Assessing Heterogeneous Risk of Type II Diabetes Associated with Statin Usage: Evidence from Electronic Health Record Data

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Abstract

There have been increased concerns that the use of statins, one of the most commonly prescribed drugs for treating coronary artery disease, is potentially associated with the increased risk of new-onset type II diabetes (T2D). However, because existing clinical studies with limited sample sizes often suffer from selection bias issues, there is no robust evidence supporting as to whether and what kind of populations are indeed vulnerable for developing T2D after taking statins. In this case study, building on the biobank and electronic health record data in the Partner Health System, we introduce a new data analysis pipeline from a biological perspective and a novel statistical methodology that address the limitations in existing studies to: (i) systematically examine heterogeneous treatment effects of stain use on T2D risk, (ii) uncover which patient subgroup is most vulnerable to T2D after taking statins, and (iii) assess the replicability and statistical significance of the most vulnerable subgroup via bootstrap calibration. Our proposed bootstrap calibration approach delivers asymptotically sharp confidence intervals and debiased estimates for the treatment effect of the most vulnerable subgroup in the presence of possibly high-dimensional covariates. By implementing our proposed approach, we find that females with high T2D genetic risk at baseline are indeed at high risk of developing T2D due to statin use, which provides evidences to support future clinical decisions with respect to statin use.

Keywords: Bootstrap; Causal Inference; Debiased Inference; Subgroup Analysis; Precision Medicine

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1 Introduction

1.1 Motivation and objectives

Coronary artery disease (CAD), a disease affecting the function of heart, is the leading cause of deaths worldwide (Skourtis et al., 2020). Over the past decades, efforts have been made in developing effective and safe drugs in preventing and treating CAD (Povsic et al., 2017). Among those novel agents, statins are perhaps the most commonly prescribed drugs due to their clear benefits in reducing the level of low-density lipoprotein (LDL) and subsequently lowering CAD risks through 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibition (Nissen et al., 2005). Despite their clear benefits in reducing CAD risks, the use of statins is potentially associated with the increased risk of new-onset type II diabetes (T2D) (Waters et al., 2013; Macedo et al., 2014; Mansi et al., 2015).

Although many studies have been conducted to investigate the potential side effects of statins in developing T2D, to date, there is still no robust evidence as to whether and on what kind of population statin use increases the risk of T2D. Take some frequently cited studies as examples. Rajpathak et al. (2009) find through meta-analysis that there is a small increase in T2D risk \(^ 1\) associated with the use of statins, but this association is no longer significant after including the results from the WOSCOPS trial (Packard et al., 1998)—the first study investigating the association between T2D and statins. Recent studies also suggest that the effect of statins on T2D risk might be heterogeneous across different sub-populations and be more pronounced in certain subgroups defined by gender and baseline T2D risk (Mora et al., 2010; Goodarzi et al., 2013). Nevertheless, existing studies may lead to untrustworthy findings in subgroups, because their statistical analyses either are conducted under randomized controlled trials with limited sample sizes whose results might not be generalizable beyond study population, or do not adjust for multiple comparisons issue when several subgroups are under consideration (Waters et al., 2013).

In this case study, leveraging Partner Health System (PHS) biobank and electronic health record (EHR) data, we conduct subgroup analyses from a novel biological perspective aiming for the following three objectives: (i) designing a rigorous causal framework that systematically examines the (heterogeneous) causal effects of stain use on T2D risk in observational data, (ii) uncovering which

\(^1\) Relative risk (RR): 1.13, 95% CI [1.03, 1.23]
patient subgroup is most vulnerable for developing T2D after taking statins, and (iii) assessing the replicability and statistical significance of the most vulnerable subgroup (identified from the data) via a bootstrap calibration procedure.

1.2 Overview of research methods and findings

From a study design perspective, to establish valid causal conclusions, our research methods not only circumvent some common issues in randomized controlled trials (RCTs), but also alleviate the concern of unmeasured confounding bias issues in observation studies.

On the one hand, while existing studies often investigate the adverse effects of stains on T2D risk in RCTs with limited sample sizes, our study design leverages the large PHS biobank with linked EHR data, providing robust evidence for assessing the heterogeneous adverse effect of statin use from observational data. Concretely, we extract and link genotype information and diagnostics from consented subjects in the Partner Health System (PHS) biobank and EHR data respectively, which leads to an EHR virtual cohort of 17,023 subjects, a much larger cohort than those from usual clinical trials, and 337 features; see Section 2.3 for detailed descriptions. Compared to study cohorts enrolled in RCTs, our study cohort can be a more representative sample of the general population.

On the other hand, because causal conclusions derived from observational studies can be susceptible to unmeasured confounding and reverse causation bias issues, to alleviate these concerns, our study design adopts a randomly inherited single nucleotide polymorphism (SNP), rs12916-T, as a surrogate treatment variable of statin use. rs12916-T is a reliable surrogate treatment variable because it resides in the HMGCR gene encoding the drug target of statins, and has been recently used as an unbiased, unconfounded proxy for pharmacological action on the target of statins (i.e., HMG-CoA reductase inhibition) (Swerdlow et al., 2015; Consortium et al., 2012). Furthermore, adopting a randomly inherited genetic variant at conception as a surrogate for statin usage in EHRs allows us to establish a clear temporal precedence between the treatment and T2D onset (which is a prerequisite to concluding causality, see Holland (1986) for example), avoiding the potential issue of reverse causation. Lastly, because the surrogate treatment variable is naturally inherited, variables observed after birth are independent of rs12916-T and can at most be mediators that belong to a different causal pathway. We shall discuss the reasoning of using rs12916-T in more
Leveraging the above study design, we further conduct subgroup analyses to assess if subjects carrying the rs12916-T allele (i.e. taking statins) have heterogeneous risks at developing T2D, and, in particular, to what extent the most vulnerable subgroup suffers from statin use. Inspired by the study designs adopted in Mora et al. (2010) and Wang and Ware (2013), we divide the study cohort into six subgroups based on gender and baseline T2D genetic risk profiles (measured by the number of T2D risk alleles of variants rs3501184-A and rs1800961-T each individual carries). While numerous methods have been proposed for identifying subgroups (Lipkovich et al., 2011; Ma and Huang, 2017) and testing subgroup homogeneity (Shen and He, 2015; Fan et al., 2017), in our case study, we focus on post-hoc inference on the most vulnerable subgroup.

The limitation of post-hoc inference on the most vulnerable subgroup is well recognized. Due to subgroup selection bias induced by multiple comparisons, such post-hoc inference often leads to false positive results (Thomas and Bornkamp, 2017). Although several attempts have been made to address the subgroup selection bias issue, existing procedures are either poorly grounded (Stallard et al., 2008; Rosenkranz, 2016) or tend to be conservative (Hall and Miller, 2010; Fuentes et al., 2018), as the latter is typically built on simultaneous inference which aims to control the family-wise error rate for all candidate subgroups. These conservative simultaneous inference procedures are usually undesirable in subgroup analysis, because they often yield false negative discoveries and have inadequate power to confirm the most vulnerable subgroup (Magnusson and Turnbull, 2013; Burke et al., 2015). In our context, because subgroup analyses need to be conducted in observational studies (Yang et al., 2020; Lu et al., 2018), the problem becomes even more challenging as subgroup treatment effects need to take possibly high-dimensional confounders into account. To address the above-mentioned issues, we provide new inferential tools to help assess the efficacy of the post-hoc identified subgroups from observational studies without having to resort to simultaneous inference methods, which are often too conservative to start with.

By applying the proposed method to our study cohort, we find that, although the overall adverse effect of statin use on developing T2D is not significant, the female subgroup with more than two T2D risk alleles is identified as the most vulnerable subgroup from the data. The statistical significance of such a finding is also confirmed by the proposed bootstrap calibration method. In sum, our case study not only provides new evidence supporting the heterogeneous adverse effect of
statin use from a biological perspective, but also suggests that more caution should be taken when
statins are prescribed, especially for females who are already at higher risk of developing T2D. The
specific actions may include preventive treatments for diabetes and recommendations on lifestyle
changes.

The remainder of the manuscript is organized as follows. Section 2 describes our study design,
data source, and model setup. We then discuss our proposed methodology in Section 3, followed by
its theoretical investigations and empirical studies in Section 4. In Section 5, we discuss our data
analysis in depth and verify our causal evidence with sensitivity analyses. Finally, we summarize
our findings and discuss the potential impacts of this case study in Section 6.

2 Data description and model setup

2.1 Study design

We adopt the genetic variant (rs12916-T) as the surrogate treatment variable of statin use. When
the treatment indicator variable \( t = 1 \), this means that “the subject carries the variant rs12916-
T.” When \( t = 0 \), this means that “the subject does not carry the variant rs12916-T.” Carrying
rs12916-T is a proxy for pharmacological action of statin use, because rs12916-T, which resides in
the \textit{HMGCR} gene encoding the drug target of statins, has been recently adopted as an unbiased,
unconfounded proxy for pharmacological action on the target of statins (i.e., HMG-CoA reductase
inhibition) (Swerdlow et al., 2015; Consortium et al., 2012). In particular, Würtz et al. (2016)
shows that the metabolic changes (e.g. decreased LDL cholesterol level) associated with statin use
have been found to resemble the association between rs12916-T and the metabolic changes with
\( R^2 = 0.94 \). Therefore, we believe that rs12916-T is a credible surrogate treatment variable of statin
use.

Furthermore, following the causal diagram of our study design in Figure 1, we argue that
adopting rs12916-T as the surrogate treatment variable of statin use invests our framework with
two key benefits.

First, because our study design ensures the temporal precedence between inheriting the variant
rs12916-T (surrogate of statin use) and T2D onset, this lifts the concern of reverse causation in
conducting causal inference from observational data. In particular, when studying the causal effect
of statin use on T2D risk from observational data, one normally assumes that statin use causes the change in T2D risk (Pan et al., 2020; Swerdlow, 2016). This suggests that only data collected from subjects who have recorded statin use status before T2D onsets can be used for credible causal analyses. Unfortunately, in our EHR data, it is impossible to establish the temporal precedence between statin use and T2D onset. Using a genetic variant (rs12916-T) as the treatment variable circumvents the above-mentioned issue. Because genetic variants are randomly inherited at conception, our study design guarantees that the cause (carrying rs12916-T [proxy for pharmacological action of statin use] or not) must occur before T2D onset. This clear temporal precedence makes the established causal relationships more plausible (see Figure 1).

Second, adopting rs12916-T as a surrogate treatment variable attenuates the concern of unmeasured confounding biases. Given rs12916-T is naturally inherited, variables observed after birth can at most be mediators that belong to a different causal pathway. Since we aim to estimate the direct causal effect between the treatment and the outcome, conditional on such (unmeasured) mediators is not necessary. Thus, unmeasured confounding bias issues are alleviated under our study design. Yet we still include additional potential confounders that are obtained before birth, such as genetic variants associated with T2D and potentially associated with rs12916-T, in order to further robustify our causal conclusion and improve statistical estimation efficiency of the underlying causal effect.

Note that while rs12916-T is sometimes used as an instrumental variable in Mendelian Random-
ization analyses (Würtz et al., 2016), we use rs12916-T as a surrogate treatment variable, instead of an instrumental variable. Our study design is thus different from Mendelian randomization (MR) (Kang et al., 2016; Windmeijer et al., 2019). Furthermore, because MR often assumes that the causal direction between two traits is known as a priori (Xue and Pan, 2020) and our data do not provide the temporal order between stain use and T2D onset, the causal direction for MR analyses can not be specified and MR is not suitable in our case study.

The outcome of interest is T2D status. We defer the technical details on defining T2D status from EHR data to Section 2.3. Considering that the existing literature (Mora et al., 2010; Waters et al., 2013) has suggested that the treatment effect of statin use on T2D risk could be heterogeneous, we conduct subgroup analyses to investigate the heterogeneous treatment effect. Inspired by the study designs in Mora et al. (2010) and Waters et al. (2013) where the authors divide patient population based on gender in the former and the number of T2D baseline risk factors in the latter, we divide our PHS study cohorts into six subgroups based on gender and baseline T2D genetic risk profiles to conduct subgroup analyses. The T2D genetic risk is measured by the number of copies of T2D risk allele of variants rs35011184-A and rs1800961-T each subject has. The more T2D risk alleles the subject has, the higher baseline T2D risk the subject bears (Lango et al., 2008). We define “low-risk” as the total number of alleles = 0, “mid-risk” as the total number of alleles = 1, and “high-risk” as the total number of alleles ≥ 2. The six subgroups are thereby divided as (1) high-risk female; (2) mid-risk female; (3) low-risk female; (4) high-risk male; (5) mid-risk male, and (6) low-risk male.

Here, we consider pre-defined subgroups instead of post-hoc identified subgroups. Post-hoc identified subgroups are often adopted when there is no prior information about the segregation of study population (Lipkovich et al., 2011; Ma and Huang, 2017). In our setting, because previous studies (Mora et al., 2010; Waters et al., 2013) suggest that T2D risk might be heterogeneous across gender and baseline T2D genetic profiles, predefined subgroups considered above are more suitable for the present case study.
2.2 Model setup

We work with the following sparse logistic regression model:

\[
\text{logit}\left\{ P(y^* = 1 \mid z, x) \right\} = z^T \beta + x^T \gamma, \quad \|\gamma\|_0 \ll p.
\]

Here, \( y \) is the observed binary outcome representing the T2D status. \( z \in \mathbb{R}^{p_1 \times n} \) includes variables representing interactions between the treatment variable and all the six subgroup indicator variables. \( x \in \mathbb{R}^{p_2 \times n} \) contains 336 covariates and an intercept (hence \( p_2 = 337 \)). The 336 covariates contain 5 subgroup indicator variables (the sixth subgroup, low-risk male, indicator variable is dropped to avoid collinearity) and 331 potential confounders (including race and age as baseline characteristics, and 329 SNPs associated with T2D related factors accounting for potential confounding issues). Note that we do not include the treatment variable as a covariate because including it causes collinearity issues. All observed covariates are obtained from Partner Health System biobank.

Following the above setup, \( \beta \in \mathbb{R}^{p_1} \) represents subgroup treatment effects on the scale of log odds ratio (OR) (hence \( p_1 = 6 \)). More concretely, under Model (1), \( \beta = (\log \alpha_1, \ldots, \log \alpha_6) \) with \( \log \alpha_j \) representing the log odds ratio of subgroup \( j \), for \( j = 1, \ldots, 6 \). Following the Neyman-Rubin causal model and our current study design, we provide rigorous causal identification results to justify why the model parametrization in (1) enables us to estimate the heterogeneous treatment effects in the pre-defined subgroups. This theoretical justification is provided in Supplementary Materials Section E. We further assume that \( \gamma \in \mathbb{R}^{p_2} \) is a sparse vector with the support set \( \mathcal{M}_0 \). The sparsity assumption not only provides a parsimonious explanation of the data but also carries our prior belief that not every genetic variant is predictive of the outcome.

2.3 Data description and exploration

Following our study design described in the previous section, we have extracted information of \( n = 17,023 \) subjects each with \( p = 337 \) features through linked diagnostics from the PHS EHR data and genotype information from the PHS biobank data; see Table 1 for data summary.

Recall that the covariates contain age, race, subgroup indicators, and genetic variants associated with T2D related factors (including LDL, high density lipoprotein and obesity). As for the definition
| Variable                   | Frequency (percent) |
|---------------------------|--------------------|
| Sex                       |                    |
| Female                    | 7,592 (45)         |
| Male                      | 9,431 (55)         |
| Age (years)               |                    |
| <40                       | 2,333 (14)         |
| 40–50                     | 1,733 (10)         |
| 50–60                     | 2,824 (17)         |
| 60–70                     | 3,971 (23)         |
| 70–80                     | 4,042 (24)         |
| ≥80                       | 2,120 (12)         |
| Race                      |                    |
| European                  | 15,048 (88)        |
| African American          | 1,004 (6)          |
| Other/Unknown             | 971 (6)            |
| Ethnicity                 |                    |
| Hispanic or Latino        | 698 (4)            |
| Other/Unknown             | 16,325 (96)        |
| Number of rs12916-T allele|                    |
| 2                         | 6,245 (37)         |
| 1                         | 8,079 (47)         |
| 0                         | 2,699 (16)         |
| With T2D                  |                    |
| Yes                       | 2,565 (15)         |
| No                        | 14,458 (85)        |

Table 1: Demographics of 17,023 PHS subjects considered in our study.

of the outcome, since the diagnostic billing code for T2D has limited specificity in classifying the true T2D status, we define the T2D status based on a previously validated multimodal automated phenotyping (MAP) algorithm (Liao et al., 2019). The area under the ROC curve (AUC) of MAP’s risk prediction score for classifying true T2D status is 0.99, and the specificity and sensitivity of its classifier are 0.97 and 0.92 respectively. These suggest that the MAP classifier of T2D can be reliably used to define the T2D outcome. Among our study cohort, MAP classifies 2,565 subjects having T2D.

To explore the association between statin use and T2D risk, we report preliminary data exploration results from a “full” logistic regression model for y against the treatment t and the covariates x in Table 2. There, although a modest association is found between carrying the rs12916-T variant and T2D status in the overall study cohort, unlike the results in Swerdlow et al. (2015), this association is not statistically significant. Moreover, our analysis reports only 16 regression coefficients having p-values < 0.05, suggesting that the logistic regression coefficient vector is likely to be
sparse. Because the overall treatment effect is marginal (estimated marginal treatment effect equals 0.04 with p-value 0.35), this motivates us to conduct subgroup analyses to further investigate the heterogeneous adverse effect of statin use on T2D risk.

| Treatment effect               | Est | SE  | Z-value | p-value | # of significant coefficients |
|--------------------------------|-----|-----|---------|---------|------------------------------|
| Full logistic regression       | 0.04| 0.04| 0.93    | 0.35    | 16                           |

Table 2: The estimated treatment effect (Est), standard error (SE), Z- and (two-sided) p-values of statins’ usage on the overall PHS study cohort. We fit the “full” logistic regression model with 337 features (age, race and genetic information). “significant coefficients” are the estimated regression coefficients with p-values < 0.05.

2.4 Challenges in statistical inference

Because our goal is to uncover the patient subgroup most vulnerable for developing T2D and assess the statistical replicability of our findings, our methodological development hence centers around delivering valid inference (accurate point estimate and valid confidence interval) on the effect size of maximal regression coefficient $\beta_{\text{max}} = \max_{j \in \{1, \ldots, p_1\}} \beta_j$ in Model (1). Making inference on this parameter allows us to inform public health researchers and regulatory agencies whether extra caution should be taken for the most vulnerable patient subgroup when prescribing statins.

In the presence of high-dimensional covariates, finding an accurate point estimate and conducting inference on $\beta_{\text{max}}$ can be a challenging task, due to the presence of the regularization and selection biases. Regularization bias occurs whenever penalization approaches are adopted to select a smaller working model to enhance the estimation efficiency of $\beta$ (Wang et al., 2019; Hong et al., 2018). Selection bias occurs whenever we use a simple sample-analogue $\hat{\beta}_{\text{max}} = \max_{j \in \{1, \ldots, p_1\}} \hat{\beta}_j$ to estimate the true maximum effect $\beta_{\text{max}}$, because $\hat{\beta}_{\text{max}}$ tends to overestimate $\beta_{\text{max}}$. Such an overestimation phenomenon is well-recognized in post-hoc subgroup analyses (see Zöllner and Pritchard, 2007; Cook et al., 2014, for example). While several approaches have been proposed to address the regularization bias issue (Zhang and Zhang, 2014; Li, 2020), and provide valid inference on a single regression coefficient, these methods cannot account for the selection bias. As for the selection bias, existing methods are mostly made for low-dimensional data and are not directly applicable to observational data with high dimensional covariates in this case study (Bornkamp et al., 2017; Guo and He, 2020). While Guo et al. (2021) proposes bootstrap-based approaches to
simultaneously address the regularization and selection bias issues in high dimensional linear models, we broaden its validity by providing a bootstrap procedure that is asymptotically valid for high dimensional logistic regression estimators with rigorous statistical guarantees. To the best of our knowledge, debiasing procedures that simultaneously remove the regularization bias and selection bias in high dimensional non-linear models have been lacking. Technical discussions on these bias issues are deferred to the Supplementary Materials Section A, and we demonstrate the selection and regularization biases in estimating $\beta_{\text{max}}$ within a simple simulated example.

Example 1 (Selection bias and regularization bias in estimating $\beta_{\text{max}}$). We use two widely adopted procedures to estimate $\beta$: (1) Lasso for generalized linear models (GLM) (Park and Hastie, 2007), which estimates $\beta$ with $(\hat{\beta}_{\text{GLasso}}^T, \hat{\gamma}_{\text{GLasso}}^T)^T$ obtained from the $\ell_1$-penalized logistic regression program without any adjustments, and (2) Refitted GLM Lasso, which estimates $\beta$ by refitting the logistic regression model based on the covariates in the support set of $(\hat{\beta}_{\text{GLasso}}^T, \hat{\gamma}_{\text{GLasso}}^T)^T$. As a benchmark, we also report the performance of the oracle estimator $(\hat{\beta}_{\text{Oracle}}^T, \hat{\gamma}_{\text{Oracle}}^T)^T$ which pretends the true support set of $\gamma$ is known and is estimated by refitting the logistic regression model with the true support set. $\beta_{\text{max}}$ is then estimated in a two-step procedure: One first obtains an estimate $\hat{\beta}$ and then estimates $\beta_{\text{max}}$ by taking the maximum, that is $\max\{\hat{\beta}_1, \ldots, \hat{\beta}_p\}$. To mimic the causal relationship in this case study, we generate Monte Carlo samples with $t_i \sim \text{Bernoulli}(0.5)$ independent of the covariate $w_i \sim N(0, \Sigma)$, where $\Sigma = (\Sigma_{jk})_{j,k=1}^{p-6}$ and $\Sigma_{jk} = 0.5|j-k|$ for $i = 1, \ldots, n$. We then generate $x_{ij} = 1(w_{ij} > 0)$ for $1 \leq j \leq p-6$, and $z_{il} = t_i x_{il}$, $l = 1, \ldots, 6$. $y_i$ is generated following Model (1). We set the sample size $n = 1,000$ and the dimension $p = 200$ and set the coefficients $\beta = (0.5, 0.5, 0, 0, 0, 0)^T$ and $\gamma = (1, 1, 0, \ldots) \in \mathbb{R}^{p-6}$. In Figure 2, we report the root-$n$ scaled bias based on 500 Monte Carlo samples.

From the results in Figure 2, we observe that all three estimators are biased. Although $\hat{\beta}_{\text{Oracle}}$ is a consistent estimator of $\beta$, its maximum is not centered around $\beta_{\text{max}}$. The residual bias in the oracle estimator $\hat{\beta}_{\text{Oracle}}$ is caused by the selection bias issue. In fact, following some explicit evidence given in Nadarajah and Kotz (2008), $\hat{\beta}_{\text{max}}$ is usually biased upward for estimating $\beta_{\text{max}}$. The magnitude of this bias crucially depends on the unknown parameters $\beta$ and the covariance structure of $\hat{\beta}_{\text{Oracle}}$. Hence, any inference procedure without adjusting for selection bias cannot be valid. On the top of the selection bias issues, the GLM Lasso and the refitted estimators suffer
Figure 2: Root-$n$ scaled bias for Example 1. The maximum Monte Carlo standard error of the above results is 0.31.

from the regularization bias and hence are also not correctly centered around $\beta_{\text{max}}$, unless in some special cases where the regularization bias and the selection bias cancel out.

To simultaneously adjust for the selection bias and the regularization bias without knowing the underlying true parameters, in the following section, we propose an inferential framework that produces a bias-reduced estimate as well as a valid confidence interval of $\beta_{\text{max}}$.

3 Methodology

3.1 Bootstrap calibrated debiased estimates

We start with describing an estimation strategy of $\beta$ that resolves the regularization bias induced by model selection and helps addressing our research objectives (ii) and (iii) discussed in Section 1.1. Regularization bias arises when the selected model is either over-fitted or under-fitted; see detailed discussion provided in the Supplementary Materials Section A. While the risk of under-fitting can be mitigated by aiming for a larger model for parameter estimation, we resolve the issue of over-fitting by sample splitting. Sample splitting divides a sample into two parts: The first part of the sample is used for model selection and the remaining part is used for estimation based on the selected model. When $\gamma$ is sparse and a larger model is selected on the first half of the sample, we expect refitted GLM estimator on the second part of the sample to be free of significant bias. Nevertheless,
sample splitting provides debiased estimator of $\beta$ at a cost of increased variability, because only a part of the sample is used for estimation. To minimize this efficiency loss due to sample splitting, we consider the method of repeated sample splitting (R-Split) that averages different estimates of $\beta$ across different splits. Our strategy, in a spirit similar to bagging and ensemble algorithms in machine learning, helps to stabilize and improve the accuracy of the estimated $\beta$ in a subsample.

**Step 1** (Repeated sample splitting that accounts for the regularization bias) For $b \leftarrow 1$ to $B_1$: (1) Randomly split the sample \( \{(y_i, x_i, z_i)\}_{i=1}^n \) into two subsamples: a subsample $T_1$ of size $n_1$ and a subsample $T_2$ of size $n_2 = n - n_1$; (2) select a model $\hat{M}_b$ to predict $y$ based on $T_1$; (3) refit the selected model with the data in $T_2$ to estimate $\hat{\beta}_b$ and $\gamma_b$ via logistic regression:

\[
(\hat{\beta}_b^T, \hat{\gamma}_b^T) = \arg \min \left\{ \sum_{l \in T_2} (y_l \cdot (z_l^T \beta + x_l^T \gamma) - \log (1 + \exp(z_l^T \beta + x_l^T \gamma))) \right\}.
\]

(4) obtain the R-Split estimate:

\[
\tilde{\beta} = \frac{1}{B_1} \sum_{b=1}^{B_1} \hat{\beta}_b.
\]

In this step, any reasonable model selection procedures may be used and the choice of model size is subjective, but the selected model needs to be large enough for the under-fitting bias to be negligible. In our simulation and real data analyses, we use GLM Lasso for model selection, and choose the model size from cross-validation (see Section 3.2 for detailed description). The choice of splits $B_1$ needs to be sufficiently large so that the R-Split estimator $\tilde{\beta}$ has a tractable asymptotic distribution. Under appropriate regularity conditions, we show that $\tilde{\beta}$ converges to a normal distribution centered around $\beta$ at a root-$n$ rate (statistical justification is provided in the Supplementary Materials Section C.2).

As $\tilde{\beta}$ provides an accurate estimate of $\beta$, we use $\tilde{\beta}$ to address our research objectives (ii) and (iii). In particular, the subgroup with the largest coefficient, $\arg \max_{j \in [p]} \tilde{\beta}_j$, is most vulnerable for developing T2D after taking statins. However, due to the selection bias, simply relying on $\tilde{\beta}$ will not lead to valid inference on $\beta_{\text{max}}$, and we need a second step to address objective (iii). Built upon an accurate estimate of $\beta$, we store an inverse Hessian matrix for the later bootstrap calibration to
adjust for selection bias:

$$\tilde{\Gamma}_n = \frac{1}{B_1} \sum_{b=1}^{B_1} \sum_{i \in T_{2,b}} \frac{1}{n_1} \sum_{i \in T_{2,b}} f_{i,b} \left( \begin{array}{c} z_i \\ x_i, \hat{M}_b \end{array} \right) (z_i^T, x_i, \hat{M}_b)^T \right)^T I_{\hat{M}_b},$$

where $f_{i,b} = \exp'(z_i^T \hat{\beta}_b + x_i^T \hat{\gamma}_b)$. Its benefits will be apparent in the following step:

**Step 2** (Calibrated bootstrap that accounts for the selection bias) For $b \leftarrow 1$ to $B_2$: generate bootstrap replicate $\tilde{\beta}^*$ from:

$$\tilde{\beta}^* = \tilde{\beta} + \tilde{\Gamma}_n \cdot \frac{1}{n} \sum_{i=1}^{n} \left( \begin{array}{c} z_i \\ x_i \end{array} \right) \nu^*_i,$$

(2)

where $\nu^*_i = u_i \tilde{\nu}_i$ is the permuted GLasso residual, $\tilde{\nu}_i = y_i - \expit(z_i^T \hat{\beta}_{GLasso} + x_i^T \hat{\gamma}_{GLasso})$.

Then recalibrate bootstrap statistics via

$$T^*_b = \max_{j \in [p_1]} (\tilde{\beta}^*_j + \bar{c}_j(r)) - \tilde{\beta}_{\max}, \quad \bar{c}_j(r) = (1 - n^{-0.5})(\tilde{\beta}_{\max} - \tilde{\beta}_j), \quad \text{where } r \in (0, 0.5).$$

In this step, rather than adopting the simple bootstrap statistics $\max_{j \in [p_1]} (\tilde{\beta}^*_j - \tilde{\beta}_{\max})$ to make inference on $\beta_{\max}$, we make an adjustment to each coordinate of $\tilde{\beta}^*$ by the amount $\bar{c}_j(r)$. This is because just as $\tilde{\beta}_{\max}$ is a biased estimator of $\beta_{\max}$, the simple bootstrap statistics $\max_{j \in [p_1]} \tilde{\beta}^*_j$ is also not centered at $\tilde{\beta}_{\max}$. The amount of adjustment $\bar{c}_j(r)$ is large when $\tilde{\beta}_j$ is small, and is small when $\tilde{\beta}_j$ is large. By adding the correction term $\bar{c}_j(r)$, under certain regularity conditions, the distributions of $\sqrt{n}(\tilde{\beta}^*_{\max} - \tilde{\beta}_{\max})$ and $\sqrt{n}(\tilde{\beta}_{\max} - \beta_{\max})$ are asymptotically equivalent, implying that our proposed method adjusts for the selection bias and the regularization bias simultaneously, where $\tilde{\beta}^*_{\max} = \max_{j \in [p_1]} (\tilde{\beta}^*_j + \bar{c}_j(r))$. We relegate the theoretical details of this bootstrap calibration procedure in the Supplementary Materials Section C. Note that $r \in (0, 0.5)$ is a positive tuning parameter (see Section 3.2 for its data adaptive choice).

At this point, we note that our procedure adopts wild bootstrap to construct bootstrapped statistics of the R-Split estimate $\tilde{\beta}$. The wild bootstrap procedure adopted here is not only computationally efficient in high dimensions, as the Hessian matrix remains unchanged across different bootstrap samples, but also provably consistent in our problem setup. Furthermore, Dezeure et al.
(2017) shows that wild bootstrap is more versatile than other residual bootstrap methods because it correctly captures the asymptotic variance in the presence of homoscedastic or heteroscedastic errors. With the help of a valid bootstrap calibration procedure in replicating $\hat{\beta}_{\text{max}}$, we are now ready to propose our final step that constructs confidence intervals and debiased estimate for $\beta_{\text{max}}$:

**Step 3** (Bias-reduced $\hat{\beta}_{\text{max}}$ and sharp confidence interval) *The level-$\alpha$ two-sided confidence interval for $\beta_{\text{max}}$ is $[\hat{\beta}_{\text{max}} - Q_{T_b^*}(\alpha/2), \hat{\beta}_{\text{max}} + Q_{T_b^*}(\alpha/2)]$, and a bias-reduced estimate for $\beta_{\text{max}}$ is $\tilde{\beta}_{\text{max}} - \frac{1}{B_2} \sum_{b=1}^{B_2} T_b^*$.*

### 3.2 Practical implementation

In Step 1 (1), we recommend a split ratio of 0.6 : 0.4 for $n_1 : n_2$ because a larger sample size for subsample $T_1$ improves model selection accuracy. In Step 1 (2), the model selection procedure can be any easily accessible procedure. In our case, since the real data have binary outcomes, we adopt GLM lasso for model selection with R package *glmnet* (Park and Hastie, 2007). The model size is selected via cross-validation with a constraint on the maximal and minimal model sizes. We recommend to set $B_1 = 500$ for the number of repeated splits and $B_2 = 1,000$ for the number of bootstrap replications.

As for the tuning parameter $r$, we propose a data-adaptive cross-validated algorithm to select $r$ as the following (Guo and He, 2020):

**Step 1** Denote $R = \{r_1, \ldots, r_m\}$ as a set of candidate tuning parameters. Randomly split the sample into $v$ equal-sized subsamples.

**Step 2** For $l \leftarrow 1$ to $m$:

For $j \leftarrow 1$ to $v$:

(a) Use subsample $j$ as reference data and the rest as training data. Obtain $\tilde{\beta}_{\text{max, reduced},j}(r_l)$ on the training data, where $r_l$ is the tuning parameter.

(b) For $i \leftarrow 1$ to $k$: Obtain $R$-Split estimate of $\tilde{\beta}_{i,j}$ and its standard error $\tilde{\sigma}_{i,j}$ on the reference data; evaluate the accuracy

$$h_{i,j}(r_l) = (\tilde{\beta}_{\text{max, reduced},j}(r_l) - \tilde{\beta}_{i,j})^2 - \tilde{\sigma}_{i,j}^2.$$
Step 3 Select the tuning parameter via \( \arg \min_r \{ \min_{i \in [k]} \left\{ \sum_{j=1}^{v_{ij}} h_{i,j}(r)/v \right\} \} \).

Intuitively, we would like to choose \( r \) that minimizes the mean squared error between the proposed bias reduced estimate \( \tilde{\beta}_{\text{max, reduced}} \) and \( \beta_{\text{max}} \). To make this operational without knowing \( \beta_{\text{max}} \), we provide an approximation of the mean squared error that can be computed from the data via cross-validation in Step 2 (b). The justification of this cross validation method for fixed \( p_1 \) can be found in Guo and He (2020). In our empirical work, we implement the above tuning selection method via three-fold cross-validation with a candidate set \( R = \{1/3, 1/6, \ldots, 1/30\} \).

4 Theoretical and empirical justification

In this section, we provide theoretical justifications of the proposed bootstrap-assisted R-Split estimator along with a simple power analysis, where we demonstrate that our approach not only has rigorous theoretical guarantee but also shows high statistical detection power. We then examine the performance of the proposed method through simulation studies.

4.1 Theoretical investigation and a power analysis

The following theorem confirms that the asymptotic distribution of \( \sqrt{n}(\tilde{\beta}_{\text{modified; max}} - \beta_{\text{max}}) \) converges to \( \sqrt{n}(\tilde{\beta}_{\text{max}} - \beta_{\text{max}}) \). This suggests that the proposed confidence interval constructed in Step 3 of Section 3.1 is “asymptotically sharp,” meaning that it achieves the exact nominal level as the sample size goes to infinity. This distinguishes the proposed procedure from other conservative methods made for subgroup analysis. The proof of Theorem 1 is provided in the Supplementary Materials Section C.3. To simplify presentation, we relegate regularity assumptions to the Supplementary Materials Section C.1.

**Theorem 1.** Under Assumptions 1-9 given in the Supplementary Materials Section C.1, when \( p_1 \) is a fixed number, the modified bootstrap maximum treatment effect estimator, \( \tilde{\beta}_{\text{modified; max}} = \max_{j \in [p_1]} (\tilde{\beta}_j + \tilde{c}_j(r)) \), satisfies:

\[
\sup_{c \in \mathbb{R}} \left| \mathbb{P}(\sqrt{n}(\tilde{\beta}_{\text{max}} - \beta_{\text{max}}) \leq c) - \mathbb{P}^*(\sqrt{n}(\tilde{\beta}_{\text{modified; max}} - \beta_{\text{max}}) \leq c) \right| = o_p(1).
\]
The above theoretical result has two direct implications. On the one hand, as the proposed bootstrap calibration strategy successfully replicates the distribution of $\sqrt{n}(\tilde{\beta}_{\max} - \beta_{\max})$, our bias-reduced estimator discussed in the Step 3 of Section 3.1 simultaneously removes the regularization bias and the selection bias in $\tilde{\beta}_{\max}$. On the other hand, although simultaneous inference also delivers valid inference on $\beta_{\max}$ with strict Type-I error rate control, our proposal delivers valid inference on $\beta_{\max}$ without sacrificing the statistical power. This property is more desirable in our problem setup as we aim to look for the subgroup with the most severe side effect of statin use while simultaneous methods often lead to overly conservative conclusions for this purpose.

To further demonstrate the merit of constructing an asymptotically sharp confidence interval for $\beta_{\max}$ and the benefit of conducting variable selection in finite samples, we compare statistical power for testing the null hypothesis $H_0 : \beta_{\max} = 0$ for four procedures: (1) the proposed bootstrap-assisted R-Split, (2) R-Split with simultaneous confidence intervals, (3) the proposed bootstrap-assisted logistic regression, and (4) the desparsified Lasso estimator discussed in Zhang and Zhang (2014) with simultaneous confidence interval (Dezeure et al., 2017; Fuentes et al., 2018). We follow the same simulation setup as in Example 1. The tuning parameter is fixed at $r = 0.15$ for simplicity. For R-Split, we choose the model size via cross-validation (see Section 3.2) with a minimal model.
size equals 3 and a maximal model size equals 10.

From Figure 3, we observe that all considered approaches control the Type-I error rate at the nominal level when $\beta_{\text{max}} = 0$. The bootstrap-assisted R-Split has the highest detection power over a range of $\beta_{\text{max}}$ among all considered procedures. The bootstrap-assisted logistic regression has the lowest detection power, which demonstrates the necessity of conducting variable selection to screen out irrelevant predictors. As we have expected, both the R-Split method with simultaneous confidence interval and the desparsified Lasso with simultaneous confidence interval do not retain sufficient statistical power to detect subgroup treatment effect heterogeneity.

4.2 Simulation studies

In this section, we consider various simulation designs to demonstrate the merit of our proposal. There are three main takeaways from this simulation. First, our proposed bootstrap calibration procedure provides confidence intervals with nominal coverage probabilities of $\beta_{\text{max}}$ in finite samples. Second, R-Split based methods provide more accurate point estimates and shorter confidence intervals than the logistic regression based approaches without variable selection. Third, the bootstrap-assisted methods have higher statistical efficiency (shorter confidence intervals) compared to the simultaneous methods.

We generate Monte Carlo samples from the following model:

$$\logit \{P(y_i = 1 \mid z_i, x_i)\} = z_i^T \beta + x_i^T \gamma, \quad i = 1, \ldots, n,$$

with $n = 2,000$. We consider two cases for $\beta$: (1) heterogeneous case with $\beta = (0, \ldots, 0, 1)^T \in \mathbb{R}^{p_1}$, meaning that there exists subgroup treatment effect heterogeneity and only one subgroup singles out; and (2) spurious heterogeneous case with $\beta = (0, \ldots, 0, 0) \in \mathbb{R}^{p_1}$, meaning that there is no subgroup with significant treatment effect in the population. We set $\gamma = (1, 1, 1, 0, \ldots, 0) \in \mathbb{R}^{p_2}$.

In all considered simulation designs, we set $p_1 \in \{4, 10\}$. We consider the case with $(n, p_2) = (2,000, 150)$ for logistic regression, R-Split, and the desparsified Lasso (Zhang and Zhang, 2014), and consider the case with $(n, p_2) = (2,000, 500)$ for R-Split and the desparsified Lasso, since logistic regression tends to provide inconsistent estimates in moderately high dimensions (Sur and Candès, 2019).
As for the covariates design, we generate $z_i$ and $x_i$ from

$$z_{ij} \sim \text{Bernoulli}(\frac{\exp(x_{i,2j-1} + x_{i,2j})}{1 + \exp(x_{i,2j-1} + x_{i,2j})}), \quad j = 1, \ldots, p_1,$$

where $x_i \sim N(0, \Sigma)$ with $\Sigma_{ij} = 0.5|i-j|$. We compare the finite sample performance of the proposed bootstrap-assisted R-Split and the bootstrap-assisted logistic regression with two benchmark methods: (1) a naive method with no bootstrap calibration, which directly uses the estimated maximum coefficient to estimate $\beta_{\max}$ and (2) the simultaneous method as discussed in Dezeure et al. (2017) and Fuentes et al. (2018). For the desparsified Lasso (Zhang and Zhang, 2014), we only consider the above-mentioned two benchmark methods: the naive method and the simultaneous method (without bootstrap calibration). For the R-Split method, we choose the model size via cross-validated GLM Lasso with a minimal model size equals 3. We report the coverage probability, the $\sqrt{n}$ scaled confidence interval length and the $\sqrt{n}$ scaled Monte Carlo bias along with their standard errors based on 1,000 Monte Carlo samples in Table 3 and Table 4.

Comparing the bootstrap-assisted methods with the naive methods, we observe that the bootstrap-assisted methods attain nominal-level coverage probabilities, while the naive methods are biased and under-covered. This comparison verifies the theoretical results in Section 4.1 that the proposed bootstrap calibration successfully adjusts for the selection bias.

Comparing the bootstrap-assisted methods with the simultaneous methods, we find that although simultaneous methods have higher coverage probabilities, the confidence intervals are rather long, implying that simultaneous methods are overly conservative. While our proposed inferential framework reaches the nominal-level coverage probabilities and has shorter confidence intervals leading to asymptotically sharp inference.

The comparison between the bootstrap-assisted R-Split with the bootstrap-assisted logistic regression shows that the latter has larger biases and lower coverage probabilities. The bootstrap-assisted logistic regression has undesirable performance because logistic regression yields biased estimates in moderately high dimensions (Sur and Candès, 2019). This comparison reveals the benefit of conducting variable selection when $\gamma$ is sparse and the dimension of covariates is large, and it confirms that R-Split alleviates the regularization bias issue. Comparing R-Split with the desparsified Lasso, in line with our earlier conjecture, we observe that the desparsified Lasso approach
has wider confidence intervals than those obtained by R-Split and tends to provide conservative inference.

This simulation study verifies that our proposed inferential framework not only achieves nominal coverage probabilities, but also mitigates the regularization and selection biases. Thus, the proposed inferential framework is sensible to consider for our case study.

5 Case study

5.1 Case study results

In this section, we investigate the adverse effect of statin use in our pre-specified six subgroups divided by gender and T2D genetic risk using the data introduced in Section 2.3. We compare the results from three methods: (1) repeated sample splitting (R-Split) without bootstrap calibration, (2) R-Split based on the simultaneous method discussed in Dezeure et al. (2017), and (3) the proposed bootstrap-assisted R-Split. We summarize our real data analyses results in Table 5, in which we have reported the estimated subgroup treatment effects from R-Split along with their $p$-values and two-sided confidence intervals, adjusted $p$-values to account for the multiple comparisons issue with simultaneous method and Bonferroni correction, and bootstrap calibrated $p$-values for the subgroup with the largest treatment effect. The results with one-sided confidence lower bounds are summarized in Supplementary Materials Section F.

From Table 5, the results of the R-Split estimator without bootstrap calibration not only indicate that the treatment effect of statins tends to vary across different subgroups, but also suggest that the high-genetic-risk female subgroup is the most vulnerable group for developing T2D with estimated log-odds ratio 0.41, 95% two-sided confidence interval $0.04 - 0.78$ (OR = 1.04 – 2.18) with $p$-value 0.030. For males with various genetic risk levels and females with lower T2D genetic risk, the adverse effects of statin use are not significant based on R-Split without bootstrap calibration. The treatment effect in the overall study cohort is slightly positive but is not significant, which is in-line with our expectation from the preliminary analysis in Section 2.3.

Although the estimates and confidence intervals from the R-Split without bootstrap calibration suggest that taking statins causes the increased risk of developing T2D for the most vulnerable subgroup, the statistical significance of this finding is unclear since R-Split is implemented without
Table 3: Simulation results (heterogeneous case)

| β = (0, ..., 0, 1) ∈ R^{p_1} (heterogeneity) | Logistic Regression (p_2 = 150) |  |  |
|---|---|---|---|
|  | Boot-Calibrated | No adjustment | Simultaneous |
| p_1 = 4 | | | |
| Cover | 0.95(0.01) | 0.89(0.01) | 0.90(0.01) |
| √nLength | 9.57(0.05) | 8.83(0.03) | 14.6(0.04) |
| √nBias | -2.51(2.70) | 4.91(4.60) | — |
| p_1 = 10 | | | |
| Cover | 0.93(0.01) | 0.86(0.01) | 0.99(0.01) |
| √nLength | 10.4(0.04) | 9.18(0.04) | 16.7(0.03) |
| √nBias | -4.07(3.89) | 5.17(4.67) | — |
| | Repeated Sample Splitting (p_2 = 150) |  |  |
| p_1 = 4 | | | |
| Cover | 0.96(0.01) | 0.94(0.01) | 0.99(0.00) |
| √nLength | 3.56(0.07) | 2.17(0.06) | 5.14(0.07) |
| √nBias | 0.11(0.26) | 0.14(0.25) | — |
| p_1 = 10 | | | |
| Cover | 0.95(0.02) | 0.92(0.01) | 0.99(0.01) |
| √nLength | 3.62(0.07) | 2.57(0.05) | 6.61(0.05) |
| √nBias | 0.25(0.39) | 0.32(0.30) | — |
| | Desparsified Lasso (p_2 = 150) |  |  |
| p_1 = 4 | | | |
| Cover | — | 0.92(0.01) | 0.99(0.00) |
| √nLength | — | 2.13(0.06) | 6.51(0.05) |
| √nBias | — | 0.29(0.22) | — |
| p_1 = 10 | | | |
| Cover | — | 0.93(0.01) | 0.99(0.01) |
| √nLength | — | 2.10(0.07) | 6.98(0.07) |
| √nBias | — | 0.27(0.17) | — |
| | Repeated Sample Splitting (p_2 = 500) |  |  |
| p_1 = 4 | | | |
| Cover | 0.95(0.02) | 0.92(0.03) | 0.99(0.00) |
| √nLength | 4.44(0.06) | 2.22(0.06) | 6.08(0.05) |
| √nBias | -0.68(0.80) | 1.22(1.18) | — |
| p_1 = 10 | | | |
| Cover | 0.93(0.02) | 0.88(0.03) | 0.98(0.01) |
| √nLength | 5.11(0.04) | 2.95(0.05) | 6.77(0.05) |
| √nBias | -0.90(0.85) | 1.36(1.20) | — |
| | Desparsified Lasso (p_2 = 500) |  |  |
| p_1 = 4 | | | |
| Cover | — | 0.90(0.01) | 0.99(0.00) |
| √nLength | — | 2.19(0.05) | 7.48(0.08) |
| √nBias | — | 1.29(1.13) | — |
| p_1 = 10 | | | |
| Cover | — | 0.91(0.01) | 0.99(0.01) |
| √nLength | — | 2.15(0.06) | 7.60(0.08) |
| √nBias | — | 1.25(1.17) | — |

Note: “Cover” is the empirical coverage of the 95% lower bound for $\beta_{max}$. “$\sqrt{n}$Bias” captures the root-$n$ scaled Monte Carlo bias for estimating $\beta_{max}$, and “$\sqrt{n}$Length” denotes the root-$n$ scaled length of the 95% lower bound for $\beta_{max}$.

Bootstrap calibration and can not address the multiple comparisons issue. After accounting for the multiple comparisons issue through conservative procedures including the simultaneous method.
|                | Logistic Regression ($p_2 = 150$) |                |                |
|----------------|----------------------------------|----------------|----------------|
|                | Boot-Calibrated                  | No adjustment  | Simultaneous   |
| $p_1 = 4$      | Cover 0.94(0.02)                  | 0.87(0.03)     | 0.99(0.01)     |
|                | $\sqrt{n}$ Length 7.90(0.05)     | 6.21(0.05)     | 11.1(0.04)     |
|                | $\sqrt{n}$ Bias 3.10(3.44)       | 5.05(4.46)     | —              |
| $p_1 = 10$     | Cover 0.91(0.01)                  | 0.83(0.02)     | 0.98(0.01)     |
|                | $\sqrt{n}$ Length 8.38(0.06)     | 7.25(0.05)     | 12.4(0.06)     |
|                | $\sqrt{n}$ Bias 5.30(4.88)       | 7.32(6.58)     | —              |
|                | Repeated Sample Splitting ($p_2 = 150$) |                |                |
|                | Boot-Calibrated                  | No adjustment  | Simultaneous   |
| $p_1 = 4$      | Cover 0.95(0.02)                  | 0.93(0.02)     | 0.98(0.02)     |
|                | $\sqrt{n}$ Length 1.87(0.04)     | 1.03(0.06)     | 5.08(0.04)     |
|                | $\sqrt{n}$ Bias 0.15(0.24)       | 0.31(0.39)     | —              |
| $p_1 = 10$     | Cover 0.95(0.01)                  | 0.91(0.02)     | 0.96(0.01)     |
|                | $\sqrt{n}$ Length 2.02(0.06)     | 1.47(0.06)     | 6.46(0.04)     |
|                | $\sqrt{n}$ Bias 0.29(0.40)       | 0.98(0.90)     | —              |
|                | Desparsified Lasso ($p_2 = 150$)  |                |                |
|                | Boot-Calibrated                  | No adjustment  | Simultaneous   |
| $p_1 = 4$      | Cover —                          | 0.92(0.01)     | 0.99(0.01)     |
|                | $\sqrt{n}$ Length —              | 1.01(0.07)     | 5.52(0.05)     |
|                | $\sqrt{n}$ Bias —                | 1.23(0.99)     | —              |
| $p_1 = 10$     | Cover —                          | 0.93(0.01)     | 0.99(0.01)     |
|                | $\sqrt{n}$ Length —              | 1.39(0.06)     | 6.20(0.07)     |
|                | $\sqrt{n}$ Bias —                | 0.97(0.85)     | —              |
|                | Repeated Sample Splitting ($p_2 = 500$) |                |                |
|                | Boot-Calibrated                  | No adjustment  | Simultaneous   |
| $p_1 = 4$      | Cover 0.95(0.02)                  | 0.91(0.02)     | 0.98(0.01)     |
|                | $\sqrt{n}$ Length 3.77(0.05)     | 3.18(0.04)     | 5.90(0.04)     |
|                | $\sqrt{n}$ Bias 0.62(0.72)       | 1.58(1.41)     | —              |
| $p_1 = 10$     | Cover 0.92(0.02)                  | 0.85(0.01)     | 0.95(0.01)     |
|                | $\sqrt{n}$ Length 3.54(0.06)     | 2.72(0.06)     | 6.52(0.05)     |
|                | $\sqrt{n}$ Bias 1.53(1.39)       | 2.82(1.97)     | —              |
|                | Desparsified Lasso ($p_2 = 500$)  |                |                |
|                | Boot-Calibrated                  | No adjustment  | Simultaneous   |
| $p_1 = 4$      | Cover —                          | 0.89(0.01)     | 0.99(0.01)     |
|                | $\sqrt{n}$ Length —              | 3.10(0.05)     | 6.88(0.08)     |
|                | $\sqrt{n}$ Bias —                | 2.30(1.90)     | —              |
| $p_1 = 10$     | Cover —                          | 0.90(0.01)     | 0.99(0.01)     |
|                | $\sqrt{n}$ Length —              | 2.68(0.05)     | 7.63(0.08)     |
|                | $\sqrt{n}$ Bias —                | 2.08(1.96)     | —              |

Note: “Cover” is the empirical coverage of the 95% lower bound for $\beta_{\text{max}}$. “$\sqrt{n}$ Bias” captures the root-$n$ scaled Monte Carlo bias for estimating $\beta_{\text{max}}$, and “$\sqrt{n}$ Length” denotes the root-$n$ scaled length of the 95% lower bound for $\beta_{\text{max}}$.

or Bonferroni correction, the $p$-values for the female high-risk group are no longer significant, seemingly suggesting that our data do not provide enough evidence to claim the existence of the
| Method                  | Subgroup (prevalence; # of case) | Est (95% CI)       | p-value       | Bonf p-value |
|-------------------------|----------------------------------|--------------------|---------------|--------------|
| R-Split (without bootstrap calibration) | High-risk female (0.14, 100)   | 0.41 (0.04, 0.78)  | 0.030         | 0.180        |
|                         | Mid-risk female (0.12, 396)     | 0.10 (−0.03, 0.24) | 0.132         | 0.792        |
|                         | Low-risk female (0.11, 630)     | −0.00 (−0.10, 0.09)| 0.990         | 1            |
|                         | High-risk male (0.24, 139)      | −0.07 (−0.38, 0.25)| 0.658         | 1            |
|                         | Mid-risk male (0.21, 561)       | 0.02 (−0.07, 0.11) | 0.673         | 1            |
|                         | Low-risk male (0.17, 739)       | −0.03 (−0.16, 0.10)| 0.651         | 1            |
|                         | Overall                          | 0.07 (−0.16, 0.39) | 0.545         | –            |
| Simultaneous            | High-risk female (0.14, 100)    | −                  | 0.256         | –            |
| Bootstrap-assisted R-Split | High-risk female (0.14, 100)   | 0.35 (0.02, 0.70)  | 0.037         | –            |

Table 5: Estimated treatment effects (Est) on the PHS cohort in six subgroups divided by gender and T2D genetic risk, together with two-sided 95% confidence intervals (CI), corresponding two-sided p-values and the Bonferroni p-values in the last column. We also present the prevalence of T2D in each subgroup.

adverse effect of statin use in the female high-risk subgroup. This might be due to the fact that both the simultaneous method and Bonferroni correction are rather conservative and tend to provide false negative discoveries. Fortunately, our proposed bootstrap assisted R-Split procedure directly conducts inference on the most vulnerable group, and our results suggest that among high-genetic-risk female patients, the odds of developing T2D after taking statins are 1.42 times the odds of developing T2D for the patients without taking statins (p-value 0.037 for two-sided test).

Our findings are in-line with reported results in existing clinical studies. For example, Mora et al. (2010) suggest that statin use incurs a larger T2D risk increment on females than on males, and Waters et al. (2013) suggest that statins only significantly increase the risk of T2D on those with at least three out of four common T2D risk factors at baseline.\(^2\) Compared with the existing studies, our findings provide more robust evidence with the new data analysis pipeline built under the causal inference framework. Our data analysis pipeline addresses several limitations of existing studies; in particular, limited sample size and multiple comparisons issue. Moreover, compared to existing studies, our findings provide a more biologically driven depiction of statins’ heterogeneous adverse effect, which can further support effective and precise clinical decisions and actions concerning the prescription of statins. Our study further demonstrates that in practice, the genetic profiles could assist T2D prevention of statin receivers to improve the quality of clinical practices.

\(^2\)The risk factors used by Waters et al. (2013) include high fasting blood glucose, history of hypertension, high body mass index, and high fasting triglycerides.
5.2 Sensitivity analysis

To evaluate the validity of causal conclusions derived from our real data analyses, we conduct sensitivity analyses with the E-value method. The E-value method computes the minimal strength of an unmeasured confounder to explain away the estimated causal effect (VanderWeele and Ding, 2017). Practitioners could then evaluate if there exists such an unmeasured confounder with the strength quantified by the E-value. A large E-value implies that the unmeasured confounder needs to have a strong association with the outcome and the treatment in order to explain away the causal evidence. The E-values for our estimated subgroup causal effects are summarized in Table 6. Table 6 shows that the E-value in the high-risk female group is 2.38, which implies that an unmeasured confounder that is associated with both the treatment and the outcome 2.38 times stronger than the measured confounders and could explain away the estimated causal effect. In other words, this E-value indicates that the association of the outcome and treatment with the unmeasured confounders should be 2.38-fold larger than their association with the observed confounders. According to a meta-study on E-value applications, most computed E-values from existing literature are below 2.0 (Ioannidis et al., 2019). In sum, the results from Table 6 imply that the causal evidence collected from our data is reasonably robust.

| Method                        | Subgroup (prevalence; # of case) | E-value |
|-------------------------------|----------------------------------|---------|
| R-Split (without bootstrap calibration) | High-risk female (0.14, 100) | 2.38    |
|                               | Mid-risk female (0.12, 396)     | 1.45    |
|                               | Low-risk female (0.11, 630)     | 1.00    |
|                               | High-risk male (0.24, 139)      | 1.23    |
|                               | Mid-risk male (0.21, 561)       | 1.11    |
|                               | Low-risk male (0.17, 739)       | 1.14    |
|                               | Overall                         | 1.23    |
| Bootstrap-assisted R-Split    | High-risk female (0.14, 100)    | 2.19    |

Table 6: Sensitivity analysis of our causal evidence measured by the E-value.
6 Discussion

In this case study, we investigate the heterogeneous T2D risk associated with statin use. To overcome the limitations of existing studies and generate more trustworthy evidence, we introduce a rigorous study design under the causal inference framework and based on the EHR and biobank data from the Partner Health System. Built on this study design, we find that although the adverse effect of statin use for developing T2D is only marginal for the overall study cohort, taking statins significantly increases the risk of developing T2D for female patients with high genetic predisposition to T2D. While the objective of this case study is to make inference on the most vulnerable subgroup, a natural question to ask is whether statin use will significantly increase the T2D risk for the other subgroups. The point estimates of statins’ side effects on T2D risk suggest that minimal risk is associated with male subjects and female subjects with low genetic predisposition to T2D. However, rigorous statistical inference for these subgroups adjusting for multiple comparisons warrants future research.

This case study is made for subgroup analysis with an exploratory purpose, as our analysis is built upon observational data. Although confirmatory clinical trials are more desirable for confirming the heterogeneous T2D risk associated with statin use, compared with existing studies, our findings can be helpful for researchers to design further confirmatory clinical trials with a focus on the high-genetic-risk female subpopulation.

This case study considers pre-defined candidate subgroups. While predefined subgroups are more suitable in our case study (as discussed in Section 2), extending the proposed method to data-adaptively identified subgroups warrant future research. Data-adaptive subgroup identification approaches include varying coefficient model (Chen and He, 2018), regression tree method (Lipkovich et al., 2011) and fused lasso (Ma and Huang, 2017). When working with data-adaptively identified subgroups, one needs to not only adjust for the regularization and selection biases, but also account for the randomness induced by subgroup identification. We leave the extension of the proposed method to future research as the primary objective of this manuscript is to investigate the heterogeneous causal effect of statin use on T2D risk.
Software and reproducibility

R code for the proposed procedures can be found in the package “debiased.subgroup” that is publicly available at https://github.com/WaverlyWei/debiased.subgroup. Simulation examples can be reproduced by running examples in the R package.

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