

Practical solutions for working with electronic health records data

Yong Chen, PhD
Rebecca Hubbard, PhD

DEPARTMENT of
**BIOSTATISTICS
EPIDEMIOLOGY &
INFORMATICS**



Perelman
School of Medicine
UNIVERSITY of PENNSYLVANIA

Course Materials

All course materials can be downloaded from https://rhubb.github.io/JSM_short_course/

This includes:

- Slides
- Reference list
- Tutorials
- Data sets used in tutorials
- R code for tutorial solutions

Schedule

- 8:30 - 10:15 Overview of EHR and claims data structure
- 10:15 - 10:30 Mid-morning Break
- 10:30 - 11:30 Extracting data elements from the EHR
- 11:30 - 12:00 Missing data issues
- 12:00 - 12:30 Tutorial 1
- 12:30 - 2:00 Lunch
- 2:00 - 3:15 Correcting for bias due to EHR data errors
- 3:15 - 3:30 Mid-afternoon Break
- 3:30 - 4:15 Distributed analysis
- 4:30 - 4:45 Tutorial 2
- 4:45 - 5:00 Conclusions & Wrap-up

Outline

Introduction

Overview of the structure of EHR and claims data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Distributed Analysis

Conclusions and Wrap-up

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

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

- In the US, increased clinical use of EHRs has been driven largely by the Medicare and Medicaid EHR Incentive Program
- Under this program health care providers receiving reimbursement from Medicare are incentivized to adopt EHRs
- The objective of this program was to
 - ▶ Improve quality, safety and efficiency of health care and reduce health disparities
 - ▶ Engage patients and families in care
 - ▶ Improve care coordination
 - ▶ Improve population and public health
 - ▶ Ensure privacy and security of personal health information
- Regardless of whether these goals have been met or not, the practical implication for researchers is that large amounts of observational medical data are now available.

Objectives

- The objective of this short course is to present an overview of some of the practical challenges that arise in the analysis of healthcare 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 healthcare data for research purposes
- Present **alternative statistical methods** to address challenges encountered in healthcare data

Outline

Introduction

Overview of the structure of EHR and claims data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Distributed Analysis

Conclusions and Wrap-up

What are the advantages of using healthcare 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 healthcare data for research?

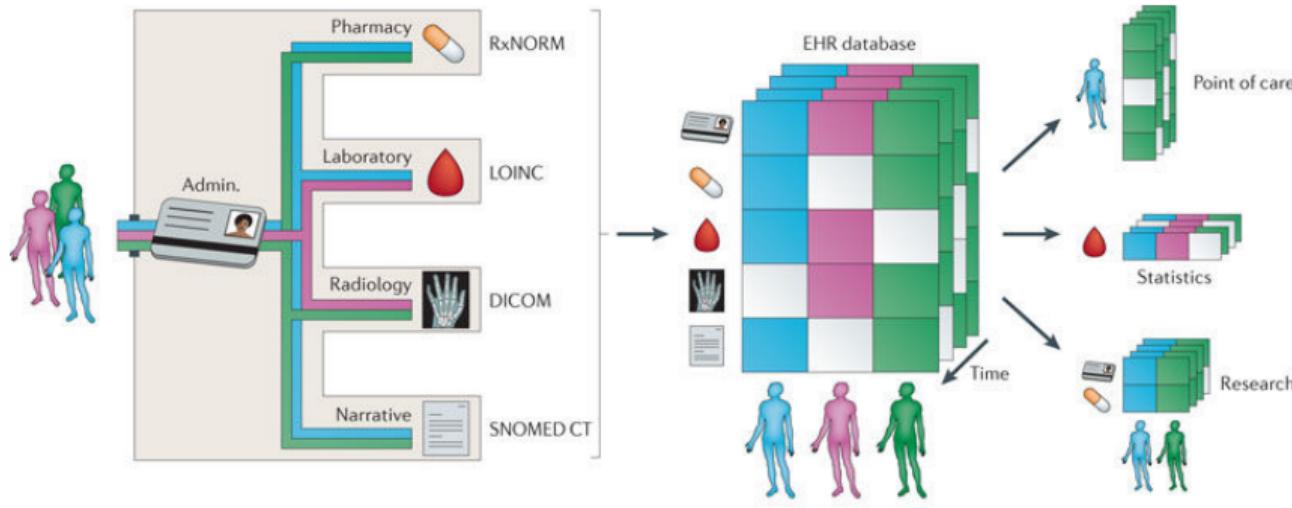
- Data quality may be poor (quantity vs quality tradeoff)
- Data collection is not systematic leading to complex missing data patterns
- Extracting data from text notes is challenging and error-prone
- Privacy protections (e.g., HIPAA) limit what data can be accessed and by whom

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

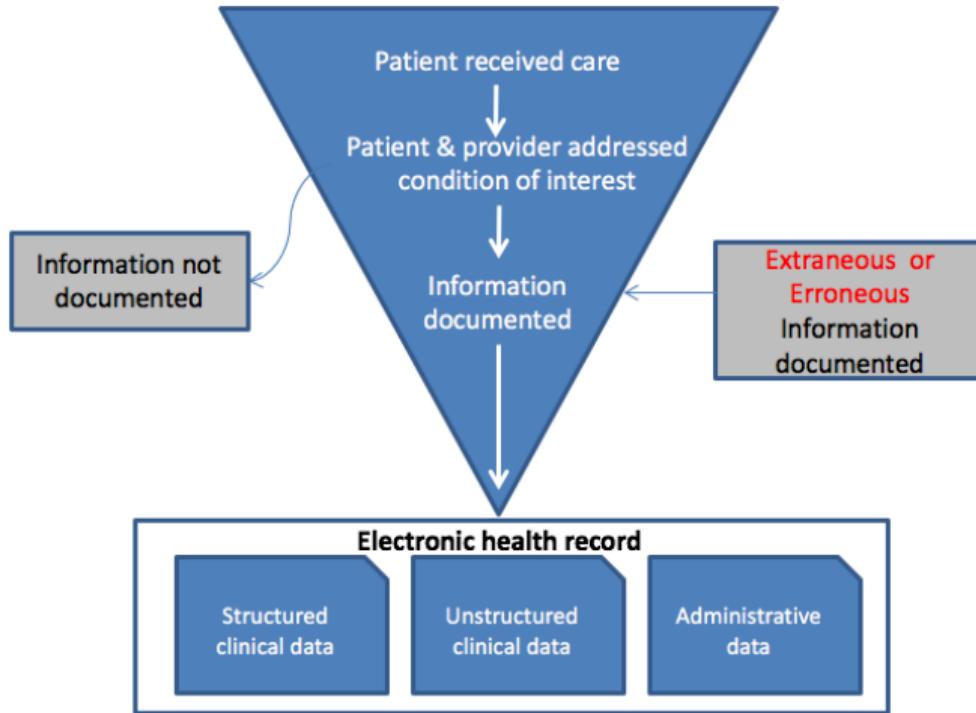
Jensen PB, Jensen LJ, Brunak S. Mining electronic health records: towards better research applications and clinical care. *Nature Reviews Genetics*. 2012;13(6):395-405.

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 healthcare 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 (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

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

- R has many tools for conducting NLP
- This can be as simple as string manipulation
- Many functions for manipulating string are included in base R installation
 - ▶ `tolower()` - convert text to lower case
 - ▶ `aspell()` - correct spelling
 - ▶ `substr()` - extract substrings
 - ▶ `regexpr()` - regular expression matching
 - ▶ `strsplit()` - splits a string (e.g. sentence) into substrings (e.g. words)
- However, for more complex settings more sophisticated tools will be necessary

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” 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.

Outline

Introduction

Overview of the structure of EHR and claims data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Distributed Analysis

Conclusions and Wrap-up

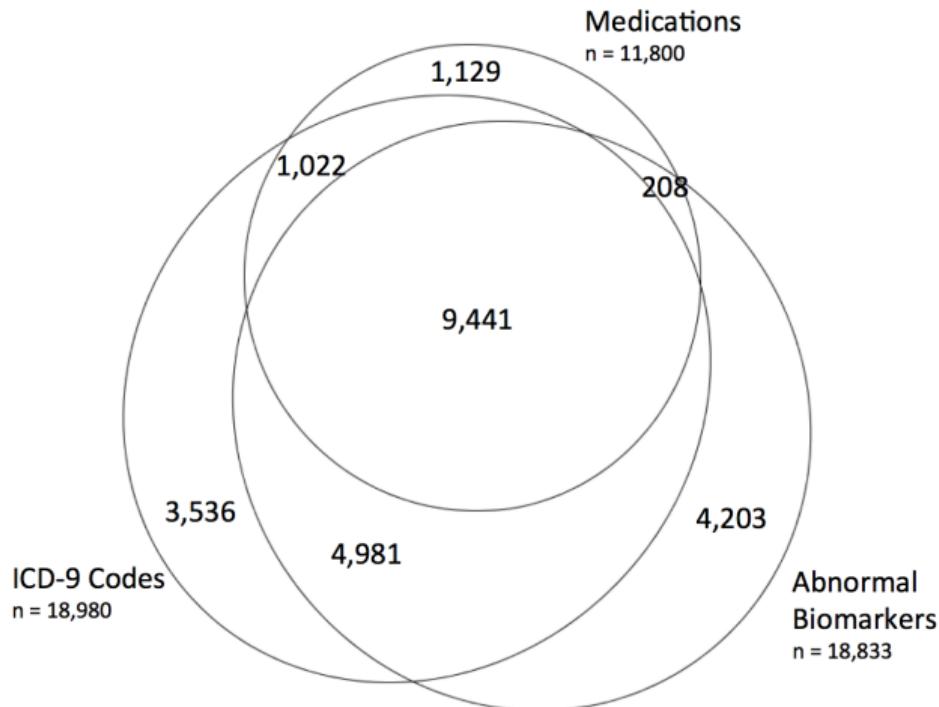
Rule-based Phenotyping

- 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

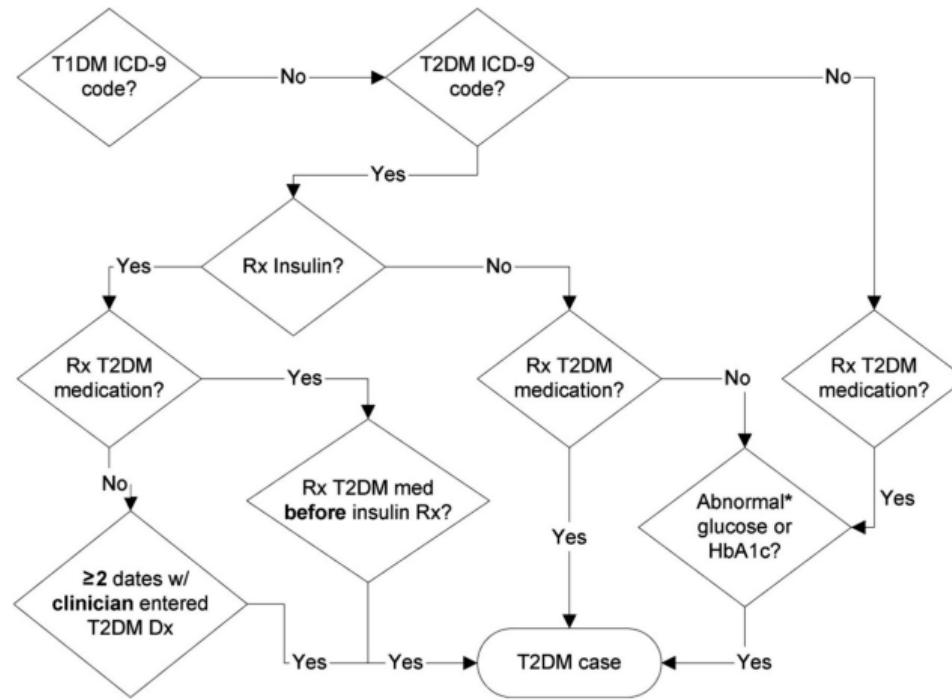
Variable type	Examples	Format
Diabetes diagnosis	<ul style="list-style-type: none">• T2DM• T1DM• DM NOS	ICD-9/10 codes
Medications	<ul style="list-style-type: none">• Insulin• Metformin	Prescribing data
Co-morbidities	<ul style="list-style-type: none">• PCOS• Obesity	ICD-9/10 codes
Biomarkers	<ul style="list-style-type: 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)

Outline

Introduction

Overview of the structure of EHR and claims data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Distributed Analysis

Conclusions and Wrap-up

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

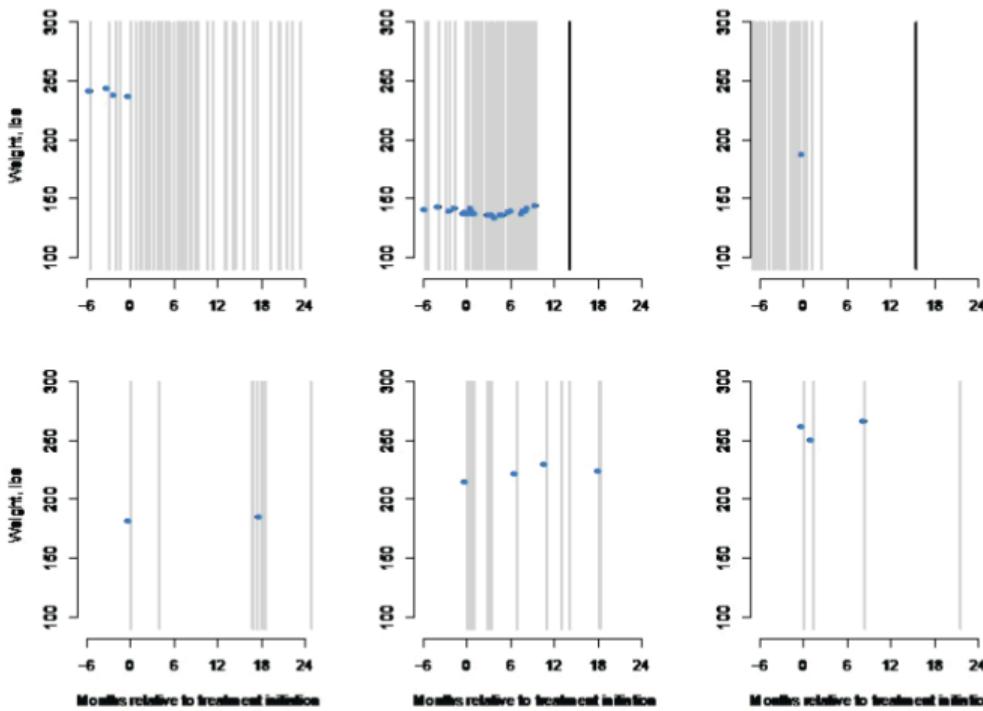
PEDSnet Example

- 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

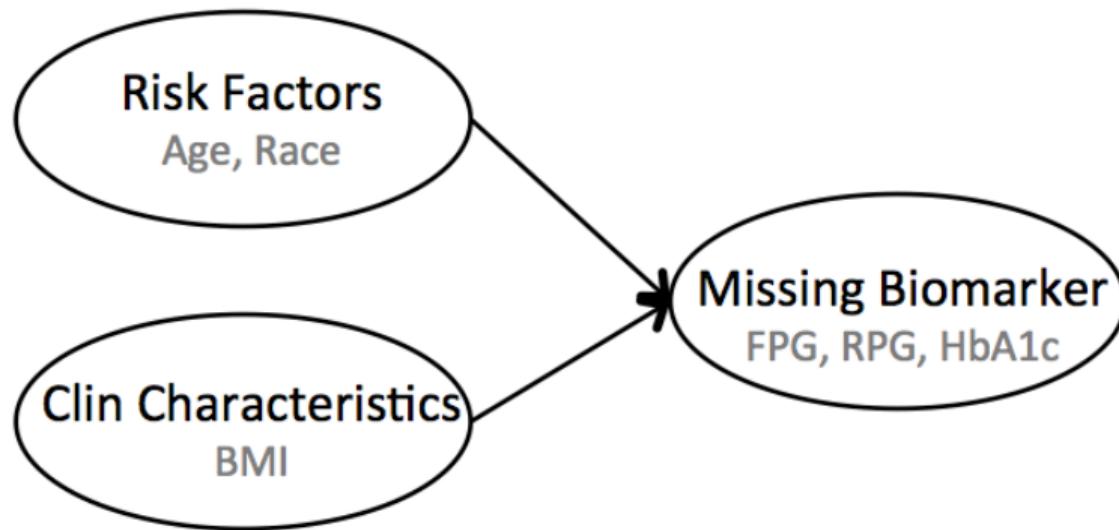


Haneuse and Daniels. 2016. eGEMS 4(1):16.

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**)

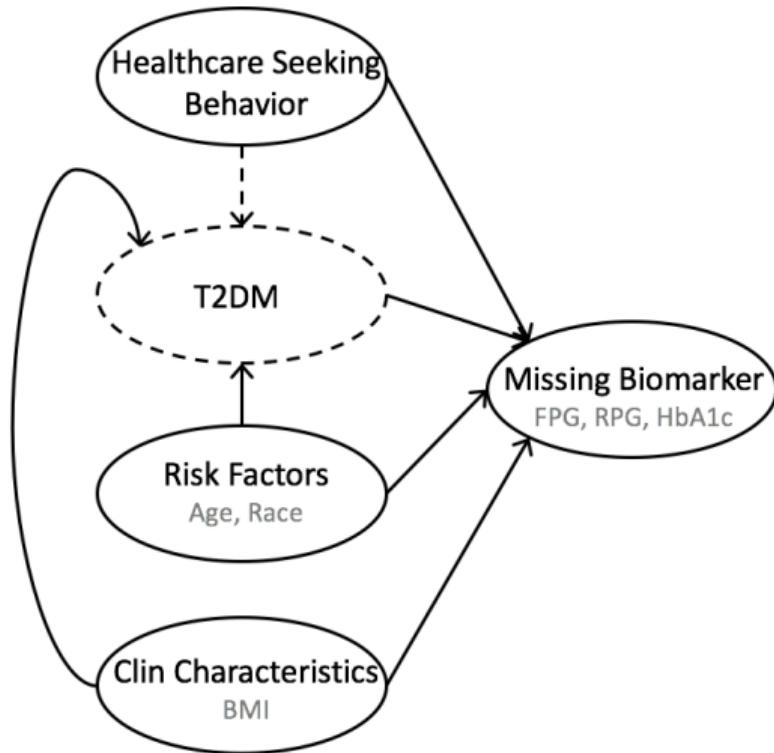
MAR missingness mechanism



- 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

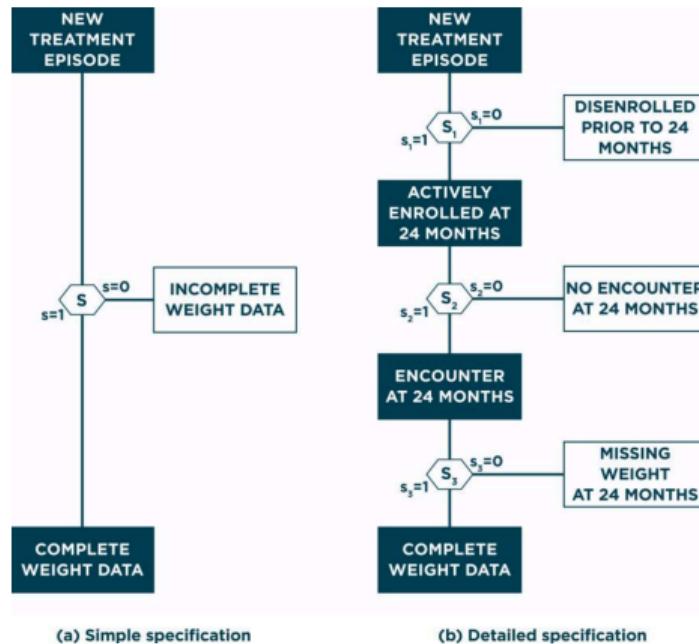


PEDSnet example: Missingness in glucose

	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

- Throughout this course 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/JSM_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

Tutorial 1

Outline

Introduction

Overview of the structure of EHR and claims data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Distributed Analysis

Conclusions and Wrap-up

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

Standard methods: GEE and GLMM

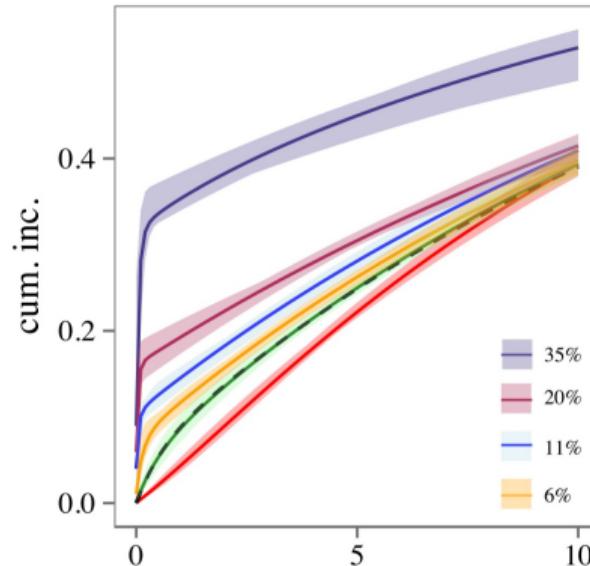
- Generalized estimating equations (GEE) is commonly used in analyses of longitudinal data due to its ability to account for correlation among repeated measurements, robustness and high efficiency
 - ▶ Standard GEE method is valid under missing completely at random.
- Generalized linear mixed effects models (GLMM) rely on additional parametric assumptions but only require the assumption of missing at random.
- If the disease process itself is related to the intensity of the observation process, this constitutes a missing not at random missingness pattern

Approaches to informative observation schemes

- Likelihood-based joint modeling fully specifies the joint distribution of the outcome process and the observation process
- Dependence between these two processes is often characterized by shared random effects or latent variables
- These models are parametric, and misspecification of either the observation process or disease model will result in bias

Bias induced by patient driven observation

Simulation results varying proportion of visit times that are “patient driven”



Lange JM et al. 2015. A joint model for multistate disease processes and random informative observation times, with applications to electronic medical records data. *Biometrics*. 71(1):90-101.

Weighted estimating equations

- A semi-parametric alternative is to use estimating equations weighted by the inverse of the intensity of the observation process
- This requires specification of the outcome process

$$E(Y_i(t)|X_i(t)) = \alpha(t) + \beta' X_i(t)$$

- And the observation process

$$E(dN_i(t)|Z_i(t)) = d\Lambda_0(t) \exp(\gamma' Z_i(t))$$

- This gives rise to unbiased estimating equations

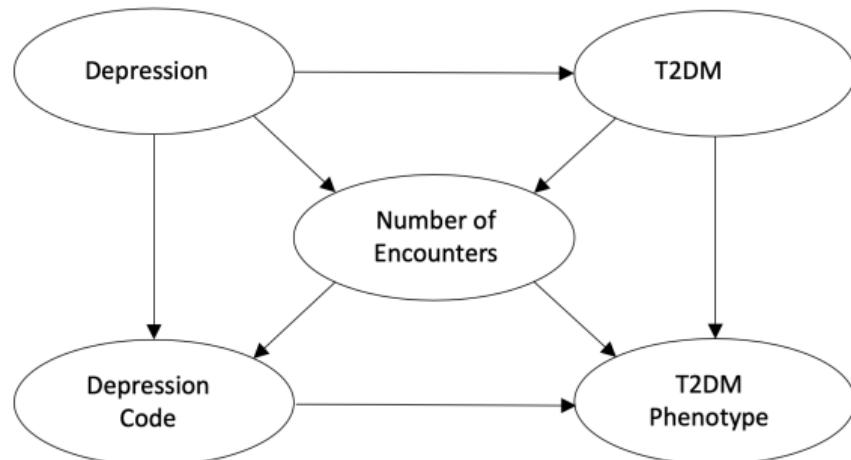
$$U(\beta) = \sum_{i=1}^n \int_0^\infty W_i(t)(X_i(t) - \bar{X}_i(t))(Y_i(t) - \bar{Y}_i(t) - \beta'(X_i(t) - \bar{X}_i(t)))dN_i(t)$$

- While this approach allows observation times to depend on covariates it assumes independence of observation process and outcome process

Buzkova P, Lumley T. Semiparametric modeling of repeated measurements under outcome-dependent follow-up. *Stat Med.* 2009; 28(6):987-1003.

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.

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

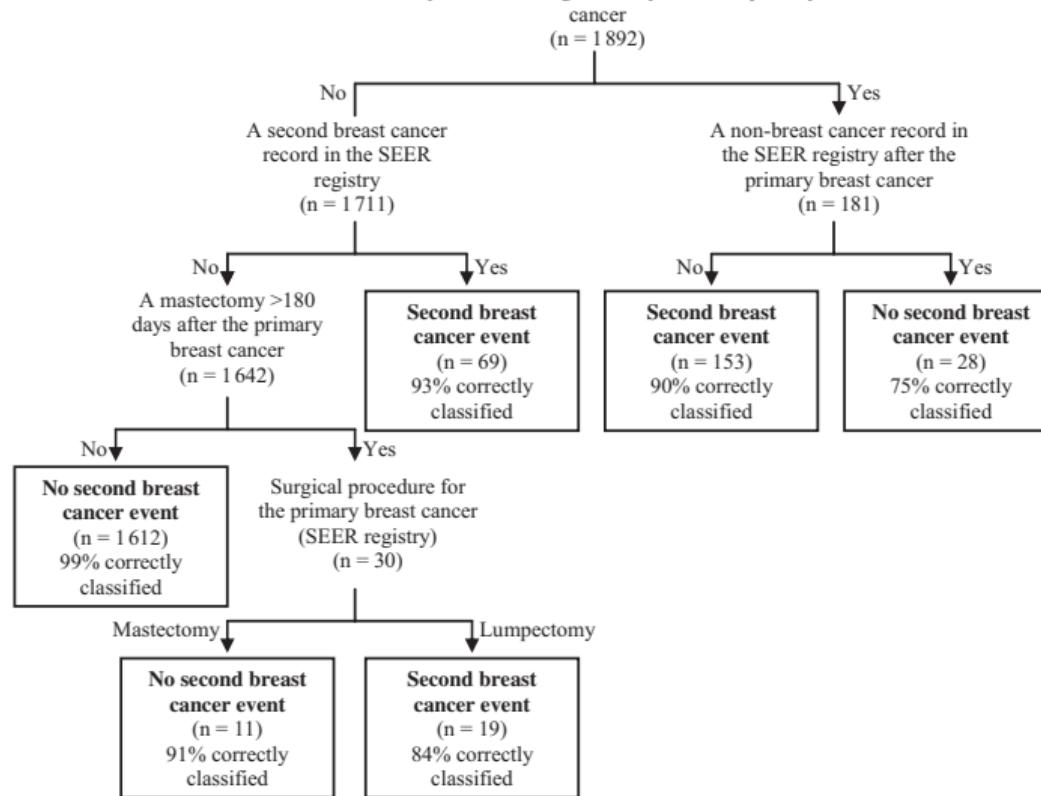
- Use of EHR data-based algorithms to identify event times may introduce error in
 - ▶ Classification as to whether or not an event occurred
 - ▶ Exact timing of event
- Example: Second breast cancer event (SBCE) in women with a history of breast cancer
 - ▶ Algorithm identifies SBCE with $Se = 89\%$, $Sp = 99\%$
 - ▶ 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

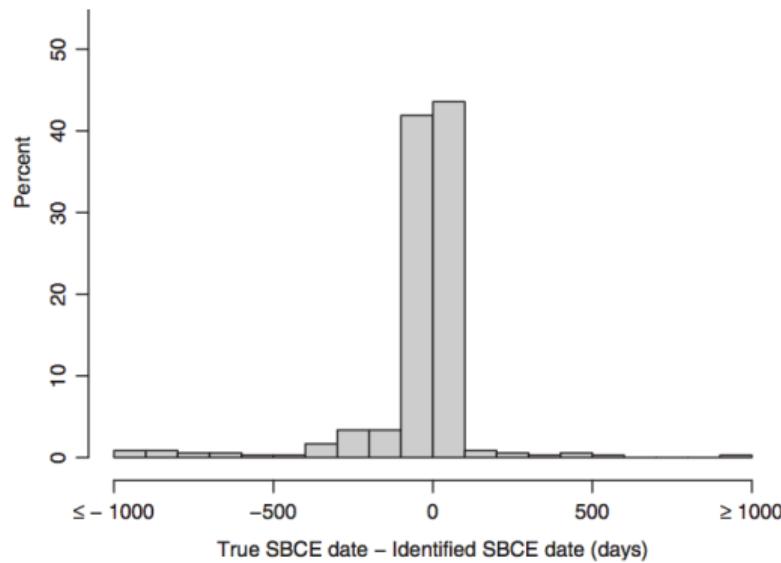
- BRAVA study developed algorithm to identify SBCEs using a combination of cancer registry and EHR data
- Validated against manual chart review
- We explored how well dates assigned based on this algorithm agreed with gold-standard
- 407 chart-reviewed SBCEs, 358 (88%) identified by algorithm

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?

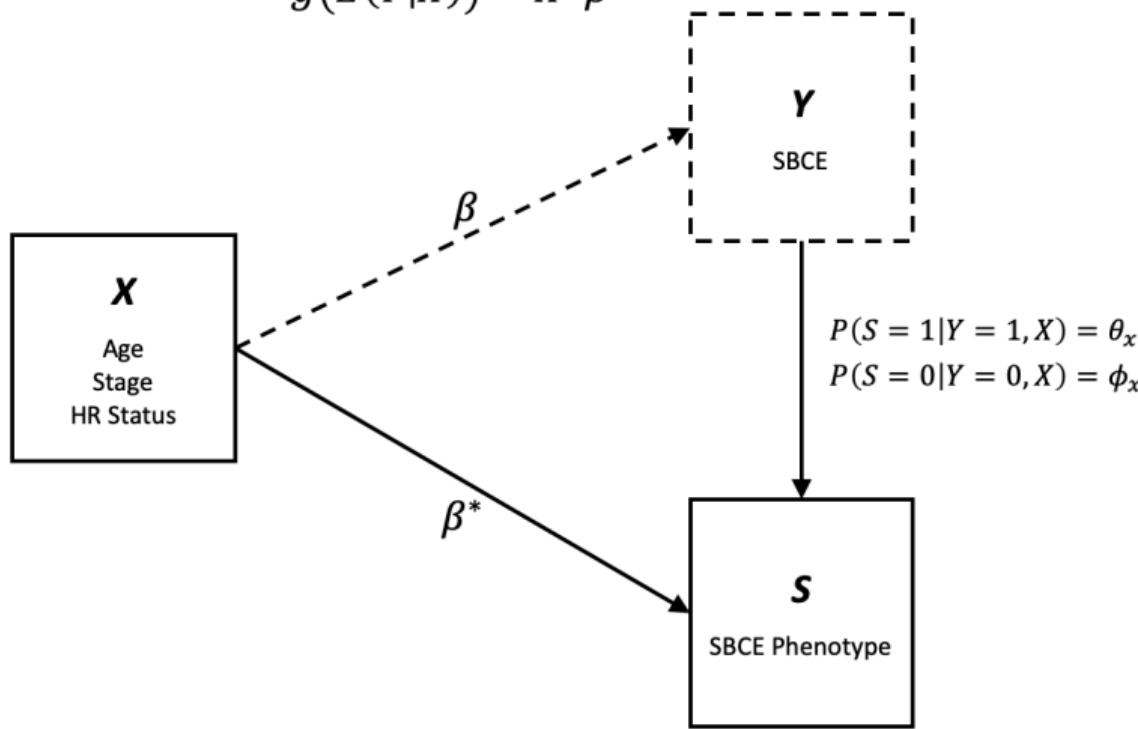
Chubak J et al. An Electronic Health Record–based Algorithm to Ascertain the Date of Second Breast Cancer Events. *Medical Care*. 2017;55(12):e81-7.

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

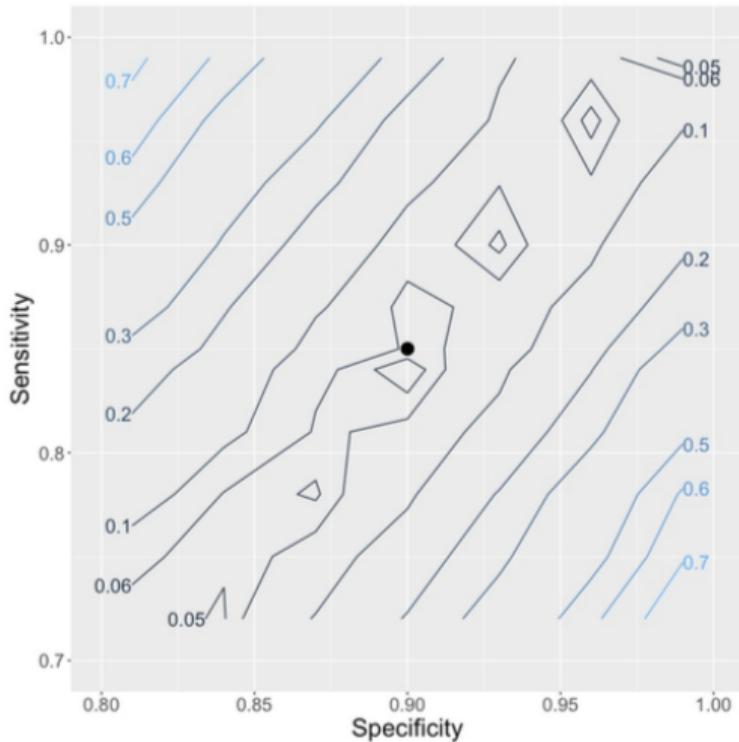
$$P(X = 1 | S = i, Y = j) = \frac{a_{j1}^i (1 - a_{j1})^{1-i} P(X = 1)}{\sum_{k=0,1} a_{jk} (1 - a_{jk}) P(X = k)}$$

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.

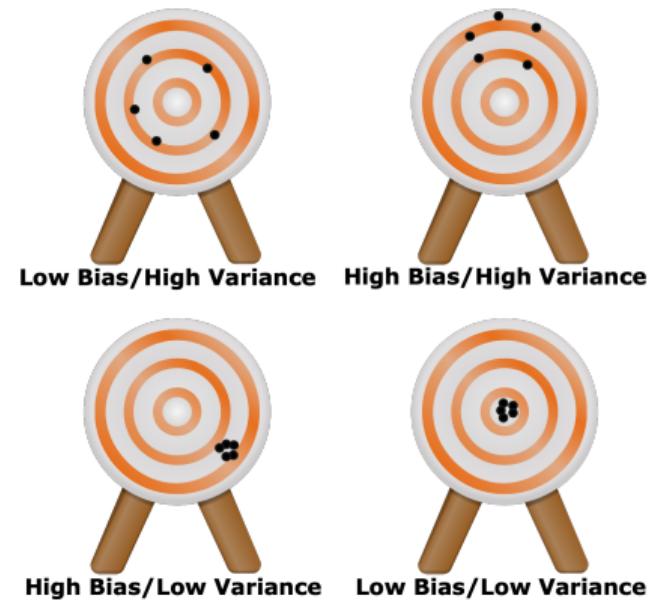
What can we do about phenotyping error?

- 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

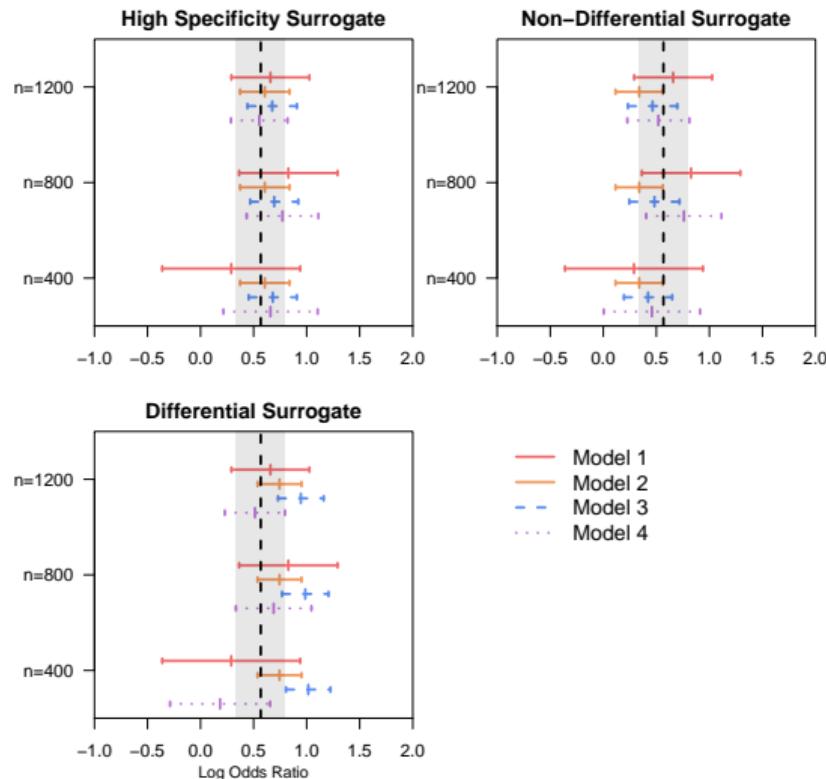
- Three models for outcome/exposure association:
 - ▶ Model 1: $Y_V \sim \beta_V X_V$
 - ▶ Model 2: $S_F \sim \gamma_F X_F$
 - ▶ $S_V \sim \gamma_V X_V$
- Model 3: Standard misclassification correction using marginal sensitivity (θ) and specificity (ϕ) (Magder & Hughes, *Am J Epidemiol.* 1997;146:195–203.)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

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

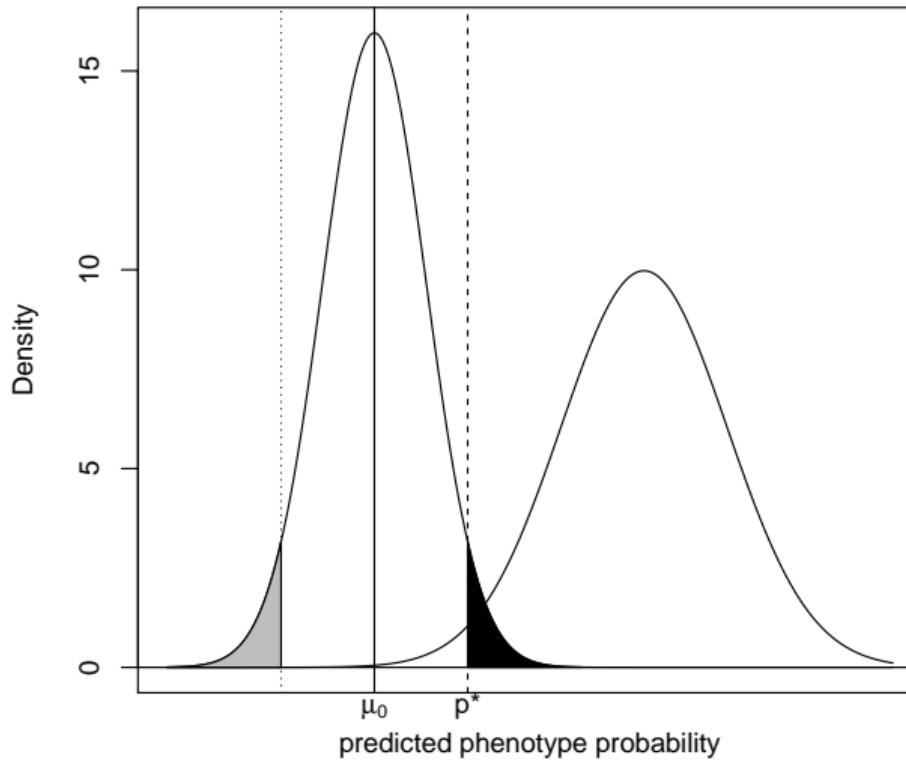
- Therefore, $\hat{\beta} = \frac{\hat{\beta}^*}{\mu_1 - \mu_0}$ is unbiased for β
- By using a Taylor series expansion to linearize $g(\cdot)$ bias correction formulas can be obtained for other link functions including log and logistic.

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

One additional complication

- Unfortunately, in the EHR context μ_0 and μ_1 will only be available in data sets with validation data
- In the data set initially used to develop the phenotype this will be straightforward to calculate by taking the mean of \hat{p} among cases and controls
- In data sets without validation data we typically have access to published validation results, typically including a proposed cutpoint, p^* , along with sensitivity and specificity for the dichotomized phenotype
- Using this information we can obtain estimates $\hat{\mu}_0$ and $\hat{\mu}_1$

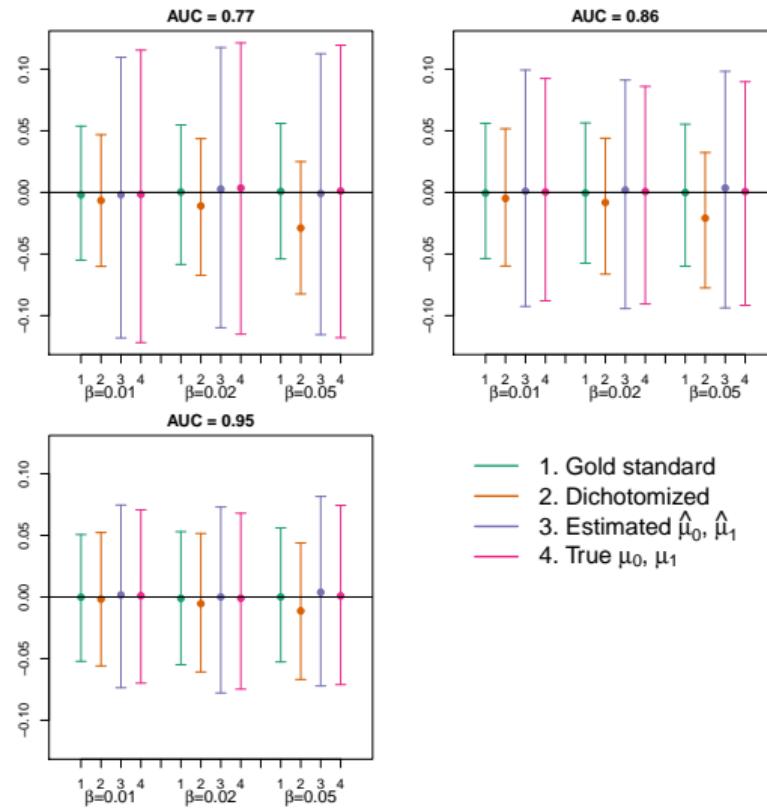
Estimating μ_0 without validation data



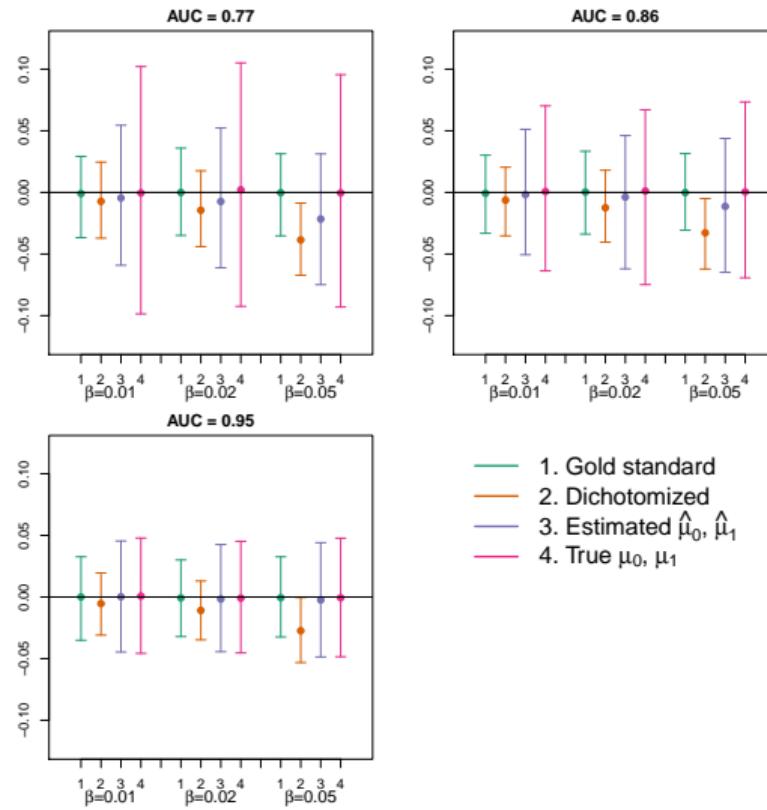
Simulation study design

- 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 = 0.5



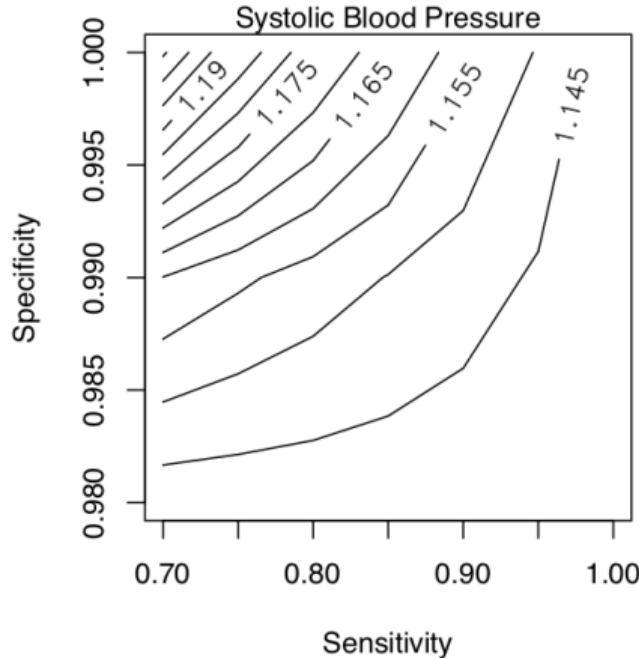
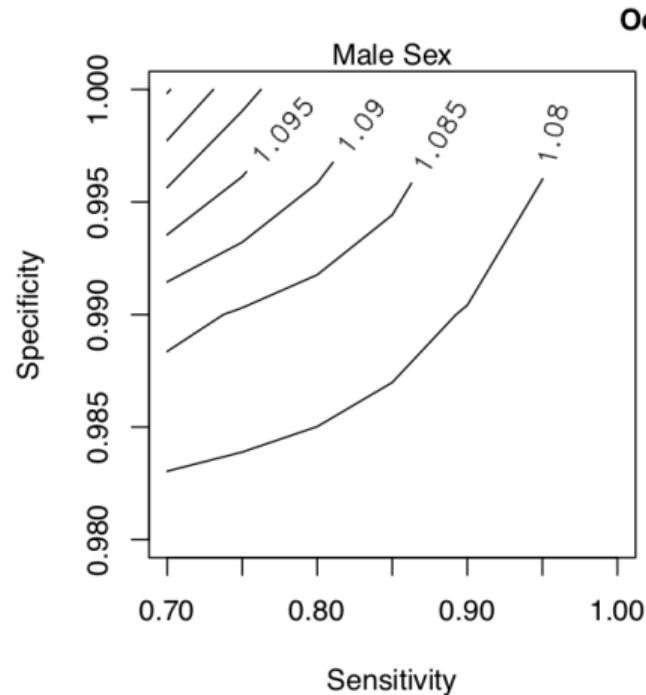
Bias: Prevalence = 0.1



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



Outline

Introduction

Overview of the structure of EHR and claims data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Distributed Analysis

Conclusions and Wrap-up

Motivation: a large-scale CER research using observational data

THE LANCET
Volume 394, Issue 10211, 16–22 November 2019, Pages 1816–1826



Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

Marc A Suchard, Martijn J Schuemie, Harlan M Krumholz, Seng Chan You, Ruijun Chen, Nicole Pratt, Christian G Reich, Jon Duke, David Madigan, George Hripcak, Patrick B Ryan

Summary

Background Uncertainty remains about the optimal monotherapy for hypertension, with current guidelines recommending any primary agent among the first-line drug classes thiazide or thiazide-like diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and non-dihydropyridine calcium channel blockers, in the absence of comorbid indications. Randomised trials have not further refined this choice.

Methods We developed a comprehensive framework for real-world evidence that enables comparative effectiveness and safety evaluation across many drugs and outcomes from observational data encompassing millions of patients, while minimising inherent bias. Using this framework, we did a systematic, large-scale study under a new-user cohort design to estimate the relative risks of three primary (acute myocardial infarction, hospitalisation for heart failure, and stroke) and six secondary effectiveness and 46 safety outcomes comparing all first-line classes across a global network of six administrative claims and three electronic health record databases. The framework addressed residual confounding, publication bias, and p-hacking using large-scale propensity adjustment, a large set of control outcomes, and full disclosure of hypotheses tested.

Lancet 2019; 394: 1816–26

Published Online
October 24, 2019

[https://doi.org/10.1016/S0140-6736\(19\)32317-7](https://doi.org/10.1016/S0140-6736(19)32317-7)

See Comment page 1782

Department of Biostatistics,
Fielding School of Public Health

(Prof M A Suchard MD,
M J Schuemie PhD),
and Department of

Biomathematics, David Geffen
School of Medicine at UCLA

(Prof M A Suchard), University
of California, Los Angeles, CA,

USA; Epidemiology Analytics,
Janssen Research &

Motivation: Distributed Health Data Networks

- ▶ No data centralization: data holders maintain control over data

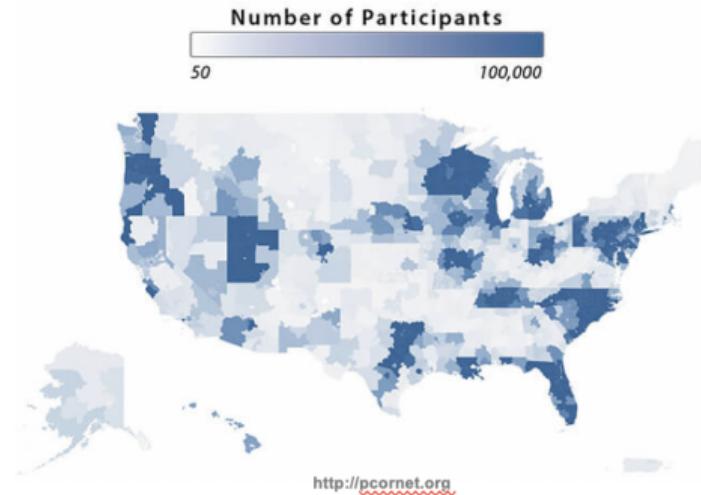
- Participants adopt common data model (CDM)
- Analyses performed distributively (email, central server, etc.)
- No patient-level data transfer

- ▶ Sentinel Initiative

- FDA: Post-market safety surveillance
- 16 data partners contribute billing data, EHRs

- ▶ PCORnet

- National patient-centered clinical research network for comparative effectiveness research
- 68 million patients





OHDSI's global research community



Promise and challenges of multi-site studies



- ▶ Covers broader population
 - Results are more generalizable
 - Better statistical power
 - Opportunities of studying rare diseases
- ▶ Ecosystem of bringing together expertise from different investigators

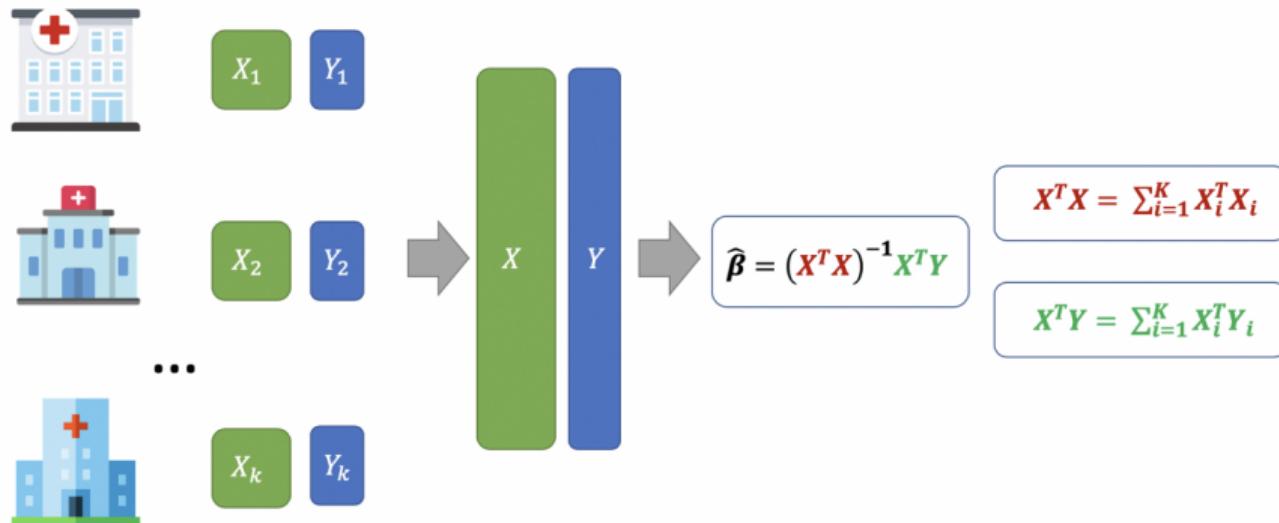
- ▶ Sharing individual-patient level data is challenging



- ▶ Need iterative collaboration/coordination among investigators from different institutes
(consuming lots of time, effort, funding)

Distributed Linear Regression - a useful result

- ▶ Do we really need to share patient-level data?



Chen et al. (2006) Regression cubes with lossless compression and aggregation.

A bit more detail

$$\begin{matrix} y \\ h_1 \left\{ \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} \right. \\ h_2 \left. \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} \right\} \end{matrix} = \begin{pmatrix} x \\ x_1 \\ x_2 \end{pmatrix} \beta + \begin{pmatrix} \varepsilon \\ \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$$
$$\hat{\beta} = (x^T x)^{-1} x^T y = \left\{ (x_1^T x_2^T) \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \right\}^{-1} (x_1^T x_2^T) \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$
$$= \underbrace{(x_1^T x_1 + x_2^T x_2)^{-1}}_{P \times P} \underbrace{(x_1^T y_1 + x_2^T y_2)}_{P \times 1}$$

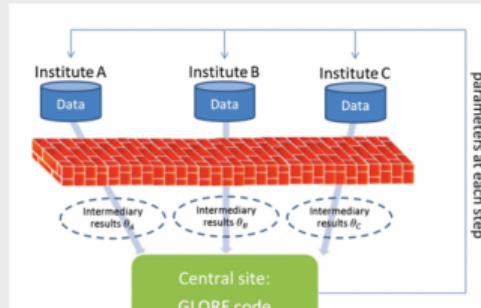
Aggregated data to communicate:

$$x_1^T x_1, x_1^T y_1, x_2^T x_2, x_2^T y_2.$$

Current algorithms of distributed analysis

► **Lossless** --- obtain the identical results as the combined analysis

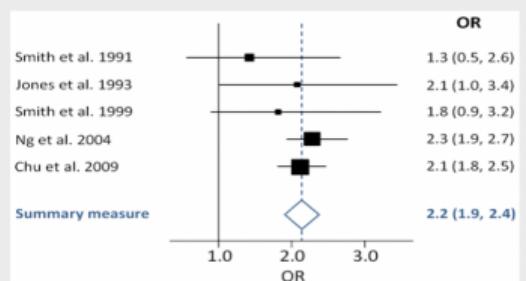
- For simple linear regression
 - **Distributed linear regression** (Chen et al. 2006)
- For non-linear regressions, iterative algorithms are needed
 - **Binary outcome**: Grid Binary LOgistic REgression (GLORE) (Wu et al. 2012)
 - **Time-to-event outcome**: WebDISCO: a Web service for distributed Cox model (Lu et al. 2015)



Wu et al. 2012, JAMIA

► **One-shot (non-iterative)** --- only requires the collaborative sites to exchange aggregated data **once**

- Averaging local estimates
 - Meta-analysis, distributed PCA (Fan et al. 2018), distributed LDA (Lu et al. 2019),
- Surrogate likelihood (Jordan et al. 2018)



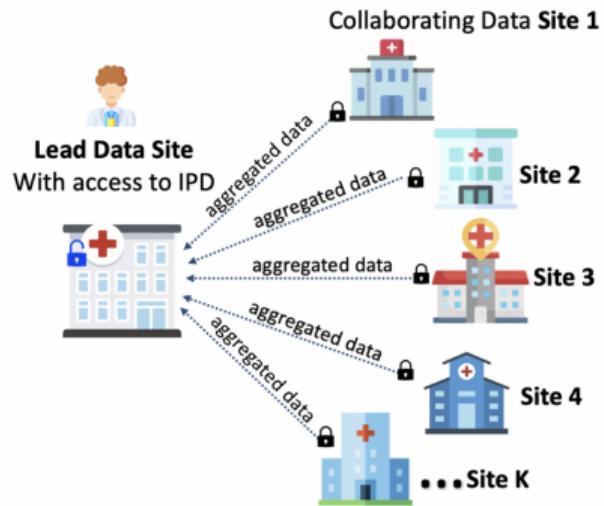


Our Goal

- **Safe** --- protect patient-level information
- **Accurate** --- provide estimates which are close to the pooled analysis results
- **Efficient** --- no iterative communication across collaborating sites

Inspiration: an interesting observation – unique architecture of DRN

- An investigator at a hospital do have access to the patient-level data of that hospital
- Collaborating hospitals can share aggregated data





Communication-Efficient Distributed Statistical Inference

Michael I. Jordan^a, Jason D. Lee^b, and Yun Yang^c

^aDepartment of Statistics, University of California Berkeley, Berkeley, CA; ^bInstitute of Computational and Mathematical Engineering, Stanford University, Cupertino, CA; ^cStatistical Science, Duke University, Durham, NC

ABSTRACT

We present a *communication-efficient surrogate likelihood* (CSL) framework for solving distributed statistical inference problems. CSL provides a communication-efficient surrogate to the global likelihood that can be used for low-dimensional estimation, high-dimensional regularized estimation, and Bayesian inference. For low-dimensional estimation, CSL provably improves upon naive averaging schemes and facilitates the construction of confidence intervals. For high-dimensional regularized estimation, CSL leads to a minimax-optimal estimator with controlled communication cost. For Bayesian inference, CSL can be used to form a communication-efficient quasi-posterior distribution that converges to the true posterior. This quasi-posterior procedure significantly improves the computational efficiency of Markov chain Monte Carlo (MCMC) algorithms even in a nondistributed setting. We present both theoretical analysis and experiments to explore the properties of the CSL approximation. Supplementary materials for this article are available online.

ARTICLE HISTORY

Received December 2016
Revised December 2017

KEYWORDS

Communication efficiency;
Distributed inference;
Likelihood approximation

An idea



**Can we use local hospital's patient-level data and collaborating
hospitals' aggregated data to do multi-site data analysis?**

ODAL

One-shot Distributed Algorithm for Logistic Regression

Journal of the American Medical Informatics Association, 27(3), 2020, 376–385

doi: 10.1093/jamia/occ199

Advance Access Publication Date: 9 December 2019

Research and Applications



Research and Applications

Learning from electronic health records across multiple sites: A communication-efficient and privacy-preserving distributed algorithm

Rui Duan ¹, Mary Regina Boland ¹, Zixuan Liu², Yue Liu³, Howard H. Chang⁴, Hua Xu⁵, Haitao Chu⁶, Christopher H. Schmid⁷, Christopher B. Forrest⁸, John H. Holmes¹, Martijn J. Schuemie ⁹, Jesse A. Berlin⁹, Jason H. Moore¹, and Yong Chen ¹

The likelihood functions

- ▶ **Combined likelihood function** (if data could be shared)

$$L(\beta) = \frac{1}{nK} \sum_{j=1}^K \sum_{i=1}^n \{y_{ij}x_{ij}^T\beta - \log\{1 + \exp(x_{ij}^T\beta)\}\}$$

- ▶ **Local likelihood function** (assume local site to be the first site, j=1)

$$L_1(\beta) = \frac{1}{n} \sum_{i=1}^n \{y_{i1}x_{i1}^T\beta - \log\{1 + \exp(x_{i1}^T\beta)\}\}$$

How to borrow aggregated information from other sites to make $L_1(\beta)$ more like $L(\beta)$?

The surrogate likelihood (SL) approach

- For an initial value $\bar{\beta}$,

$$L(\beta) = L(\bar{\beta}) + \nabla L(\bar{\beta})^T (\beta - \bar{\beta}) + \sum_{t=2}^{\infty} \frac{1}{t!} \nabla^t L(\bar{\beta}) (\beta - \bar{\beta})^{\otimes t}$$

$$L_1(\beta) = L_1(\bar{\beta}) + \nabla L_1(\bar{\beta})^T (\beta - \bar{\beta}) + \sum_{t=2}^{\infty} \frac{1}{t!} \nabla^t L_1(\bar{\beta}) (\beta - \bar{\beta})^{\otimes t}$$

$$\sum_{t=2}^{\infty} \frac{1}{t!} \nabla^t L_1(\bar{\beta}) (\beta - \bar{\beta})^{\otimes t} = L_1(\beta) - L_1(\bar{\beta}) - \nabla L_1(\bar{\beta})^T (\beta - \bar{\beta})$$

First-order
SL function

$$\tilde{L}^1(\beta) = L_1(\beta) + \{\nabla L(\bar{\beta}) - \nabla L_1(\bar{\beta})\}^T \beta$$

$$\nabla L(\bar{\beta}) = \frac{1}{K} \sum \nabla L_j(\bar{\beta}); \quad \nabla L_j(\bar{\beta}) = \frac{1}{n} \sum_{i=1}^n \{y_{ij} - \text{expit}(x_{ij}^T \bar{\beta})\} x_{ij}$$

Increase the approximation accuracy

$$L(\beta) = L(\bar{\beta}) + \nabla L(\bar{\beta})^T (\beta - \bar{\beta}) + \frac{1}{2} \nabla^2 L(\bar{\beta})(\beta - \bar{\beta})^{\otimes 2} + \sum_{t=3}^{\infty} \frac{1}{t!} \nabla^t L(\bar{\beta})(\beta - \bar{\beta})^{\otimes t}$$

$$L_1(\beta) = L_1(\bar{\beta}) + \nabla L_1(\bar{\beta})^T (\beta - \bar{\beta}) + \frac{1}{2} \nabla^2 L_1(\bar{\beta})(\beta - \bar{\beta})^{\otimes 2} + \sum_{t=3}^{\infty} \frac{1}{t!} \nabla^t L_1(\bar{\beta})(\beta - \bar{\beta})^{\otimes t}$$

Second-order
SL function $\tilde{L}^2(\beta) = L_1(\beta) + \{\nabla L(\bar{\beta}) - \nabla L_1(\bar{\beta})\}^T \beta + \frac{1}{2} (\beta - \bar{\beta})^T \{\nabla^2 L(\bar{\beta}) - \nabla^2 L_1(\bar{\beta})\}^T (\beta - \bar{\beta})$

$$\nabla^t L(\bar{\beta}) = \frac{1}{K} \sum \nabla^t L_j(\bar{\beta}), \text{ for } t = 1, 2.$$

$$\nabla L_j(\bar{\beta}) = \frac{1}{n} \sum_{i=1}^n \{y_{ij} - \text{expit}(x_{ij}^T \bar{\beta})\} x_{ij}; \quad \nabla^2 L_j(\bar{\beta}) = \frac{1}{n} \sum_{i=1}^n \text{expit}(x_{ij}^T \bar{\beta}) \{1 - \text{expit}(x_{ij}^T \bar{\beta})\} x_{ij} x_{ij}^T.$$

Surrogate likelihood estimates

- ▶ First-order algorithm (ODAL1)

$$\tilde{\beta}^1 = \operatorname{argmax}_{\beta} \tilde{L}^1(\beta)$$

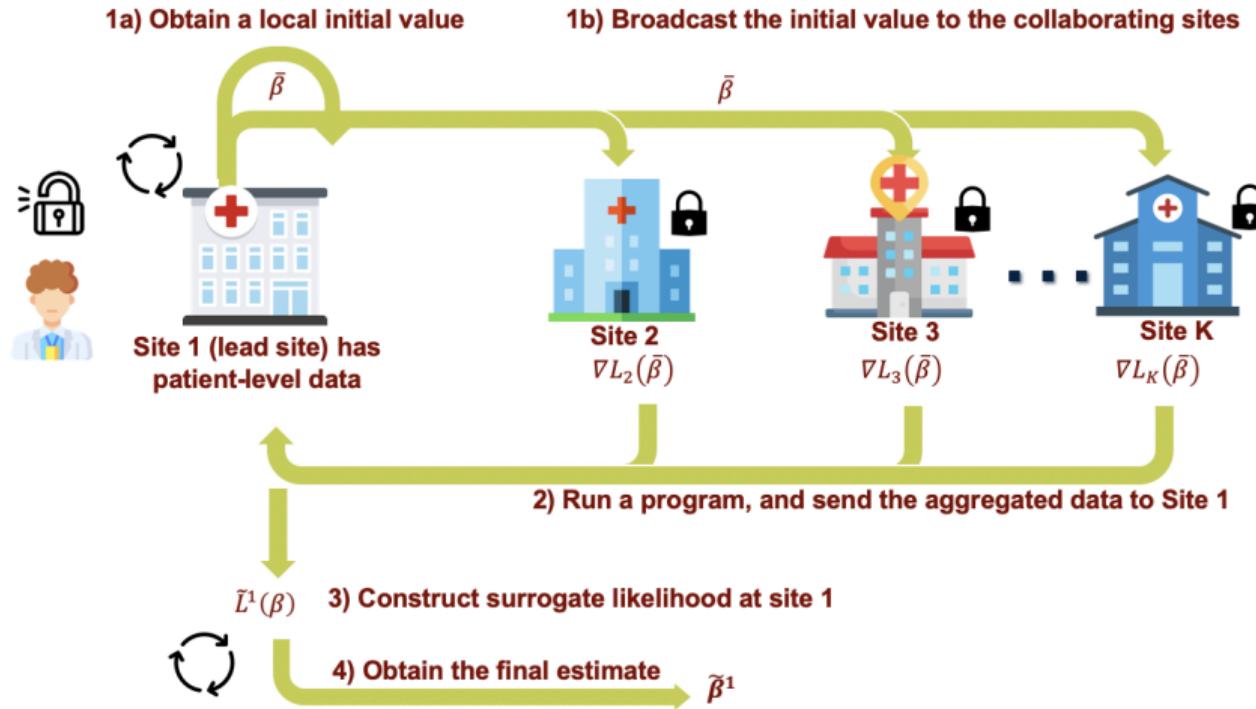
- ▶ Second-order algorithm (ODAL2)

$$\tilde{\beta}^2 = \operatorname{argmax}_{\beta} \tilde{L}^2(\beta)$$

- ▶ Initial estimator:

$$\bar{\beta} = \operatorname{argmax}_{\beta} L_1(\beta)$$

ODAL step-by-step illustration:



Theorem

Under mild regularity conditions, the proposed estimators $\tilde{\beta}^1$, and $\tilde{\beta}^2$ satisfy,

$$\sqrt{Kn}(\tilde{\beta}^t - \beta^*) \rightarrow N(0, \{\mathbb{E}\nabla^2 f(y, x; \beta^*)\}^{-1})$$

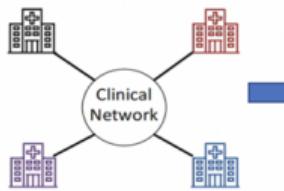
for $t = 1, 2$, as $Kn \rightarrow \infty$, where

$$f(y, x; \beta) = yx^T\beta - \log\{1 + \exp(x^T\beta)\}.$$

► Inference at local site (no extra communication)

$$\hat{V}_1 = \frac{1}{Kn}\{\nabla^2 L_1(\tilde{\beta}^1)\}^{-1}; \hat{V}_2 = \frac{1}{Kn}\{\nabla^2 L_1(\tilde{\beta}^2)\}^{-1}$$

ODAL advantages:



Research question:
What are the risk factors
of acute myocardial
infarction?

Fit a logistic model with
4 risk factors.

How to perform multicenter
analysis?

Strategy 1: pooled analysis

A screenshot of a Microsoft Excel spreadsheet titled 'Pooled Analysis'. The table contains numerous rows of data, likely patient records, with columns labeled such as 'Patient ID', 'Diagnosis', 'Treatment', and 'Outcome'. The data is presented in a grid format with many rows and columns of numerical and categorical values.

Strategy 2: ODAL

A screenshot of a Microsoft Excel spreadsheet titled 'ODAL'. The table displays a smaller set of data, specifically the coefficients for a logistic regression model. The columns are labeled with coefficients: 0.0010174, -0.1120191, 0.7630214, -1.0001602, and -0.140350. The table has fewer rows and columns than the pooled analysis table.

Two results are nearly the same.
(Duan et al. 2019)

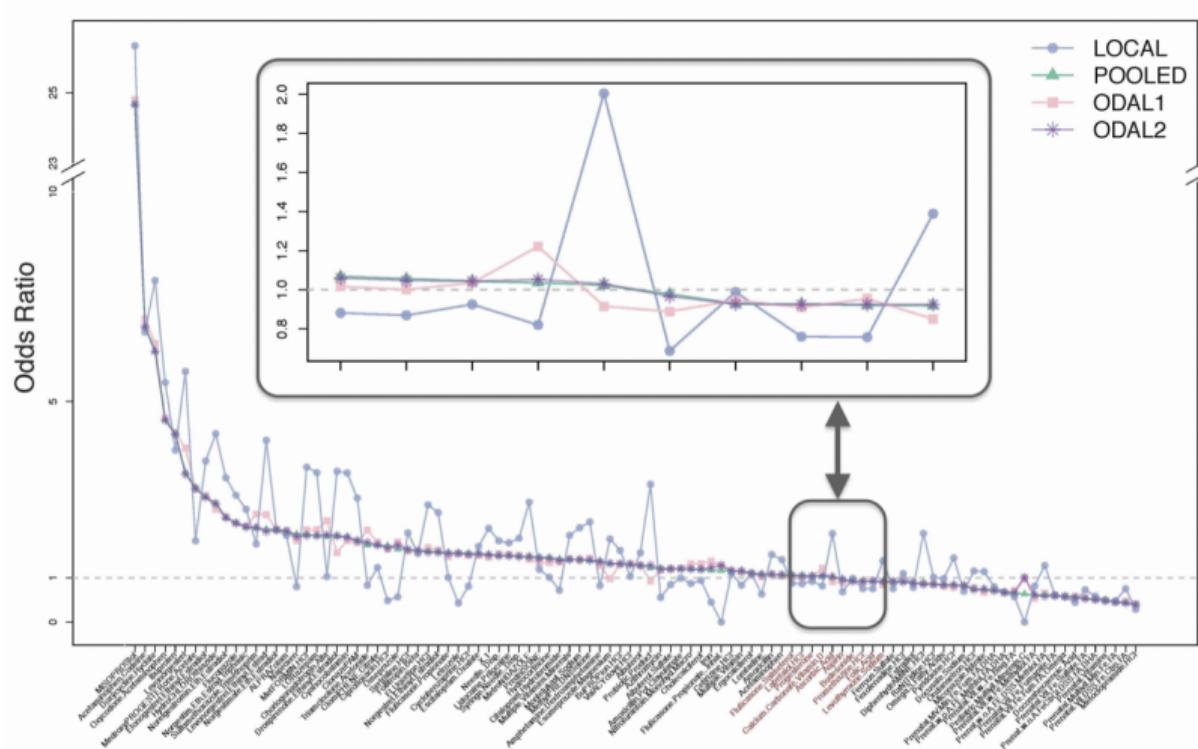
Evaluation through EHR data from Penn Medicine

- ▶ Outcome: normal pregnancy (Z34 ICD-10 codes or a V22 ICD-9 code) or a fetal loss (ICD-9 code 630-639 or ICD-10 code O00-O08)
- ▶ Exposure: 100 most common medications prescribed during pregnancy, prevalence ranging from 0.05% - 20%.

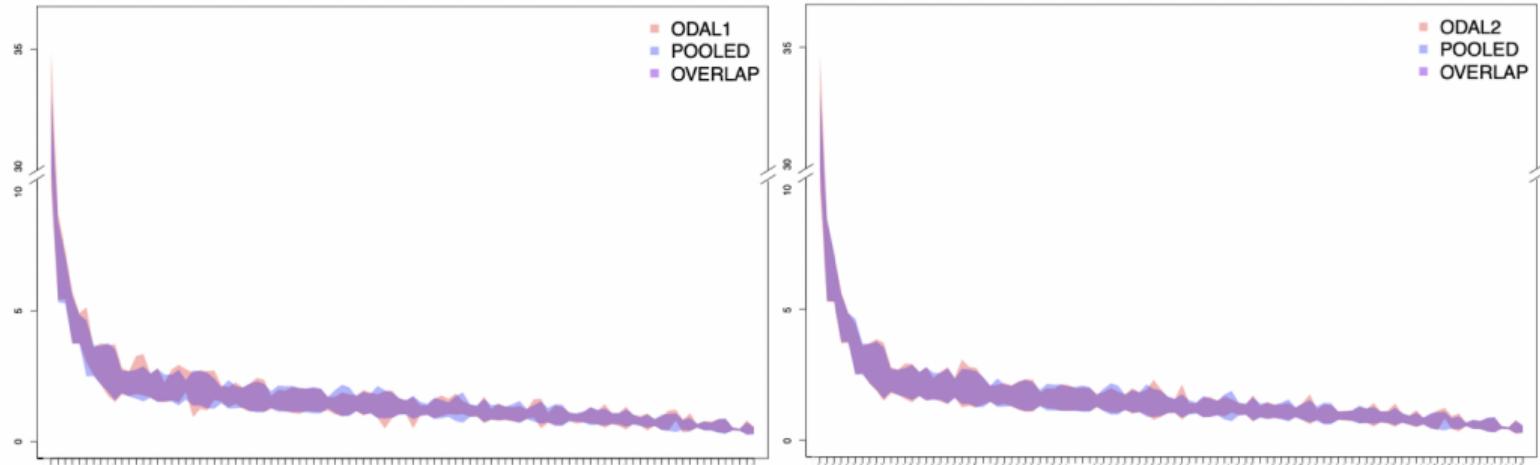
Table 1. Demographics of Pregnancies Treated at UPenn Health System (UPHS)

Demographics	Normal Pregnancy (N=30,810)	Fetal Loss (M=4,763)	P-value
Race			
White *	13911 (45.2%)	2291 (48.1%)	
African American	12918 (41.9%)	1871 (39.3%)	
Other	1916 (6.2%)	274 (5.8%)	
Asian	2065 (6.7%)	327 (6.9%)	
Age	29.40	32.15	<0.001
Weight (pounds)	123.45	115.43	<0.001
Body Mass Index	16.95	16.61	0.043

Results



Results - inference



- ▶ ODAL2 needs to transfer an extra hessian matrix.
- ▶ ODAL2 provides more accurate estimation than ODAL1.

Results - inference

- ODAL: communication-efficient distributed algorithm for logistic regression
- What's next?

ODAC One-shot Distributed Algorithm for Cox Proportional Hazards Model

Journal of the American Medical Informatics Association, 0(0), 2020, 1–9

doi: 10.1093/jamia/ocaa044

Research and Applications



Research and Applications

Learning from local to global: An efficient distributed algorithm for modeling time-to-event data

Rui Duan,^{1,†} Chongliang Luo,^{1,†} Martijn J. Schuemie ,^{2,†} Jiayi Tong,¹ C. Jason Liang,³ Howard H. Chang,⁴ Mary Regina Boland ,¹ Jiang Bian,^{5,6} Hua Xu ,⁷ John H. Holmes,¹ Christopher B. Forrest,⁸ Sally C. Morton,⁹ Jesse A. Berlin,¹⁰ Jason H. Moore,¹ Kevin B. Mahoney,¹¹ and Yong Chen¹

New technical challenges

- ▶ For the i -th observation in the j -th site

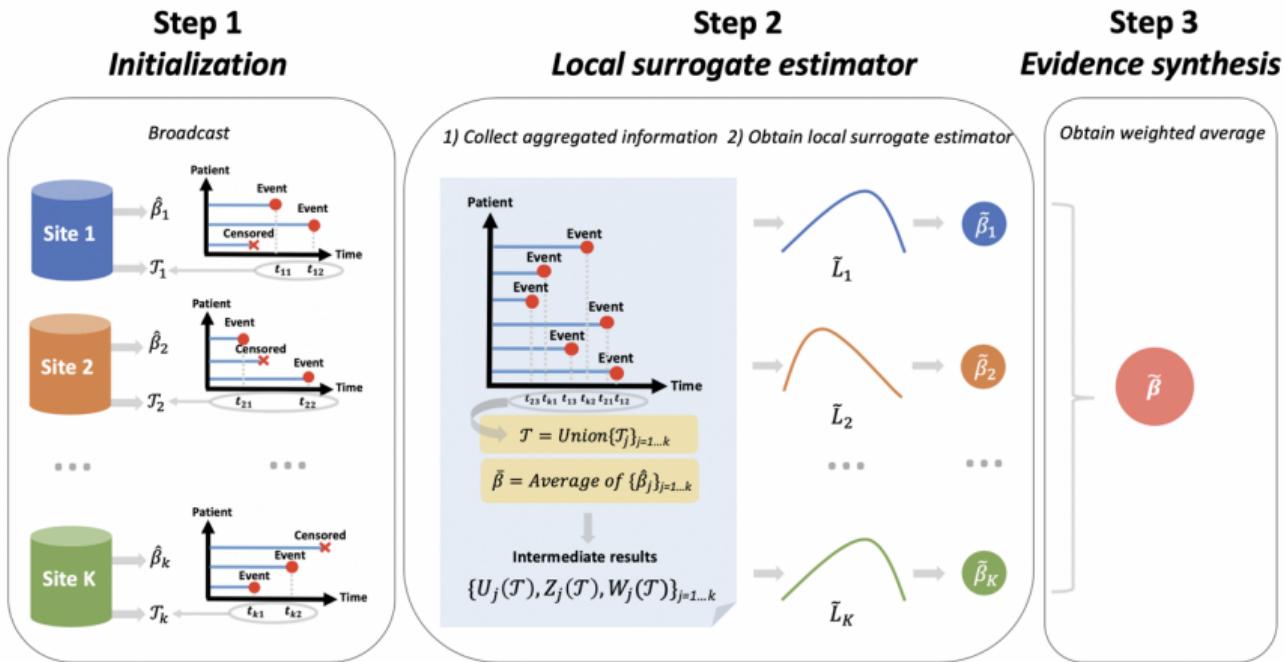
- y_{ij} --- time to event
- δ_{ij} --- censoring indicator
- x_{ij} --- observed risk factors

- ▶ Combined log partial likelihood function

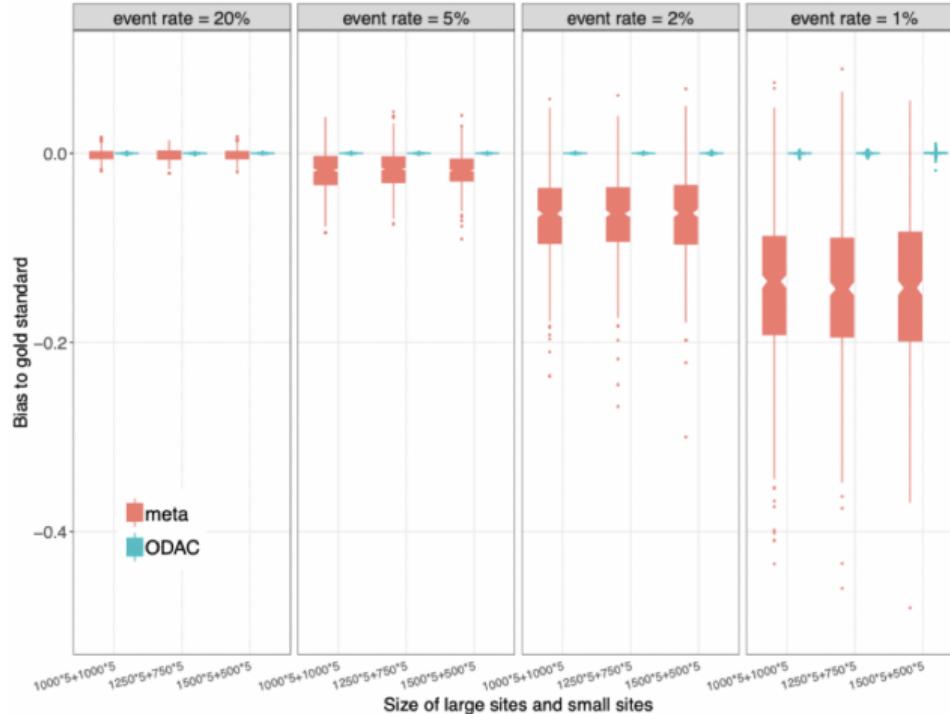
$$L(\beta) = \frac{1}{nK} \sum_{j=1}^K \sum_{i=1}^n \delta_{ij} \log \frac{\exp(x_{ij}^T \beta)}{\sum_{(l,m) \in R(y_{ij})} \exp(x_{lm}^T \beta)}$$

- ▶ Combined likelihood function cannot be written as sum of individual terms
- ▶ Denominator involves data from all sites

ODAC - step by step illustration



Benefit in studying rare events



- ▶ Meta-analysis has increasing bias when event is rarer.
- ▶ ODAC provides estimates close to the pooled analysis.

Case study

- ▶ Four claims datasets.
- ▶ Population:
pharmacologically-treated
major depressive disorder
- ▶ Outcome: acute myocardial
infarction (AMI)
- ▶ Cox regression model with
8 risk factors.

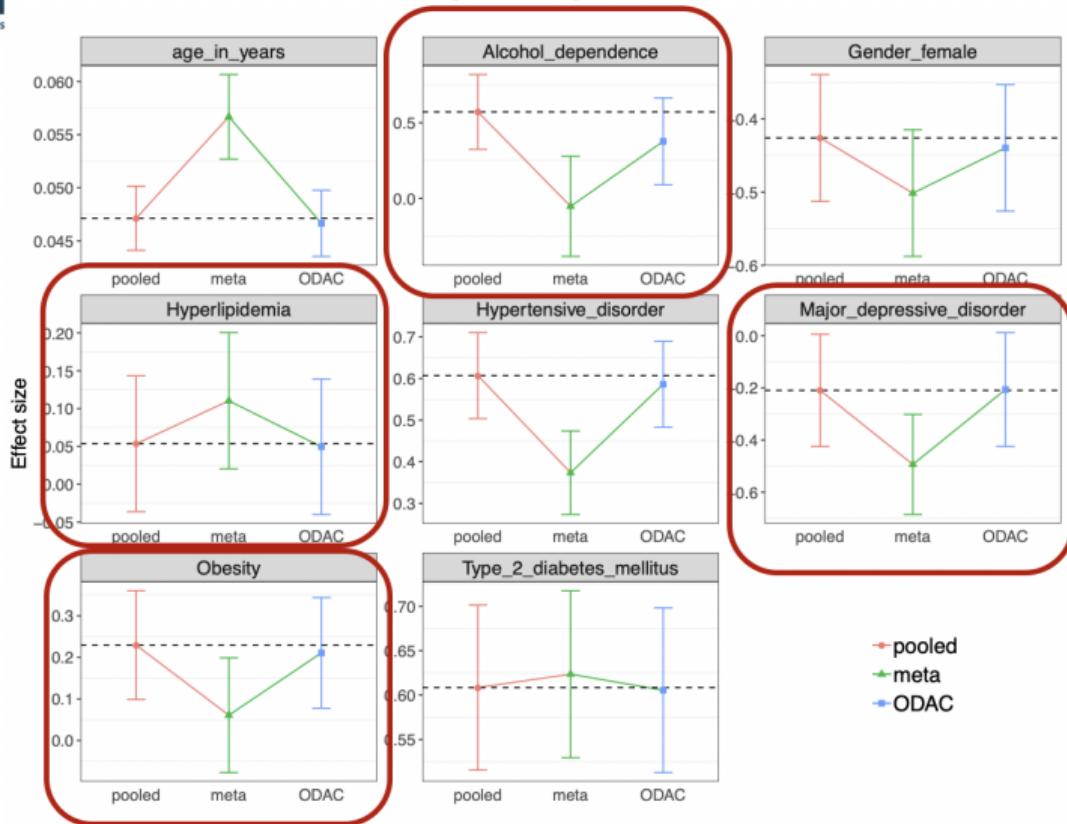
Table 1. Characteristics of the four claims datasets at OHDSI

Dataset	CCAE	MDCD	MDCR	Optum
Number of subjects	64,222	59,861	69,164	62,348
Median Age	43	35	71	47
% of Female	69.21	73.82	68.08	69.68
% of Congestive heart failure	0.70	3.06	7.58	2.61
% of Hypertensive disorder	20.81	31.80	57.70	32.96
% of Ischemic heart disease	1.70	3.82	10.27	4.10
% of Type 2 diabetes mellitus	7.49	14.63	21.83	12.71
% of Coronary arteriosclerosis	2.39	4.92	18.43	5.75
% of Renal failure syndrome	0.69	2.67	2.31	2.49
% of Transient cerebral ischemia	0.41	0.64	2.32	0.71
% of Hyperlipidemia	20.96	22.00	43.21	33.85
% of Obesity	7.15	16.54	6.71	9.62
% of Alcohol dependence	7.15	16.54	6.71	9.62
% of Major depressive disorder	4.17	3.55	3.16	3.34
% of Acute myocardial infarction	0.26	0.75	2.03	0.51
% of Stroke	0.24	0.73	1.75	0.58

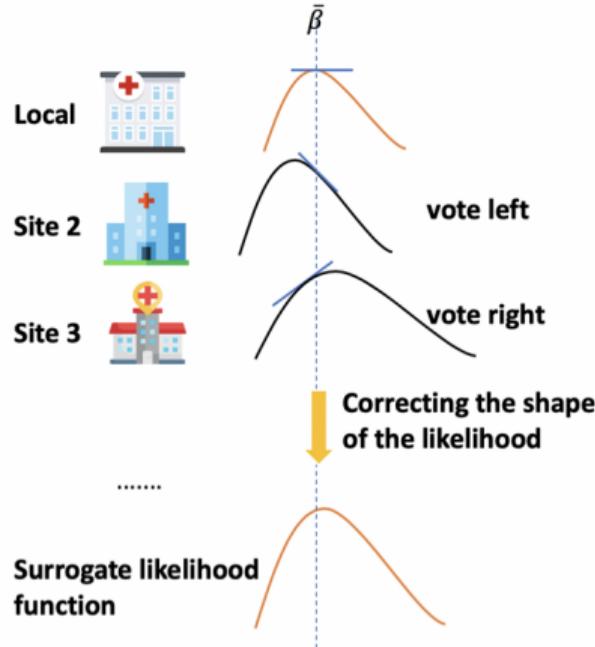
*The four claims datasets are CCAE (IBM MarketScan® Commercial), MDCD (IBM MarketScan® Medicaid), MDCR (IBM MarketScan® Medicare) and Optum (Optum© De-Identified Clininformatics).

Results (AMI)

- Risk factors for acute myocardial infarction (AMI):
 - gender
 - age
 - obesity
 - alcohol dependence
 - hypertensive disorder
 - major depressive disorder
 - type 2 diabetes mellitus
 - hyperlipidemia



Intuitions: a nice interpretation of surrogate likelihood



- ▶ Meta-analysis requires point estimate and standard error.
- ▶ In ODAL/ODAC, slopes and curvatures help to correct the shape of local likelihood function.

Recap: definition of surrogate likelihood

The surrogate likelihood (SL) approach

- For an initial value $\bar{\beta}$,

$$L(\beta) = L(\bar{\beta}) + \nabla L(\bar{\beta})^T (\beta - \bar{\beta}) + \sum_{t=2}^{\infty} \frac{1}{t!} \nabla^t L(\bar{\beta})(\beta - \bar{\beta})^{\otimes t}$$

$$L_1(\beta) = L_1(\bar{\beta}) + \nabla L_1(\bar{\beta})^T (\beta - \bar{\beta}) + \sum_{t=2}^{\infty} \frac{1}{t!} \nabla^t L_1(\bar{\beta})(\beta - \bar{\beta})^{\otimes t}$$

$$\sum_{t=2}^{\infty} \frac{1}{t!} \nabla^t L_1(\bar{\beta})(\beta - \bar{\beta})^{\otimes t} = L_1(\beta) - L_1(\bar{\beta}) - \nabla L_1(\bar{\beta})^T (\beta - \bar{\beta})$$

First-order
SL function

$$\tilde{L}^1(\beta) = L_1(\beta) + \{\nabla L(\bar{\beta}) - \nabla L_1(\bar{\beta})\}^T \beta$$

$$\nabla L(\bar{\beta}) = \frac{1}{K} \sum \nabla L_j(\bar{\beta}); \quad \nabla L_j(\bar{\beta}) = \frac{1}{n} \sum_{i=1}^n \{y_{ij} - \text{expit}(x_{ij}^T \bar{\beta})\} x_{ij}$$

Other exercises using surrogate likelihood - Poisson regression

ODAP

One-shot Distributed Algorithm for Quasi-Poisson regression

ODAP: One-Shot Distributed Algorithm for Performing Quasi-Poisson Regression

Mackenzie J. Edmondson^a, Chongliang Luo^a, Zhaoyi Chen^b, Jiang Bian^b, Yong Chen^a

- a. Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania
Perelman School of Medicine, Philadelphia, PA, USA
- b. University of Florida, Gainesville, FL, USA

Other exercises using surrogate likelihood - Hurdle regression

ODAH One-shot Distributed Algorithm for Hurdle Regression

Distributed Learning from Electronic Health Records Across Multiple Sites for Zero-Inflated Count Outcomes

Mackenzie J. Edmondson^a, Chongliang Luo^a, Rui Duan^a, Mitchell Maltenfort^b, Justine Shults^a,
Patrick B. Ryan^c, Christopher B. Forrest^b, Yong Chen^a

- a. Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
- b. Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA
- c. Janssen Research and Development, Titusville, NJ, USA

Heterogeneity in distributed research network

Hospital A



Hospital B

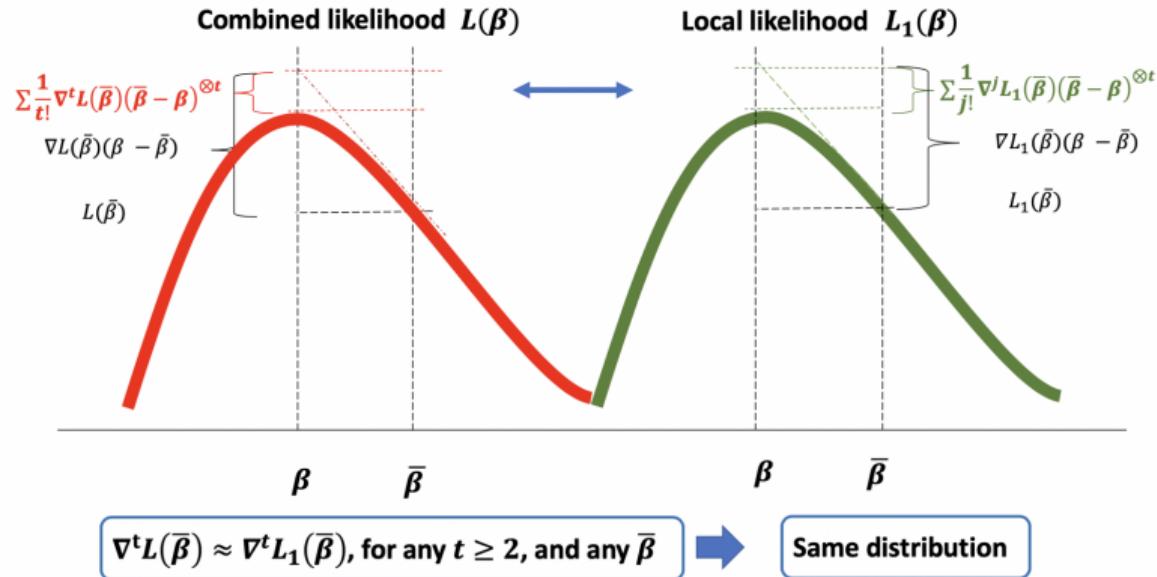


Hospital C



- Most of existing distributed algorithms ignored the intrinsic nature of between-site heterogeneity
- In real-world data, such heterogeneity cannot be ignored

Surrogate likelihood approach assumes homogeneous data



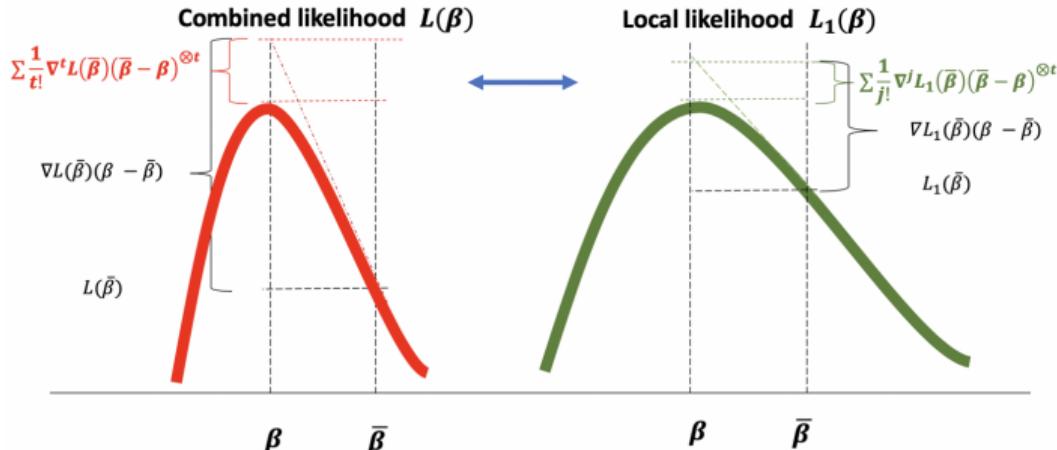
Heterogeneity assumption

- Data in the j -th site follows

$$Y_{ij} \sim f(y; \beta, \gamma_j)$$

- β is the *parameter of interest*
- γ_j is the *site-specific nuisance parameter*—allow site to be a covariate variable, allow interaction terms between site and other covariates.

Challenges



$$\nabla^t L(\bar{\beta}) \neq \nabla^t L_1(\bar{\beta})$$

- Local site cannot provide any information about nuisance parameters in other sites.

Heterogeneity-aware PDA algorithms

Biometrika (2015), 99, 1, pp. 1–17
© 2015 Biometrika Trust
Printed in Great Britain

Advance Access publication on 31 July 2015

Heterogeneity-aware and communication-efficient distributed statistical inference

BY RUI DUAN

Department of Biostatistics, Harvard University, Boston, Massachusetts 02115, U.S.A.
rduan@hsph.harvard.edu

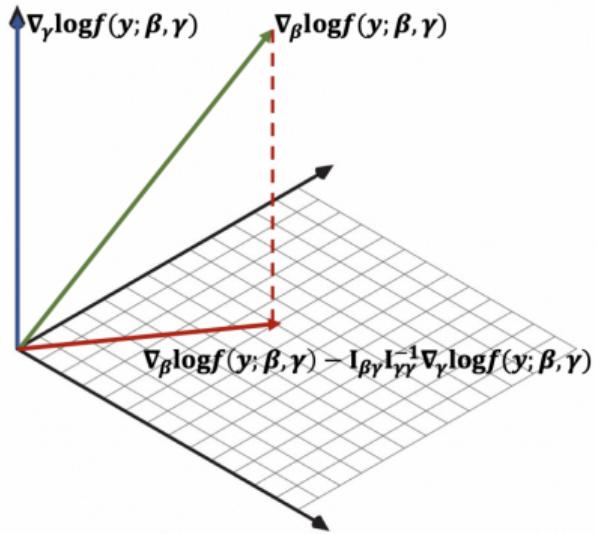
YANG NING

Department of Statistics and Data Science, Cornell University, Ithaca, New York, 14853, U.S.A.
yn265@cornell.edu

YONG CHEN

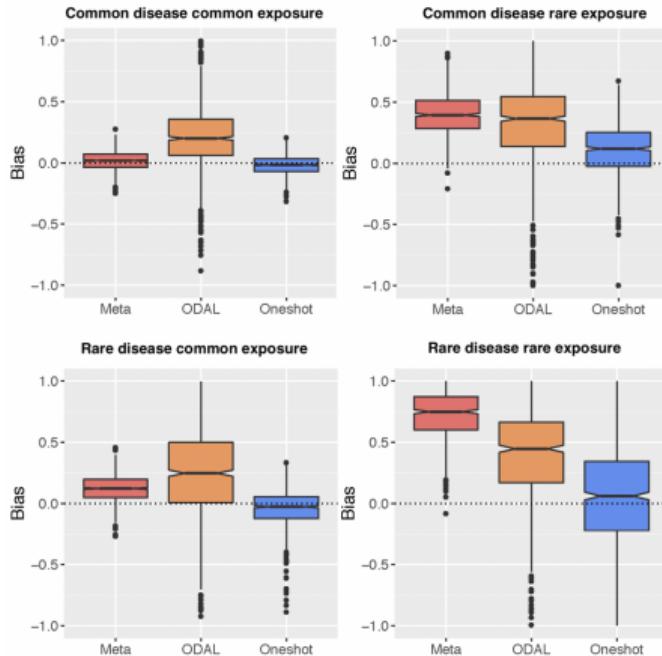
Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania,
Philadelphia, Pennsylvania 19104, U.S.A.
ychen123@upenn.edu

[arXiv:1912.09623](https://arxiv.org/abs/1912.09623) [Biometrika \(in press\)](#)



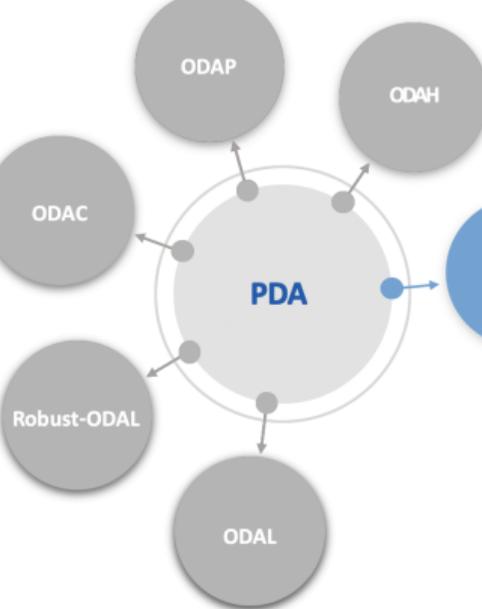
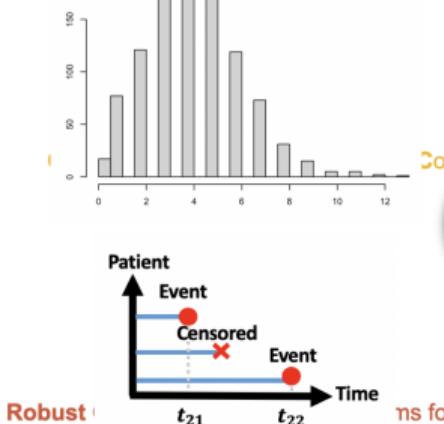
Conclusion

Desired Properties	Meta-analysis	Proposed estimator (T=1)	Proposed estimator (T=2)
Consistency	consistent	consistent	consistent
Distance to the Gold Standard Estimator	$\frac{C}{\sqrt{Kn}}$	$\asymp \frac{C}{n}$	$\asymp \frac{C}{n\sqrt{K}} + \frac{C}{n\sqrt{n}}$
Asymptotic Normality	asymptotic normal	asymptotic normal	asymptotic normal
Asymptotic Efficient	not efficient	efficient	efficient

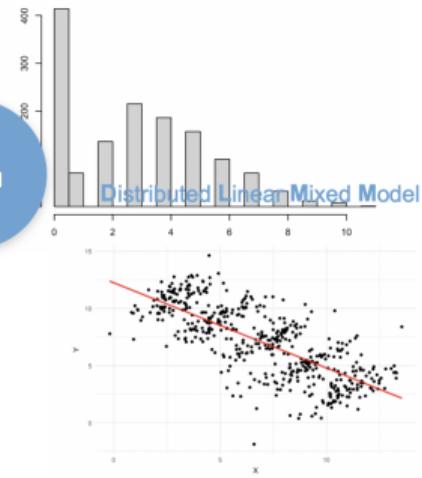


Duan, Rui, Yang Ning, and Yong Chen. "Heterogeneity-aware and communication-efficient distributed statistical inference." *arXiv preprint arXiv:1912.09623* (2019).

One-shot Distributed Algorithms for Poisson regression



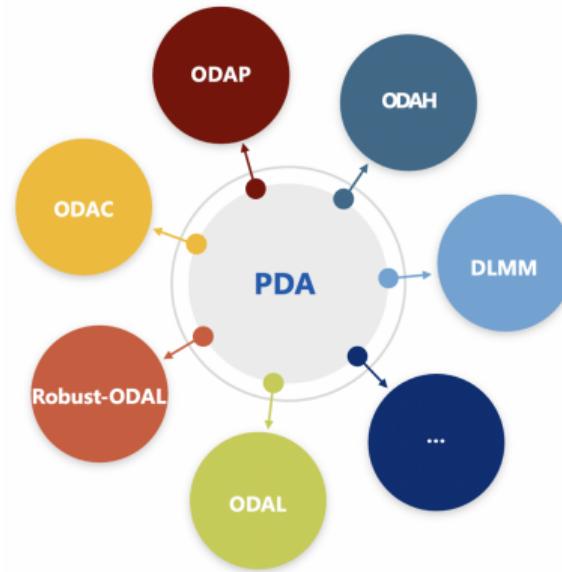
One-shot Distributed Algorithms for Hurdle regression



One-shot Distributed Algorithms for Logistic regression



PDA as a collection of distributed algorithms



R package ‘pda’: four principles



Tutorial 2

Outline

Introduction

Overview of the structure of EHR and claims data

Extracting data elements from the EHR

Missing data issues

Correcting for bias due to EHR data errors

Distributed Analysis

Conclusions and Wrap-up

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

Acknowledgments

American Statistical Association Biometrics Section