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Creating Fair Models of Atherosclerotic Cardiovascular Disease

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ABSTRACT

Guidelines for the management of atherosclerotic cardiovascular disease (ASCVD) recommend the use of risk stratification models to identify patients most likely to benefit from cholesterol-lowering and other therapies. These models have differential performance across race and gender groups with inconsistent behavior across studies, potentially resulting in an inequitable distribution of beneficial therapy. In this work, we leverage adversarial learning and a large observational cohort extracted from electronic health records (EHRs) to develop a “fair” ASCVD risk prediction model with reduced variability in error rates across groups. We empirically demonstrate that our approach is capable of aligning the distribution of risk predictions conditioned on the outcome across several groups simultaneously for models built from high-dimensional EHR data. We also discuss the relevance of these results in the context of the empirical trade-off between fairness and model performance.

CCS CONCEPTS
• Applied computing → Health informatics.

KEYWORDS
electronic health records, fairness, cardiovascular disease, adversarial learning, risk prediction, machine learning

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1 INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), which includes heart attack, stroke, and fatal coronary heart disease, is a major cause of mortality and morbidity worldwide, as well as in the U.S., where it contributes to 1 in 3 of all deaths—many of which are preventable [1]. In deciding whether to prescribe cholesterol-lowering therapies to prevent ASCVD, physicians are often guided by risk estimates yielded by the Pooled Cohort Equations (PCEs). PCEs provide a proportional hazards model [10] that leverages nine clinical measurements to predict the 10-year risk of a first ASCVD event. However this model has been found to overestimate risk for female patients [25], Chinese patients [7] or globally [33], as well as also underestimate risk for other groups such as Korean women [15]. Such mis-estimation results in an inequitable distribution of the benefits and harms of ASCVD risk scoring, because incorrect risk estimates can expose patients to substantial harm through both under- or overtreatment; potentially leading to preventable cardiovascular events or side effects from unnecessary therapy, respectively.

The inability of the PCEs to generalize to diverse cohorts likely owes to both under-representation of minority populations in the cohorts used to develop the PCEs and shifts in medical practice and lifestyle patterns in the decades since data collection for those cohorts. In attempting to correct for these patterns, one recent study [33] updated the PCEs using data from contemporary cohorts and demonstrated that doing so reduced the number of minority patients incorrectly misclassified as being high or low risk. Similar results were observed in the same study with an approach using an elastic net classifier, rather than a proportional hazards model.

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However, neither approach is able to explicitly guarantee an equitable distribution of mis-estimation across relevant subgroups, particularly for race- and gender-based subgroups.

To account for under-represented minorities and to take advantage of the wider variety of variables made available in electronic health records (EHRs), we derive a large and diverse modern cohort from EHRs to learn a prediction model for ASCVD risk. Furthermore, we investigate the extent to which we can encode algorithmic notions of fairness, specifically equality of odds, [13] into the model to encourage an equitable distribution of performance across populations. To the best of our knowledge, our effort is the first to explore the extent to which this formal fairness metric is achievable for risk prediction models built using high-dimensional data from the EHR. We show that while it is feasible to develop models that achieve equality of odds, we emphasize that this process involves trade-offs that must be assessed in a broader social and medical context [32].

2 BACKGROUND AND RELATED WORK

2.1 ASCVD Risk Prediction and EHRs

The PCEs are based on age, gender, cholesterol levels, blood pressure, and smoking and diabetes status and were developed by pooling data from five large U.S. cohorts [10] composed of white and black patients, with white patients constituting a majority. Recently, attempts [33] were made to update the PCEs to improve model performance for race- and gender-based subgroups using elastic net regression and data from modern prospective cohorts. However, this effort focused on demographic groups and variables already used to develop the PCEs and did not consider other populations or clinical measurements. The increasing adoption of EHRs offers opportunities to deploy and refine ASCVD risk models. Efforts have recently been undertaken to apply and refine existing models, including the PCEs and the Framingham score, to large EHR-derived cohorts and characterize their performance in certain subgroups [28, 30]. Beyond ASCVD risk prediction, there exist many recent works that develop prediction models with EHRs, which are reviewed in [11].

2.2 Fair Risk Prediction

We consider the case where supervised learning is used to estimate a function \( f(X) \) that approximates the conditional distribution \( p(Y|X) \), given \( N \) samples \( \{x_i, y_i, z_i\}_{i=1}^N \) drawn from the distribution \( p(X, Y, Z) \). We take \( X \in X = \mathbb{R}^m \) to correspond to a vector representation of the medical history extracted from the EHR prior to a patient-specific index time \( t_i; Y \in \{0, 1\} \) to be a binary label, which for patient \( i \), indicates the presence of the outcome observed in the EHR in the time frame \( [t_i, t_i + w_i] \), where \( w_i \) is a parameter specifying the amount of time following the index time used to derive the outcome; and \( Z \in Z = \{0, \ldots, k - 1\} \) indicates a sensitive attribute, such as race, gender, or age, with \( k \) groups. The output of the learned function \( f(X) \in [0, 1] \) is then thresholded with respect to a value \( T \) to yield a prediction \( \hat{Y} \in \{0, 1\} \).

One standard metric for assessing the fairness of a classifier with respect to a sensitive attribute \( Z \) is demographic parity [8], which evaluates the independence between \( Z \) and the prediction \( \hat{Y} \).

Formally, the demographic parity criterion may be expressed as

\[
p(\hat{Y}|Z = Z_i) = p(\hat{Y}|Z = Z_j) \forall Z_i, Z_j \in Z.
\]  

(1)

However, optimizing for demographic parity is of limited use for clinical risk prediction, because doing so may preclude the model from considering relevant clinical features associated with the sensitive attribute and the outcome, thus decreasing the performance of the model for all groups [20].

Another related metric is equality of odds [13], which stipulates that the prediction \( \hat{Y} \) be conditionally independent of \( Z \), given the true label \( Y \). Formally, satisfying equality of odds implies that

\[
p(\hat{Y}|Z = Z_i, Y = Y_k) = p(\hat{Y}|Z = Z_j, Y = Y_k)
\]  

\forall Z_i, Z_j \in Z; Y_k \in Y.

(2)

From this, it can be seen that, if equality of odds is achieved, then for a fixed threshold \( T \), both the false positive (FPR) and false negative rates (FNR) are equal across all pairs of groups defined by \( Z \). Compared to demographic parity, equality of odds is more appropriate in a clinical setting, since it does not necessarily preclude the learning of the optimal predictor in the case that a true relationship between sensitive attribute and the outcome exists [13].

Furthermore, this definition can be extended to the case of a continuous risk score by requiring that

\[
p(f(X)|Z = Z_i, Y = Y_k) = p(f(X)|Z = Z_j, Y = Y_k)
\]  

\forall Z_i, Z_j \in Z; Y_k \in Y.

(3)

In this case, the distribution of the predicted probability of the outcome conditioned on whether the event occurred or not should be matched across groups of a sensitive variable. Formulation 3 is stronger than 2 since it implies that equality of odds is achieved for all possible thresholds, thus requiring that the same ROC curve be attained for all groups. This is desirable since it provides the end-user the ability to freely adjust the decision threshold of the model without violating equality of odds.

Finally, we also note that satisfying equality of odds for a continuous risk score may be reduced to the problem of minimizing a divergence over each pair \((Z_i, Z_j)\) of distributions referenced in equation (3). Adversarial learning procedures [12] are well-suited to this problem in that they provide a flexible framework for minimizing the divergence over distributions parameterized by neural networks. As such, several related works [2, 9, 24, 34] have demonstrated the benefit of augmenting a classifier with an adversarial discriminator in order to align the distribution of predictions for satisfying fairness constraints.

2.3 Approaches for Achieving Fairness

Despite considerable interest in the ethical implications of implementing machine learning in healthcare [4, 6], relatively little work exists characterizing the extent to which risk prediction models developed with EHR data satisfy formal fairness constraints.

Adversarial approaches for satisfying fairness constraints (in the form of demographic parity) have been explored in several recent works in non-healthcare domains. One approach, [9], in the context of image anonymization, demonstrated that representations satisfying demographic parity could be learned by augmenting
We extract records from the Stanford Medicine Research Data Repository [23], a clinical data warehouse containing records on roughly three million patients from Stanford Hospital and Clinics and Lucile Packard Children’s Hospital for clinical encounters occurring between 1990 and 2017. We define a prediction task that resembles the setting in which the PCEs were developed for the purpose of guiding physician decision-making in ASCVD prevention and construct a corresponding cohort. As a first step, we identify all patients with at least two clinical encounters over at least two years for which they are 40 years of age or older. Then, for each patient we select an index time \( t_i \) uniformly at random from the interval that allows for at least one year of history and one year of follow-up. We exclude from the cohort patients that have an history of cardiovascular artery disease (including ASCVD and atrial fibrillation) or a prescription of an anti-hypertensive drug in the five years prior to the index time.

### 3 METHODS

#### 3.1 The Dataset and Cohort Definition

We consider race, gender, and age as sensitive attributes and assess model performance and fairness with respect to them. For race, we use both race and ethnicity variables to partition the cohort into six disjoint groups: Asian, Black, Hispanic, Other, Unknown, and White. Patients not considered Hispanic thus have either a non-Hispanic or unknown ethnicity. For gender, we partition the cohort into male and female populations. For age, we discretize the age at the index time into four disjoint groups: 40-55, 55-65, 65-75, and 75+ years, where the intervals are inclusive on the lower bound and exclusive on the upper bound. A summary of these groups is presented in Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>Count</th>
<th>ASCVD Incidence (%)</th>
<th>Follow-up Length (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>30,294</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Black</td>
<td>8,549</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20,240</td>
<td>2.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>19,062</td>
<td>2.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>39,964</td>
<td>0.86</td>
<td>3.1</td>
</tr>
<tr>
<td>White</td>
<td>135,438</td>
<td>2.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Female</td>
<td>149,594</td>
<td>1.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Male</td>
<td>103,953</td>
<td>2.9</td>
<td>3.3</td>
</tr>
<tr>
<td>40-55</td>
<td>121,437</td>
<td>0.95</td>
<td>3.4</td>
</tr>
<tr>
<td>55-65</td>
<td>61,214</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>65-75</td>
<td>43,800</td>
<td>3.7</td>
<td>3.2</td>
</tr>
<tr>
<td>75+</td>
<td>27,096</td>
<td>6.7</td>
<td>3.0</td>
</tr>
<tr>
<td>All</td>
<td>253,547</td>
<td>2.8</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Finally, we assign a positive ASCVD label for a patient if a diagnosis code for an ASCVD event is observed at any point in their record following the index time. The exclusion criteria (i.e. the list of cardiovascular-related diseases and medications) is provided as supplementary material, along with the list of clinical concepts used for defining ASCVD events. The patients are randomly partitioned such that 80%, 10%, 10% are used for training, validation, and testing, respectively.

#### 3.2 Sensitive Attributes

We consider race, gender, and age as sensitive attributes and assess model performance and fairness with respect to them. For race, we use both race and ethnicity variables to partition the cohort into six disjoint groups: Asian, Black, Hispanic, Other, Unknown, and White. Patients not considered Hispanic thus have either a non-Hispanic or unknown ethnicity. For gender, we partition the cohort into male and female populations. For age, we discretize the age at the index time into four disjoint groups: 40-55, 55-65, 65-75, and 75+ years, where the intervals are inclusive on the lower bound and exclusive on the upper bound. A summary of these groups is presented in Table 1.
Table 2: Distribution alignment metrics. We report the coefficient of variation (CV; the ratio of the standard deviation to the mean) of the false positive rate (FPR, CV) and false negative rate (FNR, CV) at a fixed decision threshold of 0.075 across the race, gender, and age groups. Furthermore, we compute the pairwise earth mover’s distance (EMD) between distributions of the predicted probabilities of having an ASCVD event, conditioned on the true ASCVD label $y$ for each group of each sensitive attribute and take the mean.

<table>
<thead>
<tr>
<th></th>
<th>Race</th>
<th>Gender</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
<td>EQ_race</td>
<td>Standard</td>
</tr>
<tr>
<td>FNR, CV</td>
<td>0.126</td>
<td>0.1</td>
<td>0.102</td>
</tr>
<tr>
<td>FPR, CV</td>
<td>0.538</td>
<td>0.383</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean EMD</td>
<td>$y = 0$</td>
<td>0.00749</td>
<td>0.00616</td>
</tr>
<tr>
<td>Mean EMD</td>
<td>$y = 1$</td>
<td>0.0226</td>
<td>0.0237</td>
</tr>
</tbody>
</table>

3.4 Adversarial Learning for Equality of Odds

To develop an ASCVD risk prediction model that satisfies the definition of equality of odds in (3), we consider two fully-connected neural networks: a classifier $f: \mathbb{R}^m \rightarrow \mathbb{R} \in [0, 1]$ parameterized by $\theta_f$ that predicts the probability of the ASCVD outcome $Y$ given data $X$; and a discriminator $g: \mathbb{R} \times [0, 1] \rightarrow [0, 1]^k$ parameterized by $\theta_g$ that takes as input both the logit of the output of $f$ and the value of the true label $Y$ to predict a distribution over the groups of a sensitive attribute $Z$. If $L_{cls}$ and $L_{adv}$ are the cross-entropy losses of the classifier predictions over $Y$ and the discriminator predictions over $Z$, respectively, then the training procedure may be described by alternating between the steps

$$\min_{\theta_f} L_{cls} - L_{adv} \quad \text{and} \quad \min_{\theta_g} L_{adv}.$$ (4)

3.5 Model Training and Evaluation

The training procedure is composed of four experiments and thus produces four prediction models. The first model is trained to predict the risk of ASCVD and does not use adversarial training. The other three models result from separate training runs in which each of the discrete race, gender, and age variables are considered as sensitive attributes in the adversarial training procedure. We refer to these four experiments as Standard, EQ_race, EQ_gender, and EQ_age.

For all experiments, we employ fully-connected feedforward neural networks with a fixed set of hyperparameters. The ASCVD prediction model is composed of the sum over an embedding layer of dimension 100 followed by two hidden layers of dimension 128 and leaky ReLU nonlinearities. The adversarial network maintains a similar architecture, but with one hidden layer of dimension 64 and takes the prediction logit and ASCVD outcome as inputs. Training proceeds in a batch setting with the Adam optimizer [19] with learning rate $10^{-3}$, $\beta_1 = 0.5$, and $\beta_2 = 0.9$ with batch size 256 over the training set and early stopping based on the area under the receiver operating characteristic curve (AUC-ROC) for ASCVD prediction in the validation set. All training was performed on a single GPU with the PyTorch library [27].

For each model, we compute standard metrics on the entire test set and on each subgroup. Specifically, we report the AUC-ROC, the area under the precision-recall curve (AUC-PRC), the Brier score [3] as a measure of calibration, and the false positive and false negative rates (FPR, FNR) at a fixed threshold of $T = 0.075$, in keeping with current ASCVD guidelines for the prescription of statin therapy [10, 33]. To express adherence to the standard equality of odds definition in equation 2, we report the coefficient of variation (i.e. the ratio of the standard deviation to the mean) of the FPR and FNR at $T = 0.075$ across the groups of each sensitive attribute. To assess the distance between the distributions presented in (3), we compute the earth mover’s distance (EMD, or first Wasserstein distance) between the empirical distributions of the predicted probability of ASCVD conditioned on whether ASCVD occurred or not for each group of each sensitive attribute in a pairwise fashion and take the mean within each strata.

4 RESULTS

4.1 Cohort Characteristics

The cohort extraction procedure produces a cohort of 253,547 patients having 71,554 features, with 5,886 patients labeled as positive for ASCVD (Table 1). We note that in this cohort, there are 135,438 white patients, constituting a majority, and 8,549 black patients. Across racial groups, ASCVD rates range from 2.0-3.0%, with the exception of patients with unknown race, who experience a reduced rate of 0.86%. Furthermore, we observe higher ASCVD rates for male patients compared to female patients. Finally, ASCVD rates appear to increase monotonically with age, with rates ranging from 0.95% for the 40-55 age group to 6.7% for patients age 75 or older.
### Table 4: Model performance measured on the test set stratified by group and experimental condition. EQ corresponds to training for the sensitive attribute corresponding to the subgroup of interest. FPR and FNR are computed at a fixed decision threshold of 0.075.

<table>
<thead>
<tr>
<th></th>
<th>AUC-ROC</th>
<th>AUC-PRC</th>
<th>Brier Score</th>
<th>FNR</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stand.</td>
<td>EQ</td>
<td>Stand.</td>
<td>EQ</td>
<td>Stand.</td>
</tr>
<tr>
<td>Asian</td>
<td>0.819</td>
<td>0.771</td>
<td>0.138</td>
<td>0.0196</td>
<td>0.0197</td>
</tr>
<tr>
<td>Black</td>
<td>0.753</td>
<td>0.756</td>
<td>0.162</td>
<td>0.034</td>
<td>0.0338</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.811</td>
<td>0.803</td>
<td>0.117</td>
<td>0.0142</td>
<td>0.015</td>
</tr>
<tr>
<td>Other</td>
<td>0.813</td>
<td>0.822</td>
<td>0.13</td>
<td>0.0217</td>
<td>0.0219</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.713</td>
<td>0.718</td>
<td>0.0619</td>
<td>0.00766</td>
<td>0.00812</td>
</tr>
<tr>
<td>White</td>
<td>0.774</td>
<td>0.766</td>
<td>0.146</td>
<td>0.0245</td>
<td>0.0245</td>
</tr>
<tr>
<td>Female</td>
<td>0.8</td>
<td>0.786</td>
<td>0.12</td>
<td>0.0173</td>
<td>0.0174</td>
</tr>
<tr>
<td>Male</td>
<td>0.775</td>
<td>0.769</td>
<td>0.148</td>
<td>0.0249</td>
<td>0.025</td>
</tr>
<tr>
<td>40-55</td>
<td>0.713</td>
<td>0.727</td>
<td>0.0404</td>
<td>0.0085</td>
<td>0.00922</td>
</tr>
<tr>
<td>55-65</td>
<td>0.736</td>
<td>0.708</td>
<td>0.0919</td>
<td>0.0195</td>
<td>0.0198</td>
</tr>
<tr>
<td>65-75</td>
<td>0.736</td>
<td>0.739</td>
<td>0.128</td>
<td>0.0349</td>
<td>0.0347</td>
</tr>
<tr>
<td>75+</td>
<td>0.776</td>
<td>0.763</td>
<td>0.228</td>
<td>0.053</td>
<td>0.0548</td>
</tr>
</tbody>
</table>

**Figure 1:** Empirical distribution of the predicted probability of developing ASCVD in the followup period conditioned on whether ASCVD occurred. Plots are stratified by experimental condition (Standard or EQ), true value of the ASCVD outcome \(y = 0\) or \(y = 1\), and the variable treated as sensitive (race, gender, or age).

### 4.2 Distribution Alignment with Adversarial Training

Applying the adversarial training procedure results in a alignment of the distributions of the predicted probability of ASCVD conditioned on the true outcome label (Figure 1). Without employing a adversarial discriminator, the center of mass of these distributions appears to depend significantly on the base ASCVD rate in the group. However, these differnces largely disappear when training in an adversarial setting. This results in a substantial reduction in the mean pairwise EMD between each predictive distribution in both outcome strata for both gender and age, with a negligible effect for race (Table 2). Furthermore, we note that variability in the FPRs and FNRs at a fixed threshold of 0.075 is greatly reduced following adversarial training (Table 2), indicating that the approach successfully encourages the model predictions to satisfy equality of odds.

The relative lack of success in minimizing the mean pairwise EMD between the conditional predictive distributions across racial groups (Table 2) may be largely explained by the anomalous characteristics of the group of patients having unknown race. For instance, when using standard training (Standard), the predictive distribution conditioned on a positive ASCVD outcome for the unknown race group is clearly separated from that of the five groups while the distributions for those five are mostly aligned (Figure 1). However, when training the model in an adversarial setting, it appears that the primary effect is to align the predictive distribution for the unknown race group to the region inhabited by the distributions of the remaining groups while disturbing the relative alignment between the distributions for those groups.

### 4.3 The Cost of Fairness

Satisfying equality of odds with an adversarial objective incurs a reduction in AUC-ROC, AUC-PRC, and calibration for the population at large (Table 3), with the largest negative effects observed when training to adjust for the differences across age groups (Standard...
While we have demonstrated empirically that adversarial learning using EHR data allowed a high-capacity ASCVD risk prediction model to be trained using a large and diverse cohort, this model should not be directly compared to the PCEs for several reasons. First, the PCEs estimate ten-year ASCVD risk, whereas our model estimates risk over a period of at least a year. Furthermore, we cannot rule out the existence of biases that may lead to differential rates of selection or censoring in our cohort across age, gender, and race based subgroups, nor can we establish whether the nature of these biases differ from those present in the prospective cohort studies used to derive the PCEs.

5.1 Limitations of the Predictive Model

While using EHR data allowed a high-capacity ASCVD risk prediction model to be trained using a large and diverse cohort, this model should not be directly compared to the PCEs for several reasons. The PCEs estimate ten-year ASCVD risk, whereas our model estimates risk over a period of at least a year. Furthermore, we cannot rule out the existence of biases that may lead to differential rates of selection or censoring in our cohort across age, gender, and race based subgroups, nor can we establish whether the nature of these biases differ from those present in the prospective cohort studies used to derive the PCEs.

5.2 Moving Beyond Equality of Odds

While we have demonstrated empirically that adversarial learning procedures are capable of encouraging a model to satisfy equality of odds, the use of this metric as a measure of fairness should be approached with caution. In the case that there is insufficient information in the training dataset to learn a high performing model for at least one group, optimizing for this criteria will upper bound the group-level model performance by the performance obtained for the least-well performing group. In the adversarial learning setting, this reduction in performance for some groups may be offset by performance gains for groups for which the model performs poorly when trained naively. However, we observed that if such a benefit exists, it is smaller than the reduction in performance incurred for most groups.

We have not examined the relationship between the errors of the predictive model and notions of long-term utility when deploying the model clinically. To properly analyze the effect of these errors on utility requires careful causal modeling of the sequential decision-making process following ASCVD risk prediction while accounting for individual patient characteristics. We emphasize that while such a process is crucial to evaluate the long-term impact of any prediction model, it is not possible to properly identify and model that causal process with observational data in the EHR alone [18]. Additionally, it is unclear that satisfying fairness constraints for a single-step decision, as in ASCVD risk prediction, aligns with the goal of equitably maximizing long-term utility, as it has been shown that satisfying fairness constraints for a static decision may actually cause long-term harm in settings where an unconstrained objective would not [22], particularly if the outcome is measured with bias due to systematic censoring [16]. We find those approaches [21, 26] that establish causal notions of fairness to be promising directions for future work, as they permit sequential decision making processes to be studied under the lens of fairness at both the group and individual level.

6 CONCLUSION

Existing approaches to ASCVD risk scoring perform poorly for the population at large, with more extreme risk mis-estimates for minority populations, inadvertently exposing those groups to excess harm. We develop an ASCVD prediction model using EHR data and show that we can encourage formal notions of fairness by reducing the variability in the FPR and FNR across groups. It is not yet known to what extent algorithmic notions of fairness align with other goals, including long-term utility maximization. We hope that our results will serve as an impetus for the community at large to investigate the fairness-utility trade-off during sequential clinical decision making resulting from fairness constraints imposed on clinical risk assessments.

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REFERENCES


A EXCLUSION CRITERIA: CARDIOVASCULAR ARtery DISEASES

Here we list the set of concepts from the Observational Medical Outcomes Partnership vocabulary version 5.3 used to exclude patients on the basis of a history of cardiovascular artery disease at the prediction time.

Monoplegia of dominant lower limb as a late effect of cerebrovascular accident (197303); Acute myocardial infarction (312327); Hypertensive encephalopathy (312938); Atrial fibrillation (313217); Nonpyogenic thrombosis of intracranial venous sinus (314667); Chronic ischemic heart disease (315286); Preinfarction syndrome (315296); Angina decubitus (315832); Heart failure (316139); Aneurysm of coronary vessels (316427); Cerebral atherosclerosis (316437); Coronary occlusion (316995); Coronary arteriosclerosis (317576); Postmyocardial infarction syndrome (319038); Congestive heart failure (319835); Angina pectoris (321318); Dissecting aneurysm of coronary artery (321879); Paralytic syndrome as late effect of stroke (327654); Cerebral artery occlusion (372924); Transient cerebral ischemia (373503); Basilar artery syndrome (374055); Acute ill-defined cerebrovascular disease (374060); Cerebral ischemia (374384); Cerebral embolism (375557); Vertebralbasilar artery syndrome (376114);
Moyamoya disease (378774); Cerebrovascular disease (381591); Subclavian steal syndrome (433505); Late effects of cerebrovascular disease (434056); Acute myocardial infarction of anterior wall (434376); Vertebral artery syndrome (434656); Weakness of face muscles (434657); Acute myocardial infarction of lateral wall (437606); Basilar artery occlusion (437308); Ataxia (437584); Aneurysm of heart (438168); Acute myocardial infarction of inferior wall (438170); Acute myocardial infarction of anterolateral wall (438438); Acute myocardial infarction of infero-lateral wall (438447); Multiple and bilateral precerebral arterial occlusion (439295); True posterior myocardial infarction (439693); Left heart failure (439846); Vertigo as late effect of stroke (440467); Acute myocardial infarction of interposterior wall (441579); Cerebral thrombosis (441874); Precerebral arterial occlusion (443239); Dysphagia as a late effect of cerebrovascular accident (443465); Monoplegia of dominant upper limb as a late effect of cerebrovascular accident (443525); Apraxia due to cerebrovascular accident (443551); Arteriosclerosis of coronary artery bypass graft (443563); Systolic heart failure (443580); Diastolic heart failure (443587); Paralytic syndrome of nondominant side as late effect of stroke (443599); Paralytic syndrome of dominant side as late effect of stroke (443609); Acute subendocardial infarction (444406); Infarction - precerebral (445731); Vertebralbasilar territory transient ischemic attack (4408758); Cerebral infarction due to embolism of cerebral arteries (4108356); Acute myocardial infarction of atrium (4108669); Cerebral infarction due to thrombosis of cerebral arteries (4110192); Occlusion of artery (4162038); Vertebral artery obstruction (4185117); Ischemic heart disease (4185932); Myocardial ischemia (4186397); Carotid artery obstruction (4288350); Chronic systolic heart failure (4079192); Dysphagia as late effect of cerebrovascular disease (4079575); Chronic diastolic heart failure (4079756); Aphasia as late effect of cerebrovascular disease (4080002); Sensory disorder as a late effect of cerebrovascular disease (4080449); Acute on chronic systolic heart failure (4080602); Acute systolic heart failure (4080603); Monoplegia of lower limb as late effect of cerebrovascular disease (4080938); Monoplegia of nondominant lower limb as a late effect of cerebrovascular accident (4080946); Acute diastolic heart failure (4081042); Acute on chronic diastolic heart failure (4081043); Arteriosclerosis of coronary artery bypass graft of transplanted heart (4081132); Speech and language deficit as late effect of cerebrovascular accident (4081354); Hemiplegia as late effect of cerebrovascular disease (4081762); Monoplegia of upper limb as late effect of cerebrovascular disease (4081842); Coronary atherosclerosis (4081919); Monoplegia of nondominant upper limb as a late effect of cerebrovascular accident (4082266); Residual cognitive deficit as late effect of cerebrovascular accident (4082301); Arteriosclerosis of autologous vein coronary artery bypass graft (4082638); Arteriosclerosis of nonautologous coronary artery bypass graft (4082655); Combined systolic and diastolic dysfunction (4082727); Arteriosclerosis of arterial coronary artery bypass graft (4083189); Hemiplegia of nondominant side as late effect of cerebrovascular disease (4084513); Hemiplegia of dominant side as late effect of cerebrovascular disease (4084522); Coronary arteriosclerosis in native artery (4287240); Coronary arteriosclerosis in native artery of transplanted heart (43021821); Dysarthria as late effects of cerebrovascular disease (43530687); Visual disturbance as sequel of cerebrovascular disease (43531583); Acute combined systolic and diastolic heart failure (44782718); Chronic combined systolic and diastolic heart failure (44782719); Acute on chronic combined systolic and diastolic heart failure (44782733).

**B EXCLUSION CRITERIA: ANTIHYPERTENSIVE DRUGS**

Here we list the medications from the Antomatical Therapeutic Chemical Classification System (ATC) used to exclude patients on the basis of a history of prescription of anti-hypertensive drugs at the prediction time.

- Rauwolfia alkaloids (C02AA); reserpine (C02AA02); deserpidine (C02AA05); methoxeridine (C02AA06); methyllycaconitine (C02AA18); clonidine (C02AC01); guanfacine (C02AC02); moxonidine (C02AC05); rilmenidine (C02AC06); trimetaphan (C02BA01); mecamylamine (C02BB01); prazosin (C02CA01); indoramin (C02CA02); dopamin (C02CA04); urapidil (C02CA06); betanechol (C02CC01); guanethidine (C02CC02); debrisoquine (C02CC04); diazoxide (C02DA01); diahydralazine (C02DB01); hydralazine (C02DB02); nifedipine (C02DC01); nitroprusside (C02DD01); pinacidil (C02DG01); metolazone (C02KB01); pargyline (C02KB02); ketanserin (C02KD01); bosentan (C02KX01); ambrisentan (C02KX02); macitentan (C02KX04); riociguat (C02KX05); alprostadil (C07AA01); oxprenolol (C07AA02); pindolol (C07AA03); propranolol (C07AA05); timolol (C07AA06); sotalol (C07AA07); nadolol (C07AA12); metoprolol (C07AA14); carteolol (C07AA15); tertatolol (C07AA16); bopindolol (C07AA17); bupranolol (C07AA19); penbutolol (C07AA23); propranolol (C07AB01); metoprolol (C07AB02); atenolol (C07AB03); nebivolol (C07AB04); betaxolol (C07AB05); bisoprolol (C07AB07); celiprolol (C07AB08); esmolol (C07AB09); nebivolol (C07AB12); talinolol (C07AB13); labetalol (C07AG01); carvedilol (C07AG02); metoprolol and felodipine (C07FB02); atenolol and nifedipine (C07FB03).

**C OUTCOME DEFINITION: ASCVD**

Here we list the set of concepts from the Observational Medical Outcomes Partnership vocabulary version 5.3 used to define the presence of ASCVD in the followup period.

- Acute myocardial infarction (312327); Cerebral artery occlusion (372924); Acute ill-defined cerebrovascular disease (374060); Cerebral embolism (375557); Acute myocardial infarction of anterior wall (434376); Acute myocardial infarction of lateral wall (436706); Basilar artery occlusion (437308); Acute myocardial infarction of inferior wall (438170); Acute myocardial infarction of anterolateral wall (438438); Acute myocardial infarction of infero-lateral wall (438447); Multiple and bilateral precerebral arterial occlusion (439295); True posterior myocardial infarction (439693); Acute myocardial infarction of infero-posterior wall (441579); Cerebral thrombosis (441874); Precerebral arterial occlusion (442399); Acute subendocardial infarction (444406); Infarction - precerebral (445731); Cerebral infarction due to embolism of cerebral arteries (4108356); Acute myocardial infarction of atrium (4108669); Cerebral infarction due to thrombosis of cerebral arteries (4110192); Vertebral artery obstruction (4185117); Carotid artery obstruction (4288350).