A standardized framework for risk-based assessment of treatment effect heterogeneity in observational healthcare databases

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# Abstract

One of the aims of the Observational Health Data Sciences and Informatics (OHDSI) initiative is population-level treatment effect estimation in large observational databases. Since treatment effects are well-known to vary across groups of patients with different baseline risk, we aimed to extend the OHDSI library of open-source tools with a framework for risk-based assessment of treatment effect heterogeneity. The proposed framework consists of five steps: 1) definition of the problem, i.e. the population, the treatment, the comparator and the outcome(s) of interest; 2) identification of relevant databases; 3) development of a prediction model for the outcome(s) of interest; 4) estimation of relative and absolute treatment effect within strata of predicted risk, after adjusting for observed confounding; 5) presentation of the results. We demonstrate our framework by evaluating heterogeneity of the effect of angiotensin-converting enzyme (ACE) inhibitors versus beta blockers on 3 efficacy and 6 safety outcomes across three observational databases. Patients at low risk of acute myocardial infarction (MI) received negligible absolute benefits for all 3 efficacy outcomes, though they were more pronounced in the highest risk quarter, especially for hospitalization with heart failure. The substantial risk increase of cough and angioedema with ACE inhibitors across all risk strata suggests that beta blockers provide a viable alternative to patients at low risk of acute MI. The proof of concept study demonstrates its feasibility in large observational data. Further insights may arise by application to safety and effectiveness questions across the global data network.

**Keywords**: observational data, heterogeneity of treatment effect, risk stratification, subgroup analysis

# 1 Introduction

Understanding how a treatment’s effect varies across patients—a concept described as heterogeneity of treatment effects (HTE)—has been central to the agenda for both personalized (or precision) medicine and comparative effectiveness research. More formally, HTE has been defined as the non-random variability in the direction or magnitude of a treatment effect, in which the effect is measured using clinical outcomes [1]. Usually, analyses focus on the relative scale, where treatment effects are assessed one at a time in patient subgroups defined from single covariates, an approach that suffers from low power and multiplicity issues [2,3]. However, even with well-established constant relative effects, treatment benefit (or harm) may vary substantially on the absolute scale.

In recent years, a large number of methods has been developed for the assessment of HTE, mainly in the RCT setting. Earlier work suggested separating HTE analyses into exploratory, confirmatory, descriptive and predictive [4]. Exploratory analyses focus on hypothesis generation, confirmatory analyses test subgroup effect hypotheses, descriptive analyses aim at facilitating future synthesis of subgroup effects and predictive analyses predict probabilities of benefit or harm in individual patients. Predictive HTE approaches can be further subdivided into risk modeling, treatment effect modeling and optimal treatment regime methods, based on the reference class used for defining patient similarity when making individualized predictions or recommendations [5]. We focus on “risk modeling” approaches where patients are divided into risk strata using either an existing or an internally developed risk prediction model. Risk-stratum-specific estimates provide an overview of the evolution of treatment effects with increasing risk both on the relative and the absolute scale. Recently, systematic guidance on the application of such methods has been developed [6,7].

While these approaches were developed for application in randomized controlled trials (RCTs), observational databases are also an appealing substrate. Observational healthcare databases, such as administrative claims and electronic health records, are already highly available for the analysis of pharmacoepidemiologic research questions [8,9]. They are also often larger than many typical trials, providing excellent power for HTE analysis, including heterogeneous populations. However, unlike RCTs, treatment effects are subject to confounding, while the unique structure of different databases calls for database-specific analysis plans that often are not easily transportable. Because of the latter issue, running analyses at scale demands a big investment of time and effort, as researchers are forced to map their analysis plans to the databases available to them.

The Observational Health Data Sciences and Informatics (OHDSI) collaborative has established an international network of data partners and researchers that aim to bring out the value of health data through large-scale analytics by mapping all available databases to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [10,11].

We aimed to develop a framework for implementing a risk-based predictive approach for evaluating HTE in high-dimensional observational data, extending the existing guidelines of the RCT setting. Our publicly available package provides an out-of-the-box solution for implementing such analyses at scale within the OHDSI network, taking advantage of the OMOP-CDM. We implemented the framework using existing OHDSI methods including the patient-level prediction framework and the population-level effect estimation framework based on new-user cohort design [12,13]. As a proof-of-concept we analyzed heterogeneity of the effects of first-line hypertension treatment: we compared the effect of angiotensin converting enzyme (ACE) inhibitors to beta blockers on 9 outcomes across three different US claims databases.

# 2 Materials and Methods

The proposed framework defines 5 distinct steps that enable a standardized approach for risk-based assessment of treatment effect heterogeneity for databases mapped to the OMOP-CDM. These are: 1) general definition of the research aim; 2) identification of the database within which the analyses will be performed; 3) a prediction step where internal or external prediction models are used to assign patient-level risk predictions; 4) an estimation step where absolute and relative treatment effects are estimated within risk strata; 5) presentation of the results. We developed an open-source R-package for the implementation of the proposed framework and made it publicly available. The source code can be found at <https://github.com/OHDSI/RiskStratifiedEstimation>.

## 2.1 Step 1: General definition of the problem

The typical research aim is: “to compare the effect of treatment to a comparator treatment in patients with disease with respect to outcomes ”.

Cohort definitions are crucial for this step of the framework. We define a cohort as the set of patients who satisfy one or more inclusion criteria for a duration of time. A cohort within the OHDSI setting is more than a set of specific clinical codes, providing a definition of a logic for how to use that code set. All cohort definitions consist of: an entry event, i.e. the time a patient enters a cohort; a set of inclusion criteria applied to the initial event cohort to further restrict the set of people, resulting in the construction of the construction of the qualifying cohort; cohort exit criteria that terminate the patient’s presence in the cohort. Cohort definitions are transportable, meaning that in theory they can be implemented in any database, provided that it is mapped to the OMOP-CDM.

Our framework uses a comparative cohort design. This means that at least 3 cohorts of patients need to be defined at this stage of the framework.

* A single treatment cohort () which includes patients with disease receiving the target treatment of interest. For example, a set of hypertension patients within a database that receive angiotensin-converting enzyme inhibitors, followed from the time of initiation until the time of censoring.
* A single comparator cohort () which includes patients with disease receiving the comparator (control) treatment. For example, a set of patients in a database that receive beta blockers, followed from the time of initiation until the time of censoring.
* One or more outcome cohorts () that contain patients developing the outcomes of interest. For example, the set of patients in a database that have at least one occurrence of acute myocardial infarction
  1. in their record.

## 2.2 Step 2: Identification of the database

The aim of this step is the inclusion of databases that represent the patient population of interest. It is required that the databases are mapped to the OMOP-CDM. The inclusion of multiple databases potentially increases the generalizability of results. Furthermore, the cohorts should preferably have adequate sample size with adequate follow-up time to ensure precise effect estimation, even within smaller risk strata. Other issues that may be of importance for database inclusion are the depth of data capture (the precision at which measurements, lab tests, conditions are recorded), the reliability of data entry and many more, also depending on the task at hand.

## 2.3 Step 3: Prediction

We adopt the standardized framework for the generation of patient-level prediction models using observational data that ensures adherence to existing guidelines [14,15]. This prediction framework requires the definition of two essential cohorts: a target cohort, i.e. a set of patients that satisfy one or more inclusion criteria for a duration of time, and an outcome cohort.

To generate the target cohort we pool the already defined treatment cohort and comparator cohort. Further restrictions can be applied on the target cohort to construct the final population on which the prediction model will be developed (e.g. exclude patients with a prior outcome in their history, before being included in the target cohort). To avoid deferentially fitting the prediction model to patients across treatment arms, thus introducing spurious interactions with treatment [16,17], we develop the patient-level prediction model in the propensity score-matched (1:1) subset of the population.

More specifically, we first estimate propensity scores using LASSO logistic regression and a large set of baseline covariates including demographics, drug exposures, diagnoses, measurements and medical devices. We match patients 1-1 using a caliper, i.e. the maximum distance that is acceptable for any match. The default value we use is 0.2 on the standardized logit scale for the propensity scores. Other methods of fitting the propensity scores, such as random forest and others can also be considered.

Finally, we need to define the time horizon within which we aim to make predictions and we also need to select the machine-learning algorithm we want to use to generate patient-level predictions. Currently, the available options are regularized logistic regression, random forest, gradient boosting machines, decision tree, naive Bayes, K-nearest neighbors, neural network and deep learning (convolutional neural networks, recurrent neural network and deep nets).

After model development, a performance overview of the derived prediction models including discrimination and calibration both in the propensity score matched subset, the entire population and separately for treated and comparator patients should also be reported. This is important to ensure that no overfitting of the prediction model in one of the cohorts has occurred. In addition, the performance of the prediction models is directly related to our ability to single out patient subgroups where treatment may be highly beneficial or unsafe. Kent et al [18] demonstrated that the event rate and the discriminative ability of the prediction model can predict very well the distribution of predicted risk. Lower event rate and higher c-statistic (given good calibration) result in high risk heterogeneity, thus making estimated average treatment effects uninformative. In this case, risk stratified analysis of HTE can be more effective in singling out patient subgroups that stand to benefit (or be harmed) most by treatment in question.

## 2.4 Step 4: Estimation

The aim of this step is the estimation of treatment effects (both on the relative and the absolute scale) within risk strata—typically 4 risk quarters—defined using the prediction model of step 3. Effect estimation may be focused on the difference in outcomes for a randomly selected person from the risk stratum (average treatment effect) or for a randomly selected person from the treatment cohort within the risk stratum receiving the treatment under study (average treatment effect on the treated).

Any appropriate method for the evaluation of relative and absolute treatment effects can be considered, as long as the this is done consistently in all risk strata. Common approaches are odds ratios or hazard ratios for relative scale estimates and differences in observed proportions or differences in Kaplan-Meier estimates for absolute scale estimates, depending on the problem at hand. We estimate propensity scores within risk strata which we then use to match patients from different treatment cohorts or stratify them into groups with similar propensity scores or to weigh each patient’s contribution to the estimation process [19].

Before focusing on the results of the estimation process we need to evaluate if adequate covariate balance was achieved within each risk stratum accounting for measured confounding. Common approaches include evaluation of the overlap of propensity score distributions and calculation of standardized covariate differences before and after propensity score adjustment.

A schematic overview of the prediction and estimation steps is presented in Figure 2.1.



Figure 2.1: (A) Starting from a treatment (top), a comparator (bottom) and an outcome (middle) cohort we estimate the propensity scores on the entire target population. (B) We match patients on the propensity scores and estimate the prediction model. Since we match patients we develop the prediction model on smaller subset of the initial population and, therefore, the number of patients is smaller in B compared to A. (C) We apply the prediction model on the entire population (green: lower 25% of the risk distribution; yellow: patients with risk between 25% and 50% of the risk distribution; orange: patients with risk between 50% and 75% of the risk distribution; red: patients at risk higher than 75% of the risk distribution). (D) We separate in risk subgroups, here quarters. Within risk quarters propensity scores are estimated again and relative and absolute treatment effects are estimated.

## 2.5 Step 5: Presentation of results

In the presence of a positive treatment effect and a well-discriminating prediction model we expect an increasing pattern of the differences in the absolute scale, even if treatment effects remain constant on the relative scale across risk strata. Due to this scale-dependence of treatment effect heterogeneity, results should be assessed both on the relative and the absolute scale. We find that a side-by-side presentation on a forest-like format can give a very good representation of our results.

# 3 Results

As a proof of concept, we focus on the comparison of angiotensin converting enzyme (ACE) inhibitors to beta blockers are among the most common treatment classes for hypertension, with well-established effectiveness. Beta blockers, even though initially widely used for the treatment of hypertension, more recent trials and meta-analyses have cast doubt on their relative effectiveness [20]. As a result, newer US guidelines do not consider beta blockers for initial treatment for hypertension while in the EU guidelines combination with other antihypertensive treatments is recommended [21,22]. However, another meta-analysis suggested that the efficacy profile of beta blockers is similar to other major treatment classes in younger hypertensive patients and, thus, countries like Canada still include them as a first-line treatment candidate [23,24].

## 3.1 Step 1: General definition of the problem

We consider the following research aim: “compare the effect of ACE-inhibitors () to the effect of beta blockers () in patients with established hypertension () with respect to 9 outcomes ()”. The cohorts are:

* Treatment cohort: Patients receiving any drug within the ACE-inhibitor class with at least one year of follow-up before treatment initiation and a recorded hypertension diagnosis within that year.
* Comparator cohort: Patients receiving any drug within the beta blocker class with at least one year of follow-up before treatment initiation and a recorded hypertension diagnosis within that year.
* Outcome cohorts: We consider 3 main and 6 safety outcome cohorts. These are patients in the database with a diagnosis of: acute MI; hospitalization with heart failure; ischemic or hemorrhagic stroke (efficacy outcomes); hypokalemia; hyperkalemia; hypotension; angioedema; cough; abnormal weight gain (safety outcomes).

All cohort definitions were identical to the ones used in the multinational study carried out within OHDSI that provided overall treatment effect estimates comparing all anti-hypertensive drug classes with each other [25]. More information can be found in the supplementary material.

## 3.2 Step 2: Identification of the databases

We used the following databases:

* IBM MarketScan Medicare Supplemental Beneficiaries (MDCR): Represents health services of retirees (aged 65 or older) in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service or capitated health plans. These data include adjudicated health insurance claims (e.g. inpatient, outpatient and outpatient pharmacy). Additionally, it captures laboratory tests for a subset of the covered lives.
* IBM MarketScan Medicaid (MDCD): Adjudicated US health insurance claims for Medicaid enrollees from multiple states. It includes hospital discharge diagnoses, outpatient diagnoses and procedures and outpatient pharmacy claims as well as ethnicity and Medicare eligibility.
* IBM MarketScan Commercial Claims and Encounters (CCAE): Data from individuals enrolled in US employer-sponsored insurance health plans. The data includes adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) as well as enrollment data from large employers and health plans who provide private healthcare coverage to employees, their spouses and dependents. Additionally, it captures laboratory tests for a subset of the covered lives.

Our analyses included a total of 784,561, 66,820 and 101,661 patients initiating treatment with ACE inhibitors and 395,740, 45,999 and 69,798 patients initiating treatment with beta blockers in CCAE, MDCD and MDCD respectively (Table ??). Adequate numbers of patients were included in all strata of predicted acute MI risk.

## 3.3 Step 3: Prediction

We internally developed separate prediction models for acute MI in all 3 databases.

The prediction models were estimated on the propensity score matched (1:1) subset of the population, using caliper of 0.2 and after excluding patients having the outcomes any time prior to treatment initiation. We chose a time horizon of 2 years after inclusion into the target cohort. For this demonstration, we developed the prediction models using LASSO logistic regression with 3-fold cross validation for hyper-parameter selection. For this demonstration, we developed the prediction models using LASSO logistic regression with 3-fold cross validation for hyper-parameter selection.

The models developed in the 3 databases had moderate discriminative performance (internally validated) with no major issues of overfitting to any cohort except for the case of CCAE database in which the derived prediction model performed better in the comparator cohort (Table ??). We also observed lower performance of the prediction model developed in MDCR compared to the other 2 databases. Results on the calibration of the prediction models can be found in the supplement.

## 3.4 Step 4: Estimation

Our aim was to estimate the average treatment effects on the relative and the absolute scale within strata of predicted acute MI risk.

We used patient-level predictions to stratify the patient population into 4 risk quarters. Within risk strata, relative effects were estimated using Cox regression and absolute effects were estimated from the Kaplan-Meier estimate differences at 2 years after treatment initiation. To adjust for observed confounding within risk strata, we estimated propensity scores using the same approach as in the development of prediction models. We used the estimated propensity scores to stratify patients into 5 strata, within each risk quarter.

In general, there was sufficient overlap of propensity score distribution in all risk strata (Figure 3.1). If empirical equipoise was not achieved, the validity of the comparative effectiveness estimates would be questionable.

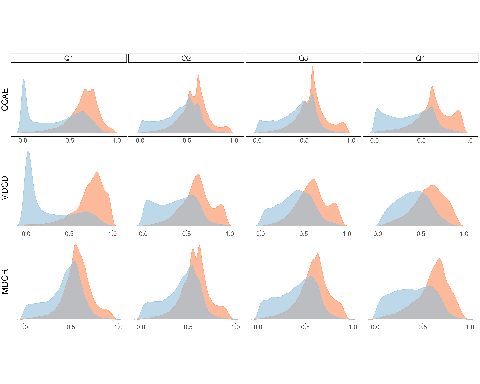


Figure 3.1: Preference score distributions for the evaluation of heterogeneity of the effect of ACE inhibitors compared to beta blockers on acute MI based on quarters of predicted acute MI risk. The preference score is a transformation of the propensity score that adjusts for prevalence differences between populations.

Propensity score adjustment achieved balance for most of the considered covariates, measured using standardized mean differences before and after adjustment (Figure 3.2). However, in lower risk strata imbalances persisted for a substantial subset of the covariates, all related to pregnancy findings. This was anticipated (use of ACE inhibitors is specifically contraindicated during pregnancy) and was already pointed out in [25].

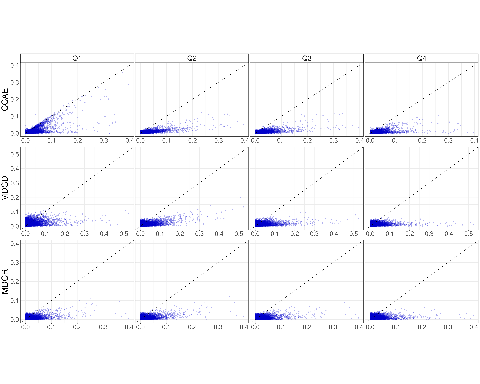


Figure 3.2: Patient characteristic balance for ACE inhibitors and beta blockers before and after stratification on the propensity scores. Each dot represents the standardized difference of means for a single covariate before (x-axis) and after (y-axis) stratification

## 3.5 Step 5: Presentation of results

For hospitalization with acute MI there was an increasing trend in favor ACE inhibitors compared to beta blockers on the relative scale (hazard ratios decreased) with increasing acute MI risk. More specifically, hazard ratios decreased from 0.98 (0.77 to 1.26; 95% CI), 1.30 (0.51 to 3.22; 95% CI) and 1.03 (0.82 to 1.29; 95% CI) to 0.76 (0.71 to 0.82; 95% CI), 0.94 (0.82 to 1.07; 95% CI) and 1.03 (0.93 to 1.15; 95% CI) in CCAE, MDCD and MDCR respectively (Figure 3.3). In terms of hospitalization with heart failure relative treatment effect estimates favored ACE inhibitors across all risk strata in all databases. We found no differences between the two treatments in their effect on stroke on the relative scale. In terms of the safety outcomes we found an increased risk of cough and angioedema on the relative scale across all risk strata. In the case of cough, this effect decreased with increasing risk of acute MI—from 1.37 (1.33 to 1.41; 95% CI), 1.35 (1.24 to 1.48; 95% CI) and 1.37 (1.29 to 1.45; 95% CI) in the lowest acute MI risk quarter to 1.26 (1.22 to 1.29; 95% CI), 1.07 (1.00 to 1.14) and 1.10 (1.04 to 1.17; 95% CI) in the highest acute MI risk quarter in CCAE, MDCD and MDCR respectively.

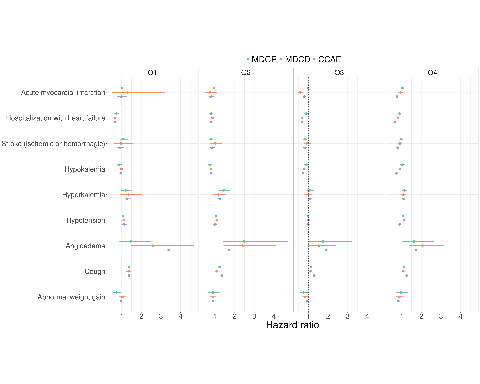


Figure 3.3: Overview of heterogeneity of ACE-inhibitors treatment on the relative scale (hazard ratios) within strata of predicted risk of acute MI. Values below 1 favor ACE inhibitors, while values above 1 favor beta blockers.

We observed an increasing trend of treatment effect on the absolute scale with increasing acute MI risk in favor of ACE inhibitors in terms of acute MI in all databases except for MDCR—from -0.03% (-0.08% to 0.01%; 95% CI), -0.05% (-0.18% to 0.08%; 95% CI) and -0.02% (-0.24% to 0.19%; 95% CI) in the lowest acute MI risk quarter to 0.54% (0.36% to 0.71%; 95% CI), 0.29% (-0.39% to 0.97%; 95% CI) and -0.39% (-0.96% to 0.18%; 95% CI) in the highest acute MI risk quarter in CCAE, MDCD and MDCR, respectively (Figure 3.4). We found no difference on the absolute scale for stroke across risk strata. Absolute risk differences did not favor ACE inhibitors compared to beta blockers in terms of cough, even though this effect again diminished with increasing acute MI risk—from -4.14% (-4.62% to -3.66%; 95% CI), -6.45% (-9.12% to -3.78%; 95% CI) and -4.81% (-5.76% to -3.85%; 95% CI) in the lowest acute MI risk quarter to -2.57% (-2.99% to -2.15%; 95% CI), -1.11% (-2.93% to 0.70%; 95% CI) and -1.69% (-2.83% to -0.55%; 95% CI) in the highest acute MI risk quarter in CCAE, MDCD and MDCR, respectively. In terms of angioedema absolute risk differences were very small due to the rarity of the outcome.

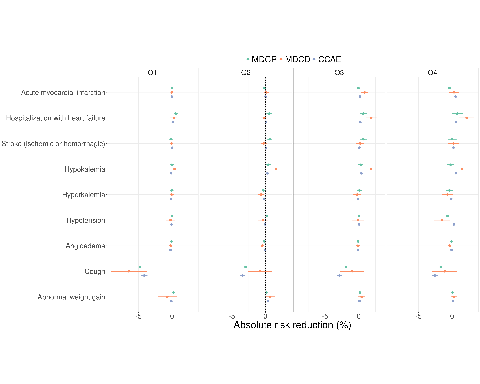


Figure 3.4: Overview of heterogeneity of ACE-inhibitors treatment on the absolute scale within strata of predicted risk of acute MI. Estimates of absolute treatment effect are derived as the difference in Kaplan-Meier estimates at 730 after inclusion. Values above 0 favor ACE inhibitors, while values below 0 favor beta blockers.

These results suggest that treatment with ACE-inhibitors, compared to treatment with beta blockers, may be focused on the higher risk patients, in whom the benefits outweigh the harms, while beta blockers may be a viable option in lower risk patients, in whom the benefit-harm tradeoff is more favorable. This is in accordance with earlier findings that beta blockers should also be considered as first-line treatment for younger hypertensive patients [23,26]. This analysis, however, was carried out as demonstration of the framework and more rigorous analyses are required to make any suggestions for clinical practice.

The results of the analyses performed can be accessed and assessed through a publicly available web application (<https://data.ohdsi.org/AceBeta9Outcomes>).

# 4 Discussion

We developed a framework for the assessment of heterogeneity of treatment effect in large observational databases using a risk modeling approach. The framework is implemented in an open source R-package in the OHDSI methods library (<https://github.com/OHDSI/RiskStratifiedEstimation>). As a proof-of-concept, we used our framework to evaluate heterogeneity of the effect of treatment with ACE-inhibitors compared to beta blockers on 3 efficacy and 6 safety outcomes.

In recent years several methods for the evaluation of treatment effect heterogeneity have been developed in the setting of RCTs [5]. However, low power and restricted prior knowledge on the mechanisms of variation in treatment effect are often inherent in RCTs, which are usually adequately powered only for the analysis of the primary outcome. Observational databases contain a large amount of information on treatment assignment and outcomes of interest, while also capturing key patient characteristics. Our framework provides a standardized approach that can be used to leverage available information from these data sources, allowing for large-scale risk-based assessment of treatment effect heterogeneity. It is an addition to the rapidly expanding literature of approaches for evaluating treatment effect heterogeneity. Multiple outcomes can be evaluated in patient subgroups of similar baseline outcome risk. Multiple outcome risk stratification schemes can also be considered. However, this should be done with caution, as it may hinder the interpretability of the results, in a similar manner as typical subgroup analyses.

Recently, guidelines on the application of risk modeling approaches for the assessment of heterogeneity of treatment effect in RCT settings have been proposed [27,28]. Our framework aims to translate these guidelines to the observational setting while also providing a toolkit for its implementation within OHDSI. It encourages open science as it requires accurate definition of the research questions translated into clear and reproducible cohort definitions that can easily be shared among researchers. Researchers with access to different databases mapped to OMOP-CDM can also very easily extend their overall analyses with risk-based assessment of treatment effect heterogeneity. This enables collaboration among multiple sites with access to different patient populations. We propose that the framework is implemented any time treatment effect estimation in high-dimensional observational data is undertaken.

Several considerations need to be made. First, estimates may be biased due to the observational nature of the data. We attempt to account for potential confounding by estimating propensity scores within strata of predicted risk. These scores are estimated using regularized logistic regression on a large set of pre-defined covariates. However, such approaches do not account for unobserved confounding [29]. Several sensitivity analyses have been proposed in the literature for measuring the robustness of results in the presence of unobserved confounding. Another approach is to calibrate estimates and confidence intervals based on a large set of negative controls [30,31]. Negative controls are treatment-outcome pairs for which a null effect has been established. Estimating these effects within available data provides an approximation of the null distribution that can be used to empirically recalibrate effect estimates. Future work may extend our framework with this type of analyses.

Our method provides a risk-stratified assessment of treatment effect heterogeneity. However, even though stratification can provide a useful overview for clinical interpretation, these results cannot be applied to individuals in a straightforward manner, as we are still estimating subgroup effects [27]. Presentation of treatment effects as a continuous function of risk would be more helpful, but is methodologically challenging. Future research is necessary for the development of methods for continuous risk-based assessment of HTE.

Ideally, externally derived and adequately validated prediction model would be preferred for analyzing treatment effect heterogeneity [6]. In the absence of such prediction models an internally-developed risk prediction model can be considered. Earlier simulations of RCT studies have shown that internal models developed on the combined treatment and control arms blinded to treatment gave relatively unbiased estimates of treatment effect across the spectrum of risk [16]. However, in observational databases treatment arms may significantly differ in sample size. Because the prediction model will possibly better fit to the larger treatment arm, spurious treatment-covariate interactions may be introduced in the prediction model, leading to sub-optimal risk stratification. As a remedy, we first match the patients in the treatment and the comparator cohorts on the basis of propensity scores. Additionally, we propose to assess model performance in the separate treatment arms to evaluate its aptness for risk stratification.

Recently, disease risk scores have been explored as an alternative to propensity scores for balancing covariates [32,33]. In our method, the objective of risk stratification is not balancing, but assessing the variation of treatment effects on multiple outcomes across patients with different levels of baseline risk. Although using the same risk model for balancing and risk-based HTE analysis may sound attractive, we note that our method only uses one risk model for stratification and one propensity score model for balancing, while separate disease risk score models would be required to analyze treatment effects for each of the multiple outcomes.

In conclusion, the proof-of-concept study demonstrates the feasibility of our framework for risk-based assessment of treatment effect heterogeneity in large observational data. The standardized framework is easily applicable and highly informative whenever treatment effect estimation in high-dimensional observational data is of interest. Our framework is a supplement to the population-level effect estimation framework developed within OHDSI and, in the presence of an adequately discriminating prediction model, can be used to make the overall results more actionable for medical decision making.

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