Selection of 51 predictors from 13,782 candidate multimodal features using machine learning improves coronary artery disease prediction

Highlights

- Elastic net regression is a useful selection tool with a large candidate variable space
- This principled approach to predictor selection can improve CAD risk prediction
- Performance improvement can be maintained in a simple Cox model using the 51 predictors

In brief

Current cardiovascular risk stratification tools are based on a relatively small number of risk factors modeled with Cox proportional hazards models and are known to imperfectly estimate risk. Here, we develop a framework to select a subset of candidate predictors for a coronary artery disease (CAD) risk prediction tool from a multimodal space of 13,782 features using machine learning. This approach is readily generalizable to a broad range of large, complex datasets and disease endpoints.
Selection of 51 predictors from 13,782 candidate multimodal features using machine learning improves coronary artery disease prediction

Saaket Agrawal,1,2,3,6 Marcus D.R. Klarqvist,1,8 Connor Emdin,1,2,3 Aniruddh P. Patel,1,2,3 Manish D. Paranjpe,1,2,3 Patrick T. Ellinor,1,2,3 Anthony Philippakis,1 Kenney Ng,2 Puneet Batra,4 and Amit V. Khera1,2,3,7,*

1Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, MA, USA
2Center for Genomic Medicine, Department of Medicine, Massachusetts General Hospital, 185 Cambridge Street, Simches Research Building | CPZN 6.256, Boston, MA 02114, USA
3Department of Medicine, Harvard Medical School, Boston, MA, USA
4Data Sciences Platform, Broad Institute of MIT and Harvard, Cambridge, MA, USA
5Center for Computational Health, IBM Research, Cambridge, MA, USA
6These authors contributed equally
7Lead contact
*Correspondence: avkhera@mgh.harvard.edu
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SUMMARY

Current cardiovascular risk assessment tools use a small number of predictors. Here, we study how machine learning might: (1) enable principled selection from a large multimodal set of candidate variables and (2) improve prediction of incident coronary artery disease (CAD) events. An elastic net-based Cox model (ML4HEN-COX) trained and evaluated in 173,274 UK Biobank participants selected 51 predictors from 13,782 candidates. Beyond most traditional risk factors, ML4HEN-COX selected a polygenic score, waist circumference, socioeconomic deprivation, and several hematologic indices. A more than 30-fold gradient in 10-year risk estimates was noted across ML4HEN-COX quintiles, ranging from 0.25% to 7.8%. ML4HEN-COX improved discrimination of incident CAD (C-statistic = 0.796) compared with the Framingham risk score, pooled cohort equations, and QRISK3 (range 0.754–0.761). This approach to variable selection and model assessment is readily generalizable to a broad range of complex datasets and disease endpoints.

INTRODUCTION

Machine learning—a discipline at the interface of statistics and computer science—is useful for identifying patterns in large, complex sets of candidate predictors.1,2 While machine learning is now ubiquitous in applications such as advertising and finance modeling, its implementation within clinical medicine—particularly risk modeling—has been considerably slower, in part due to (1) the unique importance of model transparency when supporting clinical decisions and (2) the scarcity of large clinical
cohorts that are well phenotyped enough to maximize and validate the utility of machine learning-based methods. Accelerating the clinical adoption of machine learning will require identifying methods and clinical cohorts that address these caveats and applying them to clinically familiar problems, such as coronary artery disease (CAD) risk prediction.

The current paradigm for prevention of CAD is centered around risk factor modification targeting higher-risk groups as determined by the Framingham risk score (FRS) for CAD or the pooled cohort equations (PCE) and QRISK3 for cardiovascular disease (CVD). These risk calculators were developed using Cox proportional hazards models with tens of candidate risk factors, such as age, cholesterol, and smoking status and—while relatively easy to calculate—are known to imperfectly estimate risk. Prior studies have indicated that cardiovascular risk prediction may be improved by inclusion of additional risk factors across the domains of lifestyle, biomarkers, and genetics in a data-driven manner.

As the number of candidate predictors of CAD increases from tens to thousands, the traditional approach using standard Cox regression models is prone to several limitations. First, such models do not adequately account for correlation between predictors—as the number of predictors becomes large, the correlation structure becomes increasingly complex and can lead to instability in estimates. Overfitting is also more likely in this setting, a statistical phenomenon in which a model becomes overly confident in the data used to train the model, reducing external validity. Finally, when presented with an excess of unre-
Table 1. Baseline characteristics and predicted 10-year risk of cardiovascular events in UK Biobank

| Predictor                      | Development (N = 138,619) | Holdout (N = 34,655) |
|-------------------------------|----------------------------|----------------------|
| **Age (years)**               | 56.2 (8.1)                 | 56.1 (8.1)           |
| **Males**                     | 70,896 (51.1%)             | 17,606 (50.9%)       |
| **Ethnicity**                 |                            |                      |
| White                         | 132,610 (95.7%)            | 33,092 (95.5%)       |
| Black                         | 1,945 (1.4%)               | 499 (1.4%)           |
| East Asian                    | 1,095 (0.8%)               | 290 (0.8%)           |
| South Asian                   | 1,614 (1.2%)               | 402 (1.2%)           |
| Other                         | 1,355 (1.0%)               | 372 (1.1%)           |
| Current smoker                | 14,501 (10.5%)             | 3,604 (10.4%)        |
| Diabetes                      | 6,568 (4.7%)               | 1,635 (4.7%)         |
| Cholesterol (mg/dL)           | 217.5 (37.8)               | 217.4 (37.6)         |
| HDL-C (mg/dL)                 | 55.4 (13.9)                | 55.3 (13.9)          |
| LDL-C (mg/dL)                 | 136.3 (29.2)               | 136.2 (29.0)         |
| SBP (mm Hg)                   | 137.5 (18.4)               | 137.3 (18.3)         |
| **Antihypertensive**          | 26,100 (18.8%)             | 6,501 (18.8%)        |
| Genome-wide polygenic score for CAD (GPS\textsubscript{CAD}) | −0.03 (0.99) | −0.03 (0.99) |
| Incident CAD events over median 11-year follow-up | 4,103 (3.0%) | 1,037 (3.0%) |

**Predicted 10-year risk (%)**

- FRS: 6.9 (6.4) 6.9 (6.4)
- PCE: 8.3 (7.7) 8.2 (7.7)
- QRISK3-2017 (QRISK3): 10.0 (8.4) 9.9 (8.4)

The development cohort was used for a 5-fold cross-validation procedure to build ML4HEN\textsubscript{COX}, while the holdout cohort was used to test performance in unseen data (Figure 1). GPS\textsubscript{CAD} was adjusted for the first four PCs of genetic ancestry and scaled to mean 0 and standard deviation 1. None of the above variables were significantly different between groups at the p < 0.05 level. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

ML4HEN\textsubscript{COX} includes 51 predictors for CAD

ML4HEN\textsubscript{COX} included 51 predictors (Table 2) in the final model. Laboratory values made the greatest proportional contribution to the selected predictors (48.3%) followed by a relatively equal distribution across demographics (5.9%), lifestyle (11.8%), medical history (9.8%), family history (3.9%), physical exam (5.9%), and genetics (7.8%) (Table 2).

To understand the importance of each predictor in ML4HEN\textsubscript{COX}, we performed a “leave-one-out” analysis, systematically removing each variable and quantifying the decrease in model discrimination as assessed by the C-statistic (Table S7). The top 20 predictors ranked by leave-one-out analysis included several traditional cardiovascular risk factors, such as age, sex, HDL cholesterol, LDL cholesterol, systolic blood pressure, self-reported history of hypertension, and hemoglobin A1C (Figure 3A). In addition, the selection of cystatin C, paternal history of heart disease, and sibling history of heart disease mirrored chronic kidney disease and family history of heart disease considered in QRISK3.

Several emerging risk factors of CAD not considered in clinically used algorithms were selected by ML4HEN\textsubscript{COX}. For example, a genome-wide polygenic score for CAD (GPS\textsubscript{CAD}) was the second most important predictor overall. The hazard ratio (HR) of this polygenic score (HR = 1.38 per standard deviation [SD] increment, Figure 3B) was comparable with previously reported effect sizes in the UK Biobank. This is consistent with the finding that the Pearson correlation coefficient between GPS\textsubscript{CAD} and each of the other 50 predictors in this model never exceeds 0.25 in magnitude (Figure S1), suggesting that GPS\textsubscript{CAD} is largely independent of most other proposed risk factors.

ML4HEN\textsubscript{COX} also nominated waist and hip circumference as important predictors of CAD. HRs within ML4HEN\textsubscript{COX} demonstrated an elevated risk of CAD with increasing waist circumference (HR = 1.12 per SD) and decreasing hip circumference (HR = 0.93 per SD), consistent with previous reports (Figures 3C and 3D). Apolipoprotein B, lipoprotein(a), and apolipoprotein A1 are elements of the lipid profile that are not directly considered in FRS, PCE, or QRISK3, but were selected by ML4HEN\textsubscript{COX} and have previously been shown to improve risk stratification in several studies.

Several hematologic parameters were also prioritized by ML4HEN\textsubscript{COX}, including neutrophil count, monocyte count, white blood cell count, red blood cell distribution width, mean corpuscular volume, and plateletcrit. Each of these elements of the complete blood count has previously been associated with incident CVD. Along with the selection of C-reactive protein, these data point to the potential value of the inflammatory milieu in predicting future risk of CAD.

Principal components 3 and 4 of genetic ancestry (PC3, PC4) were selected by ML4HEN\textsubscript{COX}. In the UK Biobank, increasing PC3 and PC4 track with South Asian ethnicity (Figure S2), which is increasingly being identified as a high-risk group for cardiometabolic disease. Interestingly, a marker of socioeconomic deprivation, the Townsend index, was also included in the final model. This index is computed based on geographical location and incorporates information about unemployment, household overcrowding, vehicle ownership, and home ownership, with a larger score reflecting greater material deprivation. ML4HEN\textsubscript{COX} assigned HR of 1.02 per SD to this predictor, meaning that increased material deprivation increased risk of incident CAD.

ML4HEN\textsubscript{COX} outperforms FRS, PCE, and QRISK3

We began by investigating the change in 10-year CAD risk across predicted risk quintiles of ML4HEN\textsubscript{COX} in the holdout cohort. Individuals in the bottom quintile of predicted risk had 17 events (0.25%), those in the middle quintile had 95 events (1.4%), and those in the top quintile had 539 events (7.8%) (Figure 4). The increased risk for the top versus middle quintile was...
Table 2. Predictor space stratified by category

| Category          | Initial predictor space | Selected by ML4H\textsubscript{EN-COX} |
|-------------------|-------------------------|----------------------------------------|
| **Demographics**  | 12 (0.09%)              | 3 (5.9%)                               |
|                   | age                     | sex                                    |
|                   | Townsend deprivation index at recruitment |                                      |
| **Lifestyle**     | 11 (0.08%)              | 6 (11.8%)                              |
|                   | overall health rating — fair |                                       |
|                   | smoking status — current |                                       |
|                   | smoking status — never    |                                        |
|                   | overall health rating — excellent |                                    |
|                   | weight change compared with 1 year ago — none |                              |
|                   | alcohol intake           |                                        |
| **Medical history** | 7,917 (57.4%)           | 5 (9.8%)                               |
|                   | hypertension (self-reported) |                                     |
|                   | lipid-lowering medication |                                       |
|                   | diabetes                 |                                        |
|                   | hypertension (EHR)       |                                        |
|                   | BP-lowering medication   |                                        |
| **Surgical history** | 5,740 (41.6%)           | 0                                      |
| **Family history** | 32 (0.23%)              | 2 (3.9%)                               |
|                   | illnesses of father — heart disease |                        |
|                   | illnesses of siblings — heart disease |                                |
| **Physical exam** | 7 (0.05%)               | 3 (5.9%)                               |
|                   | systolic blood pressure  |                                        |
|                   | hip circumference        |                                        |
|                   | waist circumference      |                                        |
| **Genetics**      | 5 (0.04%)               | 4 (7.8%)                               |
|                   | genome-wide polygenic score for CAD (\text{GPS}_{\text{CAD}}) |                        |
|                   | principal component 3 of genetic ancestry (PC3) |                  |
|                   | PC2                     | PC4                                    |

(Continued on next page)
| Category                  | Initial predictor space | Selected by ML4H\textsubscript{EN-COX} |
|--------------------------|-------------------------|----------------------------------------|
| Laboratory values        | 58 (0.42%)              | 28 (48.3%)                             |
| HDL cholesterol          |                         |                                        |
| glycated hemoglobin      |                         |                                        |
| LDL cholesterol          |                         |                                        |
| testosterone             |                         |                                        |
| apolipoprotein B          |                         |                                        |
| cystatin C               |                         |                                        |
| lipoprotein(a)           |                         |                                        |
| neutrophil count         |                         |                                        |
| apolipoprotein A          |                         |                                        |
| alkaline phosphatase     |                         |                                        |
| C-reactive protein       |                         |                                        |
| monocyte count           |                         |                                        |
| triglycerides            |                         |                                        |
| red blood cell distribution width |       |                                        |
| reticulocyte percentage  |                         |                                        |
| alanine aminotransferase |                         |                                        |
| basophil count           |                         |                                        |
| total protein            |                         |                                        |
| calcium                  |                         |                                        |
| total bilirubin          |                         |                                        |
| mean sphered cell volume |                         |                                        |
| white blood cell count   |                         |                                        |
| mean corpuscular volume  |                         |                                        |
| monocyte percentage      |                         |                                        |
| hemoglobin concentration |                         |                                        |
| albumin                  |                         |                                        |
| urate                    |                         |                                        |
| platelet crit            |                         |                                        |

Predictor variables selected by ML4H\textsubscript{EN-COX} are ranked by leave-one-out C-statistic change within each category (Table S4).
more pronounced for the ML4HEN-COX model (5.7-fold) compared with FRS (3.6-fold), PCE (3.4-fold), and QRISK3 (3.7-fold). Individuals in the top quintile of predicted risk by ML4HEN-COX were more likely to be older men with traditional cardiovascular risk factors (Table S8). Next, we investigated the extent to which ML4HEN-COX was correlated with three clinical algorithms. Correlation coefficients between ML4HEN-COX and the three clinical algorithms (FRS, 0.75; PCE, 0.76; QRISK3, 0.77) were lower than those for each pair of clinical algorithms (FRS-QRISK3, 0.86; PCE-QRISK3, 0.92; FRS-PCE, 0.93), suggesting that ML4HEN-COX was contributing different information compared with FRS, PCE, and QRISK3 (Figure 4).

To benchmark the performance of each model, we calculated C-statistics, a measure of discrimination. The discrimination of a model measures the probability that, for a given incident CAD/no incident CAD pair, the model will correctly predict a higher risk for the individual who developed CAD. In the holdout cohort, ML4HEN-COX demonstrated better discrimination (C-statistic = 0.796, 95% CI: 0.784–0.809) versus FRS (C-statistic = 0.756, 95% CI: 0.742–0.769), PCE (C-statistic = 0.754, 95% CI: 0.739–0.768), and QRISK3 (C-statistic = 0.761, 95% CI: 0.747–0.774) (Table 3). Discrimination was also assessed in subgroups stratified by sex and age (Table 3). Performance of ML4HEN-COX was better in women (C-statistic = 0.780, 95% CI: 0.747–0.811) compared with men (C-statistic = 0.751, 95% CI: 0.735–0.767), although the performance gain compared with clinical risk algorithms was greater in men (0.06 improvement in men, 0.02 in women). These data are consistent with previous work showing that traditional cardiovascular risk factors had higher HRs for incident myocardial infarction in women compared with men in the UK Biobank and suggest that the value of added predictors included in ML4HEN-COX is greater in men. In accordance with FRS, PCE, and QRISK3, performance of ML4HEN-COX was better in younger participants (C-statistic = 0.825, 95% CI: 0.799–0.850) compared with older participants (C-statistic 0.755, 95% CI: 0.737–0.771). Similar C-statistics were calculated in the development cohort, suggesting that no overfitting occurred (Table S9).

Finally, ML4HEN-COX was well calibrated in the development (calibration slope = 1.09, Hosmer-Lemeshow: p = 0.76) and holdout cohorts (calibration slope = 1.13, Hosmer-Lemeshow: p = 1) (Figure S3).

XGBoost and SimpleCox51 perform comparably with ML4HEN-COX.

We next benchmarked the performance of ML4HEN-COX against (1) an alternate machine-learning method and (2) a simple Cox proportional hazards model. First, a survival model...
was developed based on XGBoost, an ensemble-based machine-learning method.\textsuperscript{22,23} One advantage of this method compared with the elastic net regularization used in ML4H EN-COX is that it naturally accounts for nonlinear relationships in the predictor space, although this comes at the cost of increased computational time. Despite the fact that XGBoost selected 115 predictors, including 46 of the 51 selected by ML4HEN-COX (Table S10), its discriminatory performance in the holdout cohort (C-statistic = 0.797, 95% CI: 0.784–0.810) was almost identical to ML4H EN-COX (Table S11). With a cutoff risk of 2.5%, categorical NRIs for XGBoost against FRS (5.9%, 95% CI: 3.3%–8.5%), PCE (6.4%, 95% CI: 3.8%–9.0%), and QRISK3 (5.6%, 95% CI: 3.1%–8.2%) were comparable with ML4HEN-COX (Table S12). These results show that ML4HEN-COX performed similarly well as a more complex machine-learning method, XGBoost, which included twice as many predictors.

We next investigated whether a simple Cox proportional hazards model containing the 51 predictors selected by ML4HEN-COX (Table S10), its discriminatory performance in the holdout cohort (C-statistic = 0.797, 95% CI: 0.784–0.810) was almost identical to ML4HEN-COX (Table S11). With a cutoff risk of 2.5%, categorical NRIs for XGBoost against FRS (5.9%, 95% CI: 3.3%–8.5%), PCE (6.4%, 95% CI: 3.8%–9.0%), and QRISK3 (5.6%, 95% CI: 3.1%–8.2%) were comparable with ML4HEN-COX (Table S12). These results show that ML4HEN-COX performed similarly well as a more complex machine-learning method, XGBoost, which included twice as many predictors.

We next investigated whether a simple Cox proportional hazards model containing the 51 predictors selected by ML4HEN-COX (Table S10), SimpleCox51, could be used to achieve similar performance. Discriminatory performance of SimpleCox51 was comparable with ML4HEN-COX in the holdout cohort (C-statistic = 0.797, 95% CI: 0.784–0.811) (Table S11). With a cutoff risk of 2.5%, categorical NRIs for SimpleCox51 against FRS (6.6%, 95% CI: 4.0%–9.2%), PCE (7.1%, 95% CI: 4.6%–9.7%), and QRISK3 (6.3, 95% CI: 3.8%–8.9%) were comparable with ML4HEN-COX (Table S12). Finally, we investigated the performance of SimpleCox20, a simple Cox proportional hazards containing only the top 20 predictors selected by ML4HEN-COX (Figure 3A). In the holdout cohort, discriminatory performance (C-statistic = 0.794, 95% CI: 0.781–0.807) and reclassification indices were comparable with ML4HEN-COX and SimpleCox51 (Tables S11 and S12). These results are consistent with the hypothesis that ML4HEN-COX is most useful for prioritizing the most important predictors for an outcome, and that simple Cox proportional hazards models with all or a subset of selected predictors can be used for clinical implementation without a significant change in performance.

DISCUSSION

In this study, we applied a machine-learning method, ML4HEN-COX, to select 51 predictors of CAD from 13,782 in a data-driven manner. As large, deeply phenotyped cohorts become increasingly available, this approach offers a scalable, generalizable route for prioritizing salient predictors of a disease outcome. In this study, a relatively simple model containing only 51 predictors of CAD, ML4HEN-COX, highlighted traditional cardiovascular risk factors along with emerging risk factors, such as GPS\textsubscript{CAD}, waist and hip circumference, a measure of socioeconomic deprivation, and several hematologic parameters. The resulting model outperformed FRS, PCE, and QRISK3 in predicting 10-year risk of incident CAD.

The primary strength of this study is the magnitude of data-driven predictor reduction achieved while starting with a 13,782-dimensional predictor space spread across eight categories and with a mix of continuous and categorical predictors. Among studies with similar goals, the largest starting predictor space prior to this study contained 735 predictors.\textsuperscript{24–30} Indeed, because the initial predictor space is relatively small in most previous studies, they often utilize random survival forests to...
prioritize predictors. A random survival forest model did not converge with our data, reflecting the increased size and complexity of our predictor space. On the other hand, elastic net regression is likely to be robust to datasets even with an order of magnitude fewer candidate features and participants. Finally, both machine-learning methods developed in this study appropriately considered censoring compared with several contributions in this area that do not appropriately consider censoring, which may lead to substantial, systematic risk underestimation.31

Several risk factors for CAD not currently considered in clinically used risk algorithms were identified by ML4HEN-COX. Our finding that GPS\textsubscript{CAD} is the second most important predictor in our proposed model suggests that there is utility in integrated risk prediction tools that combine clinically established risk calculators with genetics. Several recent efforts exploring this have shown mixed results, most often demonstrating modest improvements in discrimination and reclassification with the addition of GPS\textsubscript{CAD}.32–35 Our work adds to this literature by demonstrating that GPS\textsubscript{CAD} remains a continuous, independent predictor of CAD in an integrated risk calculator containing 50 other CAD risk factors. Waist and hip circumference were also selected as predictors of CAD and are anthropometric proxies for visceral adipose tissue and gluteofemoral adipose tissue, respectively. There is mounting evidence that these measures of fat distribution are causal determinants of cardiometabolic risk profiles.16,36

ML4HEN-COX also identified key hematologic indices describing white blood cell count and differential (neutrophil count, monocyte count), red blood cell characteristics (red blood cell distribution width, mean corpuscular volume), and platelet quantity (platelet crit), consistent with a previous survival analysis for CVD.19 Hence, there may be hidden predictive value for CAD in the complete blood count, even in the healthy patient.

Our model identified increasing PC3 and PC4 of genetic ancestry as risk factors for incident CAD. In the UK Biobank genetic ancestry principal component space, increasing PC3 and PC4 track with individuals of South Asian ethnicity (Figure S2). This ethnic group is increasingly being recognized as carrying an especially high cardiometabolic burden and recent efforts have focused on developing South Asian-specific risk-prediction tools.29 Interestingly, none of the binary variables for ethnicity that were among the candidate predictors, including South Asian ethnicity, were selected by ML4HEN-COX. This is a departure from material deprivation, measured by the Townsend index, as a risk factor for CAD. Given the mounting concerns surrounding the inclusion of race—a social construct without intrinsic biological meaning—in clinical calculators, our model proposes an alternate solution for capturing sociodemographic differences in risk by considering the PCs of genetic ancestry and socioeconomic indices.37

Some previous studies similarly set out to predict CAD and related outcomes, noting value for inclusion of additional features, such as metabolites or imaging-based assessments of the coronary vasculature. Although such features were not available for our study, additional efforts that include multimodal forms of data input are likely to be of considerable interest.38–40

The performance increase of ML4HEN-COX over FRS, PCE, and QRISK3 can be conceptualized as consisting of “predictor gain” and “modeling gain.” Predictor gain refers to added predictive value associated with adding more predictors to a model, while modeling gain refers to added predictive value associated with modeling those predictors in more complex ways, such as considering nonlinear relationships between predictors. Our finding that a simple Cox proportional hazards model, including the 51 predictors selected by ML4HEN-COX, performs as well as ML4HEN-COX suggests that the majority of the performance increase is attributable to predictor gain. The pattern of a simple Cox model performing as well as the machine-learning method that selected its predictors has previously been demonstrated in a medical context.32 Our finding that XGBoost, an ensemble method that inherently considers nonlinear interactions, does not outperform ML4HEN-COX provides further evidence for this conclusion.

A key barrier to the clinical implementation of machine-learning-derived tools for disease prediction is model complexity. While we report most performance metrics in this study in the context of a 51-predictor model, we note that the vast majority of performance improvement over clinically used algorithms could be achieved with a simple Cox proportional hazards model including only the top 20 predictors selected by ML4HEN-COX. These results suggest a general paradigm for developing new, relatively simple disease prediction models from large, complex cohorts. First, elastic net regularization offers a computationally inexpensive approach for prioritizing a small fraction of predictors from tens of thousands. Our addition of a clinician-review step, a departure from some previous implementations of elastic net regularization, enables further model simplification with a trivial impact on performance.
Table 3. C-statistics for ML4HEN-COX and comparator models in holdout cohort

| Model         | Entire holdout (n = 34,655) | Men (n = 17,606) | Women (n = 17,049) | Age < 55 (n = 15,134) | Age ≥ 55 (n = 19,521) |
|---------------|-----------------------------|------------------|--------------------|-----------------------|-----------------------|
| ML4HEN-COX   | 0.796 (0.784, 0.809)        | 0.751 (0.735, 0.767) | 0.780 (0.747, 0.811) | 0.825 (0.799, 0.850) | 0.755 (0.737, 0.771)  |
| FRS          | 0.756 (0.742, 0.769)        | 0.690 (0.670, 0.709) | 0.758 (0.728, 0.790) | 0.766 (0.736, 0.794) | 0.712 (0.695, 0.730)  |
|              | p < 0.001                  | p < 0.001        | p < 0.001          | p < 0.001             | p < 0.001             |
| PCE          | 0.754 (0.739, 0.768)        | 0.689 (0.671, 0.707) | 0.749 (0.719, 0.781) | 0.770 (0.740, 0.796) | 0.707 (0.688, 0.725)  |
|              | p < 0.001                  | p < 0.001        | p < 0.001          | p < 0.001             | p < 0.001             |
| QRISK3       | 0.761 (0.747, 0.774)        | 0.695 (0.676, 0.714) | 0.763 (0.734, 0.793) | 0.790 (0.763, 0.816) | 0.709 (0.691, 0.727)  |
|              | p < 0.001                  | p < 0.001        | p < 0.001          | p < 0.001             | p < 0.001             |

Bootstrapped 95% confidence intervals indicated in parentheses. p values listed below each C-statistic correspond to DeLong’s test comparing each C-statistic with reference (ML4HEN-COX). C-statistics in the development cohort are displayed in Table S7.

In conclusion, we proposed a machine-learning model, ML4HEN-COX, that selected 51 predictors of CAD from 13,782 starting features in the UK Biobank. ML4HEN-COX outperformed FRS, PCE, and QRISK3 for predicting 10-year risk of CAD on the basis of discrimination and reclassification indices. The methodology outlined here may be useful in developing relatively simple, population-specific risk prediction calculators.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Amit V. Khera (avkhera@mgh.harvard.edu).

Materials availability

There were no physical materials associated with this study.

Data and code availability

The raw UK Biobank data are made available to researchers from universities and other research institutions with genuine research inquiries, following IRB and UK Biobank approval. Representative code used in this work can be found at the following Github repository: https://github.com/broadinstitute/ml4h/tree/master/model_zoo/ml_feature_selection.

Study population and outcome definition

The UK Biobank is an observational study that enrolled over 500,000 individuals between the ages of 40 and 69 years between 2006 and 2010. Detailed genetic and health information ascertained from nurse interviews, electronic health records, and blood tests are available for each individual. In this study, we excluded individuals with prevalent cardiovascular disease (defined as CAD, myocardial infarction, stroke, heart failure, or peripheral vascular disease ascertained by ICD-10 codes, ICD-9 codes, OPCS-4 surgical procedure codes, and national death registries) and individuals with missing data in the categories of demographics, lifestyle, family history, physical exam, genetics, and laboratory values (Tables S1–S4).

Table 4. Categorical reclassification indices in holdout cohort when ML4HEN-COX is compared with each of the three clinical risk algorithms

| Categorical NRI cutoff | Comparator model | FRS | PCE | QRISK3 |
|------------------------|------------------|-----|-----|--------|
|                        |                  | 6.0% (3.5%–8.6%) | 6.6% (4.1%–9.1%) | 5.8% (3.3%–8.3%) |
| 2.5%                   |                  | 6.1% (3.1%–9.1%) | 8.2% (5.1%–11.2%) | 7.5% (4.6%–10.5%) |

All reclassification indices were significant at the p < 0.001 level.

reduction in performance. Finally, selected predictors—or even a subset of the most important predictors—can be combined in a simple Cox proportional hazards model. This paradigm may accelerate the incorporation of new insights from deeply phenotyped cohorts into clinical prediction tools.

Our results should be interpreted within the context of several limitations. First, ML4HEN-COX does not inherently consider nonlinear relationships in the predictor space. This was addressed by verifying that the performance of an ensemble method that does consider nonlinear relationships, XGBoost, does not outperform ML4HEN-COX. Second, the UK Biobank has a low incidence of CAD compared with the general population and consists predominantly of a white European population. It could be the case that the predictors identified by ML4HEN-COX have predictive value specific to cohorts with these attributes. To minimize the risk of this, we used a rigorous cross-validation and holdout procedure and demonstrated that the vast majority of predictors selected by ML4HEN-COX—particularly those among the top 20 in predictive value—have previously been associated with cardiovascular disease. Nonetheless, external validation of these results would be a crucial next step prior to any proposed clinical implementation. Third, the greater number of predictors included in ML4HEN-COX compared with FRS, PCE, and QRISK3 inherently makes transportability more challenging. Automated input and calculation at the level of the health system or payer level using data in the electronic health records is possible in principle, but in practice has proven challenging to implement to date. Future work may implement an additional machine-learning step—possibly weighted by the clinical transportability of each feature—to further prioritize the 51 selected predictors in this study.
The 173,274 individuals included in this study were randomly assigned to either a development cohort (80%, n = 138,619) or a holdout cohort (20%, n = 34,655). The authors were blinded to the holdout cohort until model development was completed. For both machine-learning models developed in this study (ML4HEN-COX and XGBoost), a 5-fold cross-validation procedure was performed in the development cohort to minimize risk of overfitting.

The primary outcome was incident CAD, defined as myocardial infarction, unstable angina, revascularization (PCI/CABG), or death from CAD as determined on the basis of ICD-10 codes, ICD-9 codes, OPICS-4 surgical procedure codes, and national death registries (Table S5).

**Recalibrating clinical risk algorithms**

The FRS for CAD, PCE for cardiovascular disease, and QRISK3 for cardiovascular disease were computed as described previously.4–6 QRISK3 was unavailable for 1.4% of the analyzed cohort. Mean 10-year predicted risk of the outcome from each of these calculators (FRS, 6.9%; PCE, 8.3%; QRISK3, 10.0%) was significantly greater than the observed 10-year event rate of CAD (2.6%) in the development cohort (Figures S4–S6). This discrepancy is likely due to a combination of (1) healthy volunteer selection bias in UK Biobank, (2) secular trends in lower rates of CAD in contemporary practice as compared with the data used to train these calculators, particularly FRS and PCE, and (3) the latter two calculators predicting a broader cardiovascular disease outcome (including stroke) rather than just CAD.42

To account for this discrepancy, all three risk calculators were recalibrated to the incidence of CAD in the development cohort using methodology described previously.4–6 Calibration plots predicted by predicted risk deciles supported successful recalibration for all three clinical algorithms (Figures S4–S6). Recalibrated models were used for all subsequent analyses.

**Preparing candidate predictors**

We curated 13,782 candidate predictors assessed at time of study enrollment across the domains of demographics, lifestyle, medical history, surgical history, family history, physical exam, genetics, and laboratory values (Table S6). Medical history and surgical history variables included both self-reported history collected during a verbal interview with a trained nurse at time of enrollment and ICD-10 and OPICS-4 surgical procedure codes from the participant’s electronic health record.

Candidate genetic variables included ancestral background as quantified by the first four PCs of genetic ancestry returned to the UK Biobank and a previously validated genome-wide polygenic score for CAD (GPS\textsubscript{CAD}).4 This score has previously been associated with risk of prevalent disease among UK Biobank and other study participants.15,16 In brief, raw GPS\textsubscript{CAD} values were generated by multiplying the genotype dosage for each allele by its respective effect size followed by summing across all variants included in the score. To adjust for differences in variant frequencies according to genetic ancestry—needed to standardize the score distribution—an ancestry-adjusted GPS\textsubscript{CAD} was generated by taking the residual of a linear regression model predicting raw GPS\textsubscript{CAD} with the first four PCs of genetic ancestry.47

Continuous variables were scaled to a mean of 0 and variance of 1. Categorical variables with n categories were split into n binary variables.

**Development of machine-learning models for variable selection and prediction**

We developed the ML4HEN-COX using a two-step process. First, an elastic net regularized Cox proportional hazards model was fit in the development cohort. Elastic net regularization was first developed in the context of linear regression and later extended to Cox survival analysis.47,48 This approach is conceptually similar to a traditional Cox model, but adds an elastic net penalty term to the regression, which controls the fraction of candidate predictors that remain in the final model (Equation 1)

$$
\hat{\beta} = \arg \min \left\{ \sum_{i=1}^{n} \left[ \frac{1}{2} (y_i - \hat{y}_i)^2 + \frac{1}{2} \lambda \left( \alpha \| \beta \|_1 + \frac{1}{2} (1 - \alpha) \beta^T \beta \right) \right] \right\}
$$

(1)

where $|\beta|$ corresponds to a lasso penalty (L1) and $\beta^T \beta$ corresponds to a ridge regression penalty (L2). The hyperparameter $\alpha$ weights the relative contribution of the L1 and L2 terms, while the hyperparameter $\lambda$ controls the overall magnitude of the penalty term. In this study, $\alpha$ was set to 0.5, allowing for an equal contribution of the L1 and L2 penalties. The overall magnitude $\lambda$ was optimized through a 5-fold cross-validation procedure (Figure 1). Increasing $\lambda$ corresponds to a more aggressive penalty, leading to fewer predictors selected in the final model (left side of Figure 2). Reciprocally, decreasing $\lambda$ results in more predictors in the final model (right side of Figure 2). The output of this step for each of the five folds was a matrix consisting of $\lambda$, a list of predictors selected at the given $\lambda$, the C-statistic in the training data at the given $\lambda$, and the C-statistic in the test data at the given $\lambda$.

Second, we implemented a clinician review step to investigate the models in a narrow window of $\lambda$ immediately prior to the largest C-statistic in the test data (peak of the test curve in Figure 2). We found that there was a range of $\lambda$ (green region in Figure 2) where the complexity of the model increased substantially (from 40 to 150 predictors) concomitant to a moderate increase in C-statistic (ranging from $\sim0.005$ to $\sim0.01$ increase). An expert panel of clinicians reviewed models in this range and ultimately chose the model containing 51 predictor variables as the most reasonable, balancing model performance with interpretability of included variables. The relative importance of the 51 predictors selected by ML4HEN-COX was investigated by measuring the C-statistic decrease when a given predictor was removed from the model.

To benchmark ML4HEN-COX against a more sophisticated machine-learning approach, we additionally developed a model using XGBoost, an ensemble machine-learning method that allows for nonlinear interactions between candidate variables.25,23 Hyperparameter optimization of this model was performed with respect to the Cox partial log likelihood. The best-performing model resulted in 115 predictors (Table S10). Finally, we studied a simple, unregularized Cox proportional hazard model, SimpleCox51, using the 51 predictor variables selected by ML4HEN-COX and SimpleCox20, using the top 20 predictors selected by ML4HEN-COX.

Elastic net regression (ML4HEN-COX) and XGBoost were the selected machine-learning approaches in this study because they had readily available implementations for survival analysis, penalized unimportant candidate variables to zero, and were computationally efficient enough to scale to tens of thousands of features across hundreds of thousands of participants.

ML4HEN-COX and XGBoost models were developed with the scikit-survival 0.13.1, and xgboost 1.2.0 packages in Python. SimpleCox51 and SimpleCox20 were assessed with the survival package in R.

**Statistical methods for benchmarking model performance**

Calibration of developed models was assessed in the development and holdout cohorts by examining plots comparing predicted and observed 10-year risk of CAD and the Hosmer-Lemeshow test. To investigate the gradient in risk of CAD across a range of model predictions, the observed 10-year risk of CAD was determined for quintiles of risk predicted by ML4HEN-COX, FRS, PCE, and QRISK3. The concordance of predicted risk between ML4HEN-COX and the three clinical algorithms (FRS, PCE, and QRISK3) was investigated by computing the Pearson correlation coefficients between the models’ absolute risk predictions. The evaluate model discrimination, C-statistics were computed for ML4HEN-COX, FRS, PCE, QRISK3, XGBoost, SimpleCox51, and SimpleCox20; 95% confidence intervals were constructed with bootstrapping with 1,000 iterations. The DeLong test was used to evaluate statistical significance of differences between C-statistics. Categorical NRI comparing ML4HEN-COX with FRS, PCE, and QRISK3 were calculated in the holdout cohort with cutoff risks of 2.5% and 5.0%. A cutoff of 2.5% was selected because it was close to the observed 10-year CAD event rate in the analyzed cohort, while 5.0% was selected to investigate model behavior at higher risk. Categorical NRI with identical cutoff risks were additionally computed comparing XGBoost, SimpleCox51, and SimpleCox20 with each of the three clinical algorithms. Statistical analyses were done in R 3.6.0.

**SUPPLEMENTAL INFORMATION**

Supplemental information can be found online at https://doi.org/10.1016/j.patter.2021.100364.

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AUTHOR CONTRIBUTIONS
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DECLARATION OF INTERESTS
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