The role of data provenance in the estimation and analysis of EHR-derived phenotypes

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Overview

I: EHR-based Phenotyping

II: Effect of Phenotyping Error on Bias and Type I Error

III: Accounting for Phenotyping Error in Analyses

Conclusions
Data provenance refers to the process by which data come to be captured in the EHR.

Unlike data from a designed study, the data capture process in EHR-based studies is entirely outside the control (and often awareness) of the researcher.

Challenging aspects of data provenance for research include:
- Availability, type, and amount of data varies across patients.
- Clinical practices including frequency of visits, data that are recorded, tests that are ordered, etc may vary across clinics.
EHR data provenance

- Patient received care
- Patient & provider addressed condition of interest
- Information documented
- Extraneous or Erroneous Information documented

Electronic health record
- Structured clinical data
- Unstructured clinical data
- Administrative data
Phenotype estimation using EHR data

- Phenotype = collection of characteristics describing a patient
- Motivated by lack of gold-standard for many patient characteristics of interest
- Need ways to deduce characteristics that are not explicitly recorded
- The complexities of data provenance create challenges for phenotyping
Rule-based Phenotyping

- Most of the existing literature on EHR-derived phenotyping relies on “clinical decision rules”
- Algorithm based on clinical knowledge of the phenotype and coding practices
  - Simple or complex
  - Including one data element or many
  - May include a time component
- May incorporate structured data as well as unstructured data, often via NLP
## Example: Rule-based Phenotyping for T2DM

<table>
<thead>
<tr>
<th>Variable type</th>
<th>Examples</th>
<th>Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes diagnosis</td>
<td>T2DM, T1DM, DM NOS</td>
<td>ICD-9/10 codes</td>
</tr>
<tr>
<td>Medications</td>
<td>Insulin, Metformin</td>
<td>Prescribing data</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>PCOS, Obesity</td>
<td>ICD-9/10 codes</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Glucose, HbA1c</td>
<td>Procedure codes for test administration; numerical results</td>
</tr>
</tbody>
</table>
Example: eMERGE T2DM Rule

Kho et al. *J Am Med Inform Assoc* 2012;19:212-218
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
- Example of patient-driven observation
Typically, rule-based phenotypes have used a naive approach to missingness

Absence of evidence = evidence of absence

For conditions where all high risk individuals are evaluated for disease this may be reasonable

However, it ignores the fact that EHR represent a combination of biological information and information about interaction with health care system
A latent phenotype model

Unobserved true phenotype

Observable features (e.g., codes, medications, biomarkers)

Missingness in features

Priors for model parameters

\[ Y_i \sim \text{Bernoulli}(\theta_i) \]

\[ X_i \sim D(\mu_{ik}^X | Y_i = k) \]

\[ R_i \sim D(\mu_{ik}^R | Y_i = k) \]

\[ \pi(\theta_i), \pi(\mu_{ik}^X), \text{etc} \]

\[
L(\theta_i, \mu_i^X, \mu_i^R) = \sum_{k=0,1} P(Y_i = k | \theta_i) \prod_{j=1}^J f(R_{ij} | Y_i = k, \mu_{ik}^R) f(X_{ij} | Y_i = k, \mu_{ik}^X)^{R_{ij}}
\]

Posterior distribution for \( \theta_i | X_i, R_i \) can be used as a measure of the phenotype

Why Bayesian estimation?

• Bayesian framework combines strengths of formal statistical prediction and clinical knowledge-base
  ▶ Data can be used to identify patterns of data elements indicative of disease
  ▶ Likelihood incorporates all data elements available for an individual

• Expert opinion on predictive performance of biomarkers incorporated into prior distributions
Application to PEDSnet data

- We applied this approach to an EHR-derived data set from two PEDSnet sites
- Children age 10-18 years, at least two clinical encounters between 2001-2017 separated by at least 3 years
- On at least one occasion BMI z-score in excess of the 95th percentile for age and sex
- Cohort consisted of 32,553 children from site A and 24,342 children from site B
# T2DM Predictors in PEDSnet cohort

<table>
<thead>
<tr>
<th></th>
<th>Site A</th>
<th>Site B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Random Glucose</td>
<td>95.0 (35.0)</td>
<td>101.8 (44.5)</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>5.8 (1.2)</td>
<td>6.0 (1.4)</td>
</tr>
<tr>
<td>Endocrinologist</td>
<td>2,411 (7.4)</td>
<td>4,617 (19.0)</td>
</tr>
<tr>
<td>Metformin</td>
<td>357 (1.1)</td>
<td>1,460 (6.0)</td>
</tr>
<tr>
<td>Insulin</td>
<td>360 (1.1)</td>
<td>691 (2.8)</td>
</tr>
<tr>
<td>T1D Codes</td>
<td>408 (1.3)</td>
<td>787 (3.2)</td>
</tr>
<tr>
<td>T2D Codes</td>
<td>164 (0.5)</td>
<td>365 (1.5)</td>
</tr>
<tr>
<td>Missing glucose</td>
<td>6,382 (19.6)</td>
<td>8,204 (33.7)</td>
</tr>
<tr>
<td>Missing HbA1c</td>
<td>29,057 (89.3)</td>
<td>18,630 (76.5)</td>
</tr>
<tr>
<td>eMERGE T2DM</td>
<td>111 (0.3)</td>
<td>207 (0.9)</td>
</tr>
</tbody>
</table>
### Posterior means and CIs for model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Site A</th>
<th></th>
<th>Site B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean shift in glucose</td>
<td>135.24 (131.21, 139.25)</td>
<td>141.24 (138.87, 143.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2DM code sensitivity</td>
<td>0.20 (0.16, 0.24)</td>
<td>0.26 (0.23, 0.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2DM code specificity</td>
<td>1.00 (1.00, 1.00)</td>
<td>0.99 (0.99, 0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrinologist code sensitivity</td>
<td>0.95 (0.93, 0.97)</td>
<td>0.98 (0.97, 0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endocrinologist code specificity</strong></td>
<td>0.94 (0.94, 0.94)</td>
<td>0.84 (0.83, 0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin code sensitivity</td>
<td>0.29 (0.25, 0.33)</td>
<td>0.33 (0.30, 0.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metformin code specificity</strong></td>
<td>0.99 (0.99, 0.99)</td>
<td>0.95 (0.95, 0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR missing glucose</td>
<td>0.38 (0.31, 0.46)</td>
<td>0.20 (0.17, 0.23)</td>
<td></td>
<td></td>
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Error in EHR derived phenotypes

- EHRs provide the opportunity to identify novel risk factors
- However, EHR-derived phenotypes may exhibit exposure-dependent differences in data quality
  - More data available for patients with high intensity of contact with healthcare system (higher sensitivity among exposed)
  - High intensity patient also have more opportunity for erroneous codes to appear in charts (lower specificity)
- **Example:** Second breast cancer event (SBCE) in women with a history of breast cancer
  - Algorithm identifies SBCE with Se = 88%, Sp = 99%
  - Can algorithm be used to identify date of SBCE?
  - What are implications for estimation and hypothesis testing if imperfectly ascertained outcomes are used?
Second breast cancer events

- COMBO 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 cancer event (n = 1892)

No

A second breast cancer record in the SEER registry (n = 1711)

No

A mastectomy >180 days after the primary breast cancer event (n = 1642)

No

No second breast cancer event (n = 1612) 99% correctly classified

Mastectomy

Second breast cancer event (n = 11) 91% correctly classified

Yes

Surgical procedure for the primary breast cancer (SEER registry) (n = 30)

Lumpectomy

Second breast cancer event (n = 19) 84% correctly classified

Yes

A non-breast cancer record in the SEER registry after the primary breast cancer event (n = 181)

No

Second breast cancer event (n = 153) 90% correctly classified

Yes

No second breast cancer event (n = 28) 75% correctly classified
82% of events were within 60 days of algorithm-based date

Is this good enough?
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

<table>
<thead>
<tr>
<th>Sensitivity/specificity</th>
<th>Error in date</th>
</tr>
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<tbody>
<tr>
<td>Non-differential</td>
<td>Non-differential</td>
</tr>
<tr>
<td>Non-differential</td>
<td>Later event detection in exposed</td>
</tr>
<tr>
<td>Non-differential</td>
<td>Earlier event detection and less variability</td>
</tr>
<tr>
<td>Non-differential</td>
<td>Later event detection and more variability</td>
</tr>
<tr>
<td>Higher sensitivity/lower specificity</td>
<td>Non-differential</td>
</tr>
<tr>
<td>Higher sensitivity/lower specificity</td>
<td>Earlier event detection and less variability</td>
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</table>
## Simulation study for imperfect time to event outcomes

<table>
<thead>
<tr>
<th>Sensitivity/specificity</th>
<th>Error in date</th>
<th>% Bias in HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-differential</td>
<td>Non-differential</td>
<td>-2.2</td>
</tr>
<tr>
<td>Non-differential</td>
<td>Later event detection in exposed</td>
<td>0.4</td>
</tr>
<tr>
<td>Non-differential</td>
<td>Earlier event detection and less variability</td>
<td>-0.9</td>
</tr>
<tr>
<td>Non-differential</td>
<td>Later event detection and more variability</td>
<td>-3.8</td>
</tr>
<tr>
<td>Higher sensitivity/lower specificity</td>
<td>Non-differential</td>
<td>6.5</td>
</tr>
<tr>
<td>Higher sensitivity/lower specificity</td>
<td>Earlier event detection and less variability</td>
<td>8.1</td>
</tr>
</tbody>
</table>

In addition to bias, inflated type I error rates are of high importance as they indicate the frequency of spuriously identified risk factors.

Using COMBO data on EHR-derived SBCE and patient and cancer characteristics, we simulated an exposure variable \((E)\) that was independent of the outcome.

However, the sensitivity and specificity of the surrogate outcome \((Y^*)\) varied according to exposure status.
Type I error due to phenotyping error

- We then analyzed the association between \( Y^* \) and \( E \) using logistic regression.
- We varied the difference in sensitivity and specificity between exposed and unexposed across a range of values, with sensitivity in the unexposed fixed at 0.85 and specificity 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.
• 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%.

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What can we do about phenotyping error?

- We have seen that phenotyping error can lead to substantial bias and inflated type I error
- Numerous statistical methods have been developed to account for misclassified outcomes
- Despite this, the vast majority of EHR-based analyses in the applied literature use standard methods with no correction for misclassification
An approach for predicted probabilities

- Increasingly, phenotyping is using statistical or machine learning approaches that provide predicted probabilities of phenotype, $\hat{p}$
- More sophisticated phenotyping allows for covariate-specific phenotypes
- 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 unbiased estimates for regression coefficients.

A simple bias correction for risk differences

- In the context of logistic regression, this approach requires specialized software.
- In the context of risk difference regression, however, this approach gives rise to a very simple bias correction

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

- Therefore, \( \hat{\beta} = \frac{\beta^*}{\mu_1 - \mu_0} \) is unbiased for \( \beta \)
One additional complication

- Unfortunately, in the EHR context $\mu_0$ and $\mu_1$ 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 $\mu_0$ 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 $\mu_0$ and $\mu_1$

- Varying: AUC of $\hat{p}$, strength of effect ($\beta$), prevalence of $Y$
Bias: Prevalence = 0.5

AUC = 0.77

AUC = 0.86

AUC = 0.95

1. Gold standard
2. Dichotomized
3. Estimated $\hat{\mu}_0$, $\hat{\mu}_1$
4. True $\mu_0$, $\mu_1$
Bias: Prevalence = 0.1

AUC = 0.77

AUC = 0.86

AUC = 0.95

1. Gold standard
2. Dichotomized
3. Estimated $\hat{\mu}_0$, $\hat{\mu}_1$
4. True $\mu_0$, $\mu_1$
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• Consideration of data provenance is critical to appropriate development and analysis of phenotypes
• Efforts should be made to improve phenotypes
  ▶ Consider routine practice for how patients are treated and how frequently
  ▶ Don’t assume phenotypes are transportable across clinical sites
  ▶ Incorporate information on intensity of interaction with healthcare system
• Phenotyping error can result in substantial bias and type I error
• A variety of approaches exist to account for phenotyping error or conduct sensitivity analyses to determine if results are robust


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