kidney disease) have more frequent contact with healthcare system; capture health outcomes data more frequently and accurately
 - ▶ Screening test performance: patients experiencing symptoms of the disease of interest more likely to come in for screening tests
- If intensity of interaction with the healthcare system is related to the disease of interest, this results in an informative observation scheme, violating the assumptions of many standard statistical methods

Informative observation processes

- Intensity of healthcare utilization can be considered a marker of health
- In this case, patients with many visits may be systematically different from those with few
- One way to deal with this is to condition on number of encounters
- This has been shown to effectively account for informative observation processes in some cases, but can induce M-bias



Goldstein BA et al. Controlling for informed presence bias due to the number of health encounters in an electronic health record.
Am J Epidemiol. 2016 Dec 1;184(11):847-55.

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Issues arising in the analysis of EHR-derived phenotypes

- Regardless of the approach to phenotyping, some residual error will typically remain
- Statistical methods for misclassified outcomes can be adapted to this context
- Some additional challenges in the context of EHR-based research arise due to limited access to validation data
- Accuracy parameters for phenotypes may also exhibit lack of transportability
- We will discuss some alternative approaches to these challenges

Example: Error in EHR derived SBCE dates

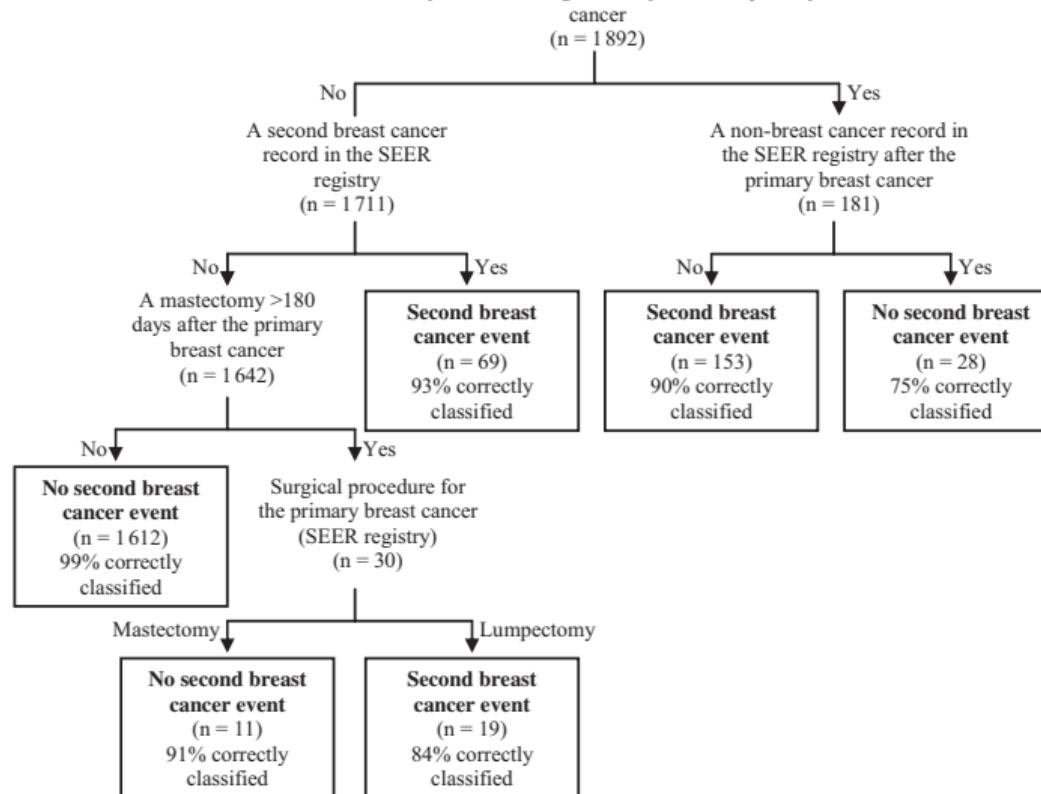
- Use of EHR data-based algorithms to identify event times may introduce error in
 - ▶ Classification as to whether or not an event occurred
 - ▶ Exact timing of event
- Example: Second breast cancer event (SBCE) in women with a history of breast cancer
 - ▶ Algorithm identifies SBCE with $Se = 89\%$, $Sp = 99\%$
 - ▶ Can algorithm be used to identify date of SBCE?
 - ▶ What are implications for estimates of exposure/outcome associations if imperfectly ascertained outcomes are used?

Second breast cancer events

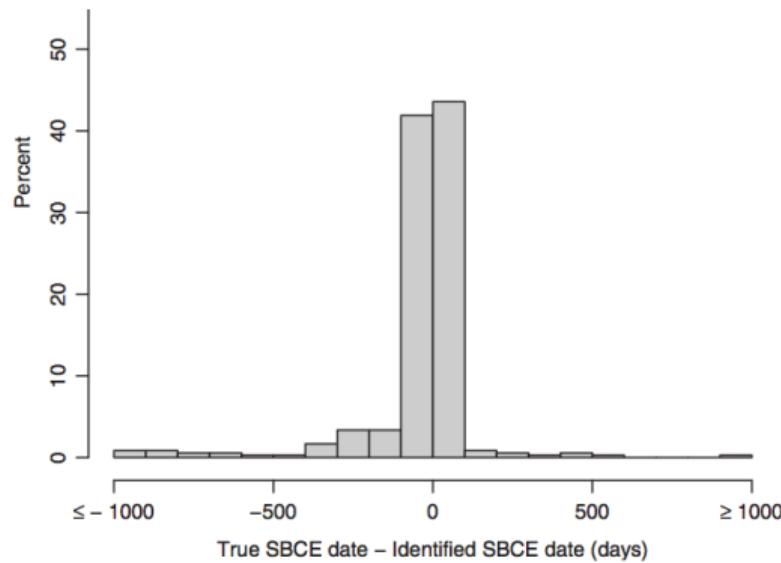
- BRAVA study developed algorithm to identify SBCEs using a combination of cancer registry and EHR data
- Validated against manual chart review
- We explored how well dates assigned based on this algorithm agreed with gold-standard
- 407 chart-reviewed SBCEs, 358 (88%) identified by algorithm

High specificity algorithm

Two visits with a code for a secondary malignant neoplasm
within 60 days and occurring >365 days after the primary breast



Error in date assignment for SBCE



- 82% of events were within 60 days of algorithm-based date
- Is this good enough?

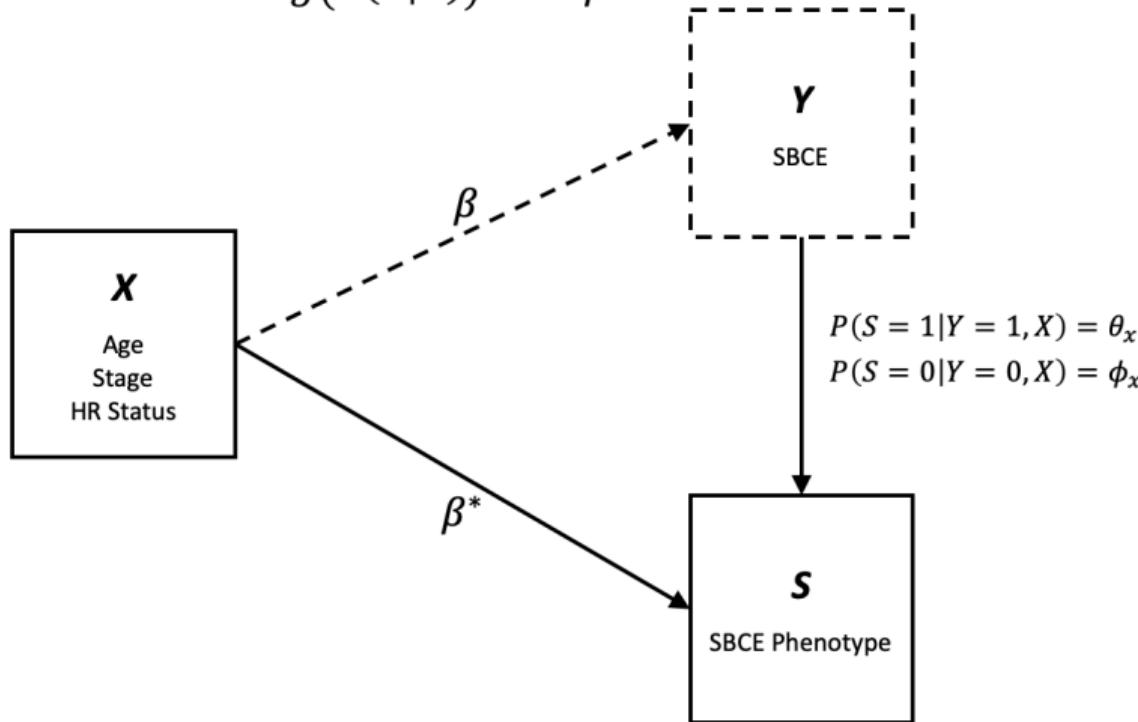
Chubak J et al. An Electronic Health Record–based Algorithm to Ascertain the Date of Second Breast Cancer Events. *Medical Care*. 2017;55(12):e81-7.

Using the EHR to study novel exposures

- EHRs provide the opportunity to identify novel risk factors for disease incidence or outcomes
- Cancer registry data collection is narrowly focused on cancer characteristics and treatment
- EHR allows us to explore a variety of novel risk factors such as treatments for other conditions and co-morbidities
- However, EHR-derived outcomes may exhibit exposure-dependent differences in data quality
 - ▶ Only observe the outcome if documented at a healthcare encounter (higher sensitivity among exposed)
 - ▶ Patients interacting with the healthcare system also have more opportunity for erroneous codes to appear in charts (lower specificity)
- If EHR is used for discovery, screening many potential risk factors, type I error is of particularly high concern

Inference with imperfect phenotypes

$$g(E(Y|X)) = X^T \beta$$



Simulation study for imperfect time to event outcomes

- Conducted a simulation study with event and error rates for dates motivated by SBCE study
- Estimated HRs using imperfectly assigned SBCE dates and compared to true HRs used to simulate data

| Sensitivity/specificity | Error in date |
|--------------------------------------|--|
| Non-differential | Non-differential |
| Non-differential | Later event detection in exposed |
| Non-differential | Earlier event detection and less variability |
| Non-differential | Later event detection and more variability |
| Higher sensitivity/lower specificity | Non-differential |
| Higher sensitivity/lower specificity | Earlier event detection and less variability |

Simulation study for imperfect time to event outcomes

| Sensitivity/specificity | Error in date | % Bias in HR |
|--------------------------------------|--|--------------|
| Non-differential | Non-differential | -2.2 |
| Non-differential | Later event detection in exposed | 0.4 |
| Non-differential | Earlier event detection and less variability | -0.9 |
| Non-differential | Later event detection and more variability | -3.8 |
| Higher sensitivity/lower specificity | Non-differential | 6.5 |
| Higher sensitivity/lower specificity | Earlier event detection and less variability | 8.1 |

Type I error due to outcome misclassification

- In addition to bias, inflated type I error rates are of high importance as they indicate the frequency of spuriously identified risk factors
- Using BRAVA data on the EHR-derived outcome and patient and cancer characteristics, we simulated an exposure variable (X) that was independent of the outcome
- Let $a_{jk} = P(S = 1 | Y = j, X = k)$ represent exposure-specific sensitivity and 1-specificity
- Simulating X from a Bernoulli distribution with probability

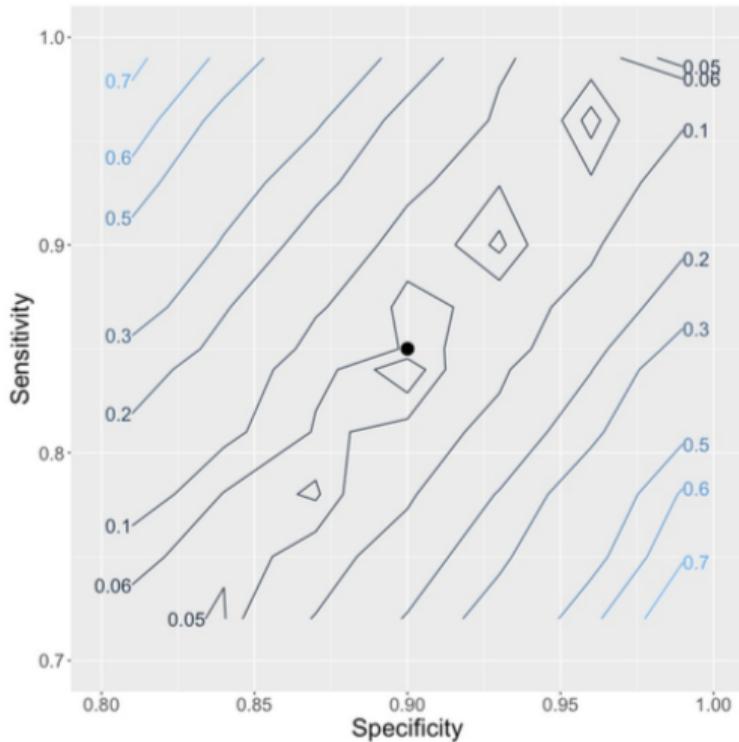
$$P(X = 1 | S = i, Y = j) = \frac{a_{j1}^i (1 - a_{j1})^{1-i} P(X = 1)}{\sum_{k=0,1} a_{jk} (1 - a_{jk}) P(X = k)}$$

induces exposure-dependent outcome misclassification

Type I error due to outcome misclassification

- We then analyzed the association between S and X using logistic regression
- We varied $a_{10} - a_{11}$ and $a_{00} - a_{01}$ (the difference in sensitivity and specificity between exposed and unexposed) across a range of values, with a_{10} fixed at 0.85 and $1 - a_{00}$ fixed at 0.9.
- Each scenario was repeated 1,000 times
- Type I error was computed as the proportion of hypothesis tests rejected at the $\alpha = 0.05$ level across the 1,000 simulations

Type I error results



- Holding specificity equal in exposed and unexposed individuals, when sensitivity was 10% higher in exposed individuals compared to unexposed (i.e., 0.95 vs 0.85) the type I error rate increased to 14%.
- Similarly, holding sensitivity equal between the two groups, a 10% decrease in specificity between exposed and unexposed individuals (i.e., 0.80 vs 0.90) resulted in a type I error rate of 33%.

Chen Y et al. *Pharmacoepidemiology & Drug Safety*. 2019 Feb;28(2):264-8.

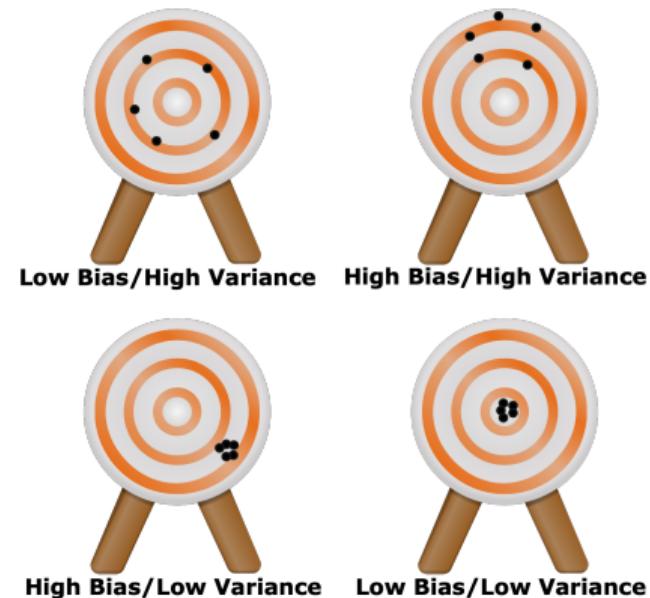
What can we do about phenotyping error?

- Phenotyping error can lead to substantial bias and inflated type I error
- How can we obtain unbiased estimates in association analyses using EHR-derived phenotypes?
- Challenges in the EHR setting
 - ▶ Validation data are costly to obtain and in many cases completely unavailable
 - ▶ Phenotyping accuracy is often unknown and may vary widely between derivation data set and other data sets

With big data comes big responsibility

- **Bias:** missing data, selection bias, measurement error and other limitations of the healthcare data create the risk of substantial bias in parameter estimates
- **Variance:** healthcare databases may include millions of records, allowing us to generate low variance estimates

Large healthcare databases create risk of generating extremely precise, biased estimates.



Classic approach to outcome misclassification

- One binary predictor (X)
- Misclassified binary outcome (S)
- Known sensitivity (θ) and specificity (ϕ); $0 < \theta, \phi < 1$
- Assumes non-differential outcome misclassification, i.e.

$$\theta = P(S = 1 | Y = 1, X) = P(S = 1 | Y = 1) \text{ and}$$

$$\phi = P(S = 0 | Y = 0, X) = P(S = 0 | Y = 0)$$

| | | Classified as | |
|---------|--------------|---------------|--------------|
| | | Diseased | Not diseased |
| Exposed | Diseased | a | b |
| | Not diseased | c | d |

Classic approach to outcome misclassification

- Naive: $\widehat{OR}_{standard} = (ad)/(bc)$
- Misclassification adjusted: $\widehat{OR} = \frac{a/(a+b)-(1-\phi)}{c/(c+d)-(1-\phi)} \times \frac{d/(c+d)-(1-\theta)}{b/(a+b)-(1-\theta)}$
- Note that

$$\begin{aligned}\widehat{OR} &> \widehat{OR}_{standard} \text{ if } \widehat{OR}_{standard} > 1 \\ \widehat{OR} &< \widehat{OR}_{standard} \text{ if } \widehat{OR}_{standard} < 1\end{aligned}$$

Magder LS, Hughes JP. 1997. Logistic regression when the outcome is measured with uncertainty. *Am J Epidemiol.* 146(2):195-203.

Extension to logistic regression

- Assume non-differential misclassification
- Let $P(Y_i = 1) = \text{expit}(\beta^T X_i)$ then by Bayes rules
 - ▶ $\hat{P}(Y_i = 1|S_i = 1) = \frac{\theta \text{expit}(\beta^T X_i)}{\theta \text{expit}(\beta^T X_i) + (1-\phi)(1 - \text{expit}(\beta^T X_i))}$
 - ▶ $\hat{P}(Y_i = 1|S_i = 0) = \frac{(1-\theta)\text{expit}(\beta^T X_i)}{(1-\theta)\text{expit}(\beta^T X_i) + \phi(1 - \text{expit}(\beta^T X_i))}$
- An EM algorithm to estimate β
 1. Perform weighted logistic regression, each subject included as both diseased and non-diseased with weights $\hat{P}(Y_i = 1|S = k)$
 2. Update weights using new values for $\hat{\beta}$
 3. Return to (1)

Augmented estimation using validation data

| | SBCE status (True Phenotypes, Y) | SBCE status (Surrogate, S) | year | age | stage | ER_PR | |
|---------------------------------|--|----------------------------------|------|------|-------|-------|--|
| Validation set, V (size = n) | 0 | 0 | 1996 | 55.4 | 1 | 3 | |
| | 1 | 0 | 1995 | 67.9 | 1 | 1 | |
| | 1 | 1 | 2003 | 84.7 | 2 | 1 | |
| | 0 | 0 | 2004 | 46.3 | 1 | 1 | |
| | 0 | 1 | 1996 | 54.2 | 1 | 1 | |
| | . | . | . | . | . | . | |
| | . | . | . | . | . | . | |
| | . | . | . | . | . | . | |
| | | | | | | | |
| | | | | | | | |
| Full cohort, F (size = N) | | 0 | 1999 | 48.5 | 1 | 2 | |
| | | 1 | 2002 | 41.0 | 2 | 2 | |
| | | 1 | 1999 | 32.6 | 1 | 1 | |
| | | 0 | 2004 | 82.9 | 1 | 3 | |
| | ? | 1 | 2004 | 72.7 | 1 | 1 | |
| | ? | 0 | 2001 | 42.4 | 1 | 1 | |
| | ? | 1 | 1994 | 31.7 | 1 | 1 | |
| | ? | 0 | 1998 | 38.2 | 2 | 2 | |
| | ? | 0 | 2000 | 34.8 | 1 | 1 | |
| | ? | 0 | 2006 | 63.2 | 1 | 3 | |
| | . | . | . | . | . | . | |
| | . | . | . | . | . | . | |
| | . | . | . | . | . | . | |

Legend:
Light gray box: Not available
Dark gray box: Available

Features of augmented estimation

- Requires validation data for a subset of study population
- Accommodates differential and non-differential misclassification
- No need for explicit misclassification model
- Improves efficiency of estimation relative to analysis of gold-standard outcome alone

Augmented estimation procedure

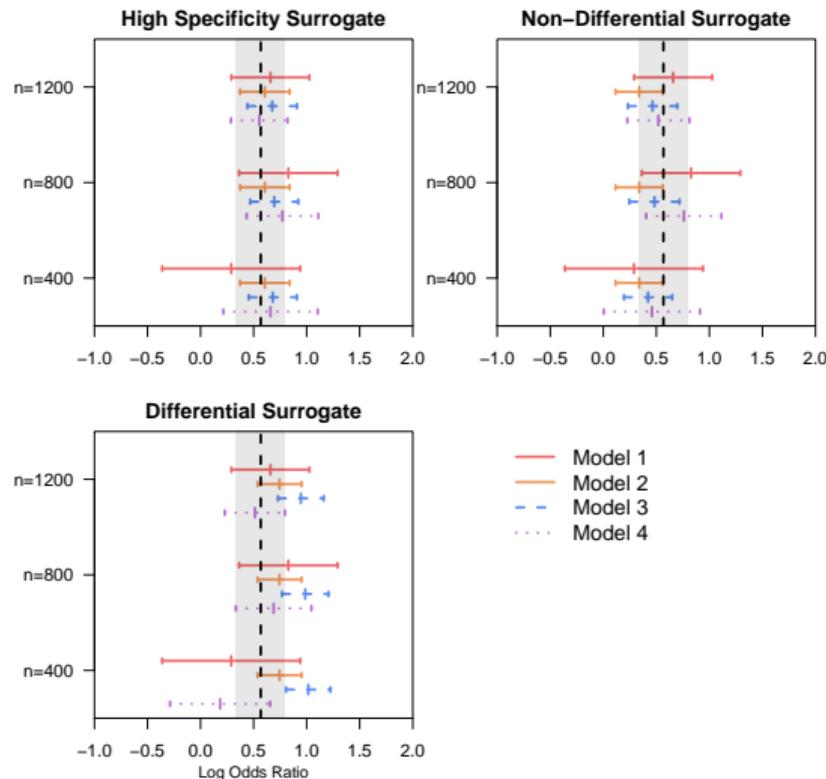
- Three models for outcome/exposure association:
 - ▶ Model 1: $Y_V \sim \beta_V X_V$
 - ▶ Model 2: $S_F \sim \gamma_F X_F$
 - ▶ $S_V \sim \gamma_V X_V$
- Model 3: Standard misclassification correction using marginal sensitivity (θ) and specificity (ϕ) (Magder & Hughes, *Am J Epidemiol.* 1997;146:195–203.)
- Model 4: Augmented estimator

$$\hat{\beta}_A = \hat{\beta}_V - \hat{\Omega} \hat{\Sigma}^{*-1} (\hat{\gamma}_V - \hat{\gamma}_F)$$

where $\hat{\Omega}, \hat{\Sigma}^*$ are covariance matrices.

- Compare performance varying validation sample size and algorithm operating characteristics using BRAVA data

Performance across sample sizes and phenotypes



Tong J et al. 2020. An augmented estimation procedure for EHR-based association studies accounting for differential misclassification. *J Am Med Informat Assoc.* 7(2):244-53.

An approach for predicted probabilities

- Increasingly, phenotyping uses statistical or machine learning approaches that provide probabilistic phenotypes, \hat{p}
- Sinnott et al. 2014 developed a bias correction approach for analyses using these predicted probabilities as outcomes
- Suppose we wish to estimate the association between a phenotype, Y , and exposure, Z adjusting for confounders W

$$g(P(Y = 1|Z, W)) = \alpha + \beta Z + \gamma W.$$

- Let $f(\hat{p}) = (\hat{p} - \mu_0)/(\mu_1 - \mu_0)$, where $\mu_k = E(\hat{p}|Y = k)$
- Sinnott et al. showed that regressing $f(\hat{p})$ on Z and W provides consistent estimates for regression coefficients.

Sinnott et al. 2014. Improving the power of genetic association tests with imperfect phenotype derived from electronic medical records. *Human Genetics*. 133:1369-82.

A simple bias correction for risk differences

- In the context of risk difference regression in which the link function, $g(\cdot)$, is the identity link, this approach gives rise to a very simple bias correction

$$\begin{aligned} E(f(\hat{p})|Z, W) &= \alpha + \beta Z + \gamma W \\ E[(\hat{p} - \mu_0)/(\mu_1 - \mu_0)|Z, W] &= \alpha + \beta Z + \gamma W \\ E[\hat{p}|Z, W] &= \alpha^* + (\mu_1 - \mu_0)(\beta Z + \gamma W) \\ E[\hat{p}|Z, W] &= \alpha^* + \beta^* Z + \gamma^* W \end{aligned}$$

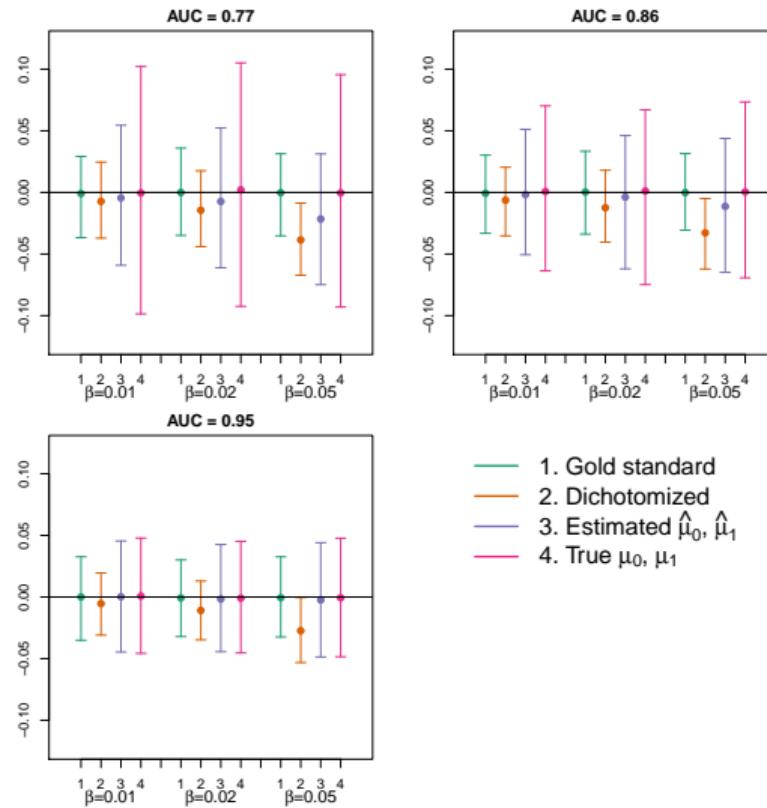
- Therefore, $\hat{\beta} = \frac{\hat{\beta}^*}{\mu_1 - \mu_0}$ is unbiased for β
- By using a Taylor series expansion to linearize $g(\cdot)$ bias correction formulas can be obtained for other link functions including log and logistic.

Hubbard et al. 2020. Reducing bias due to outcome misclassification in epidemiologic studies using EHR-derived probabilistic phenotypes. *Epidemiology*. 31(4):542-50.

Simulation study design

- Compared
 1. Gold standard true phenotype
 2. Dichotomized phenotype based on predicted probability
 3. Bias correction using estimated $\hat{\mu}_0$ and $\hat{\mu}_1$
 4. Bias correction using true μ_0 and μ_1
- Varying: AUC of \hat{p} , strength of effect (β), prevalence of Y

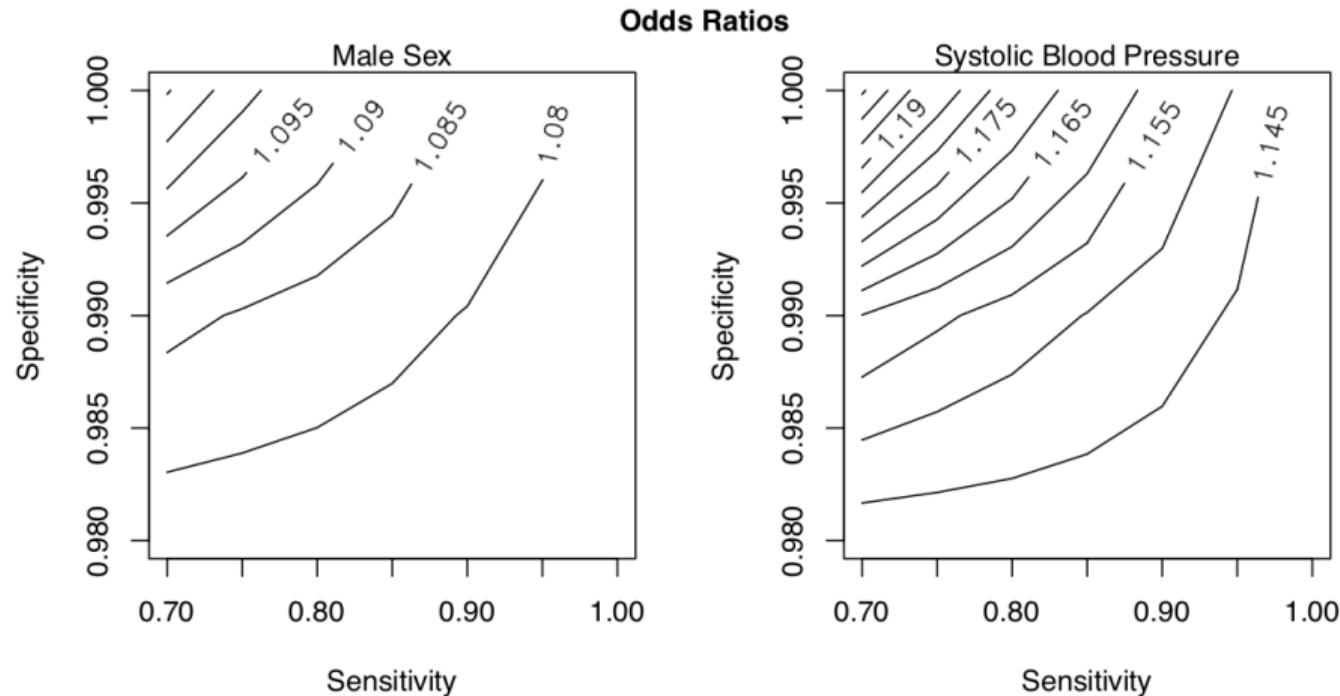
Bias: Prevalence = 0.1



Application to PEDSnet data

- Applied this approach to data from the PEDSnet network
- Previously developed phenotype probability for T2DM
- Prevalence estimated at 1.5%
- Based on latent class model so no sensitivity and specificity available
- In this setting can look at results across a range of values for sensitivity and specificity as a sensitivity analysis

Sensitivity analysis for PEDSnet



- We will use a synthetic (i.e., fake) EHR-derived data set based on the structure of the PEDSnet dataset to explore some of the challenges of EHR data and strategies for dealing with them we will be discussing
- The PEDSnet synthetic data sets and R code for working with them are available at https://rhubb.github.io/Deming_short_course/
- These data sets were generated by sampling from the distributions of data elements contained in the real PEDSnet data
- The result is a set of data sets that reflect the features of the PEDSnet data but avoid issues of privacy protection that accompany real EHR-derived data

R Tutorial

Outline

FDA Framework for Real World Evidence

Overview of the structure of EHR data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Conclusions

Exploring EHR data

- If you are interested in exploring EHR data there are a number of sources available online
- **MIMIC IV:** publically available data on 40,000 critical care patients
 - ▶ <https://mimic.physionet.org>
 - ▶ Requires DUA for full data access
- **healthdata.gov:** open access data from the US government
 - ▶ Includes data from many sources including Medicare claims
 - ▶ Some data sets are limited to aggregate data
 - ▶ Medicare PUF include individual-level data but not suitable for research

Concluding thoughts

- Due to financial incentives and operational efficiencies, EHR will become the dominant mode of clinical/administrative documentation of health encounters
- This creates a vast research resource but also requires knowledge of its complexities to use appropriately
- A key component of data science is expert knowledge about data sources
- To effectively use EHR data we (statisticians) must be willing to learn about where these data come from and how they are used clinically/administratively
- We wouldn't analyze observational data without reading the protocol!

Recommendations

- Engaging with clinicians, coders, informaticians allows us to
 - ▶ Understand data quality
 - ▶ Make smart choices about when and how EHR data can be used
 - ▶ Identify appropriate methods to mitigate limitations
 - ▶ Develop new statistical methods to fill gaps in available methodology
- EHR data can be messy but don't despair!
- Staying engaged in the research process from data extraction through analysis, interpretation, and reporting of results ensures higher quality research and gives us a seat at the table to help improve processes for the future

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