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Cardiometabolic Disease Staging and Major Adverse Cardiovascular Event Prediction in 2 Prospective Cohorts

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Abstract

BACKGROUND—Cardiometabolic risk prediction models that incorporate metabolic syndrome traits to predict cardiovascular outcomes may help identify high-risk populations early in the progression of cardiometabolic disease.

OBJECTIVES—The purpose of this study was to examine whether a modified cardiometabolic disease staging (CMDS) system, a validated diabetes prediction model, predicts major adverse cardiovascular events (MACE).

METHODS—We developed a predictive model using data accessible in clinical practice [fasting glucose, blood pressure, body mass index, cholesterol, triglycerides, smoking status, diabetes status, hypertension medication use] from the REGARDS (REasons for Geographic And Racial

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

APPENDIX For the CMDS for CVD prediction equation as well as supplemental tables and figures, please see the online version of this paper.

Differences in Stroke) study to predict MACE [cardiovascular death, nonfatal myocardial infarction, and/or nonfatal stroke]. Predictive performance was assessed using receiver operating characteristic curves, mean squared errors, misclassification, and area under the curve (AUC) statistics.

RESULTS—Among 20,234 REGARDS participants with no history of stroke or myocardial infarction (mean age 64 ± 9.3 years, 58% female, 41% non-Hispanic Black, and 18% diabetes), 2,695 developed incident MACE (13.3%) during a median 10-year follow-up. The CMDS development model in REGARDS for MACE had an AUC of 0.721. Our CMDS model performed similarly to both the ACC/AHA 10-year risk estimate (AUC 0.721 vs 0.716) and the Framingham risk score (AUC 0.673).

CONCLUSIONS—The CMDS predicted the onset of MACE with good predictive ability and performed similarly or better than 2 commonly known cardiovascular disease prediction risk tools. These data underscore the importance of insulin resistance as a cardiovascular disease risk factor and that CMDS can be used to identify individuals at high risk for progression to cardiovascular disease.

Keywords

cardiometabolic disease; cardiovascular events; risk stratification

Cardiometabolic disease indicates a common pathophysiological process resulting in both metabolic and cardiovascular disease (CVD). At the core of cardiometabolic disease is insulin resistance, which involves defects in glucoregulation, inflammation, dysregulated secretion of factors from adipose tissue, and endothelial dysfunction. The insulin-resistant state remains subclinical until it gives rise to identifiable states of high risk in the form of metabolic syndrome, prediabetes, prehypertension, dyslipidemia, ventral adiposity, and hepatic steatosis.[1,2] The clear majority of patients are overweight or obese, exacerbating insulin resistance and accelerating progression of cardiometabolic disease. These clinical manifestations mark individuals at high risk for progression to end-stage sequela, namely, CVD, congestive heart failure, type 2 diabetes (T2D), hypertension, and nonalcoholic steatohepatitis.[1–6] Unfortunately, population prevalence of obesity, CVD, and diabetes continues to rise,[7] creating an increasing burden of patient suffering and social costs.

Approaches seeking to identify high-risk populations early in the progression of cardiometabolic disease are critically needed for rational targeting of preventive interventions. While weight loss therapy is effective for prevention and treatment of cardiometabolic disease outcomes,[8–11] with roughly 41% of the U.S. adult population having obesity and rising rates across the globe,[12] it is not feasible to treat all individuals with intensive weight-loss therapies efficacious in improving cardiovascular[10] and diabetes[8] outcomes. Efforts that identify high-risk patients would enable clinicians to target patients for aggressive treatments, optimizing benefit/risk ratio for interventions. One potential strategy is to utilize information in the electronic medical record (EMR) to identify patients at highest risk using both clinical[13,14] and socioeconomic[15–17] data. This can be accomplished using risk stratification with cardiometabolic risk prediction models.[9,18]

Prior work from our group has pioneered a model to quantify the future risk of T2D among individuals with overweight or obesity using quantitative clinical parameters called cardiometabolic disease staging (CMDS).[1,19,20] CMDS incorporates the presence and severity of metabolic syndrome traits (body mass index [BMI], blood glucose, blood pressure, high-density lipoprotein cholesterol, and triglycerides). CMDS reflects severity of insulin resistance[21] and robustly predicts the future risk of diabetes.[1,19,20] Moreover, CMDS predicted effectiveness of weight-loss therapy to prevent diabetes in a pooled cohort of 3 randomized controlled trials, ie, lower number-needed-to-treat to prevent 1 case of T2D in those with a higher baseline risk.[9]

We sought to examine the ability of CMDS to predict CVD events to develop a comprehensive CMDS model used to predict T2D *and* CVD outcomes. Our rationale was presence and severity of metabolic syndrome traits[22] and CMDS scores,[21] which reflect severity of insulin resistance, which is responsible for accelerated atherogenesis within the context of cardiometabolic disease. Indeed, lowering low-density lipoprotein cholesterol (LDL-c) levels in statin cardiovascular outcome trials results in average risk reduction of 30%, leaving a preponderant degree of 'residual' risk.[11] Insulin resistance may account for the bulk of this residual risk.[23] In developing a CMDS equation predicting CVD outcomes as well as T2D, we added the parameters of smoking status, non-high-density lipoprotein cholesterol (HDL-c), and hypertension medication use and controlled for diabetes status. We developed and validated the modified CMDS for CVD using data from 2 prospective cohorts: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study and the ARIC (Atherosclerosis Risk In Communities) study. Our purpose was to develop a robust prediction model using data accessible in EMRs to predict progression to *both cardiovascular and diabetes endpoints* in keeping with current calls for encouraging the use of big data to address population cardiovascular outcomes.[14,17]

METHODS

STUDY POPULATION AND SETTING.

CMDS for CVD prediction (equation is available in the Supplemental Appendix) was developed in the REGARDS cohort and validated externally using the ARIC cohort. Institutional review board approvals were obtained for each study, and informed consent was collected from study participants.

REGARDS.

REGARDS is a longitudinal cohort established to investigate high rates of stroke in the Southeastern United States. The cohort enrolled 30,239 individuals from the United States, oversampling the Southeast; age of participants was ≥45 years at time of baseline assessment (2003-2007).[24] Assessments included a telephone survey, followed by an in-home visit to collect anthropometric and biological samples with adjudication of cardiovascular outcomes (every 6 months) through 2017. Blood, urine samples, and physical measurements were collected using standardized protocols.

ARIC.

The ARIC study, a longitudinal, ongoing prospective study initiated in 1987 to understand risk factors for developing heart disease and stroke, enrolled 15,792 adults age 45 to 64 years from 4 U.S. communities in Mississippi, North Carolina, Minnesota, and Maryland.[25] Individuals were assessed at 4 time points between 1990 and 2013, with annual calls to ascertain outcome endpoints. To roughly match the 10-year follow-up in REGARDS, we used baseline assessment (1987-1989) values to predict incident outcomes ascertained through 1998. Biological samples and physical measurements were collected per study protocols.[25]

CARDIOVASCULAR OUTCOMES.

Our primary outcome was a composite outcome endpoint frequently used in diabetes drug trials[26]— the 3-point major adverse cardiac event (MACE). MACE includes the presence of cardiovascular death, nonfatal myocardial infarction, and/or nonfatal stroke. Cardiometabolic risk factors have been associated with an increase in MACE.[27,28] Cardiovascular endpoints were adjudicated through 2017 in REGARDS and 1998 in ARIC.

CARDIOMETABOLIC DISEASE.

Our primary predictor of interest was the CMDS, developed using presence of metabolic syndrome traits to predict progression to diabetes.[1,19] The current CMDS uses continuous clinical measures,[20] and was developed in REGARDS with validation in ARIC.[20] For purposes of adapting CMDS to predict CVD outcomes, we extended the model to include smoking [current vs none], hypertension medication use, and non-HDL-c values since they are highly associated with cardiac events. Age, gender, race (White/Black) and T2D status at baseline (yes/no) were included as covariates. We also examined a model using waist circumference instead of BMI; a model including interactions of clinical values with diabetes status; and a model utilizing LDL-c instead of non-HDL-c to compare our model (as a sensitivity analysis) with other existing cardiovascular risk prediction scores-ACC/AHA pooled cohort risk equations (PCE)[29,30] and Framingham 10-year coronary heart disease (CHD) risk score.[31] We used CMDS values collected at baseline in each respective cohort to predict future MACE events. Table 1 indicates predictors used in each CMDS model.

STATISTICAL METHODS.

Descriptive statistics were used to characterize study cohorts overall and by presence of each outcome (MACE, CVD mortality, nonfatal myocardial infarction, and nonfatal stroke), respectively. Characteristics by outcome status were compared using 2-sample t-tests and chi-squared tests as appropriate. We used Bayesian logistic regression models to analyze our data to jointly fit clinical predictors and covariates to predict MACE and individual outcomes. In accordance with Gelman et al,[32] we assigned weakly informative priors (ie, Cauchy distributions with center 0 and scale 2.5) to coefficients in the logistic regressions. We fit models with Cauchy priors by incorporating an approximate expectation-maximization algorithm into usual iteratively weighted least squares in classical logistic regression. We first fitted a Bayesian logistic regression model using the CMDS with BMI

for each outcome; then a CMDS model with waist circumference instead of BMI; and finally, a CMDS model with LDL-c instead of non-HDL-c. All models included age, sex, race, and diabetes status. We compared a main-effects model with a model that interacted main effects with diabetes status. We compared differences between models using DeLong's test.

We built the Bayesian logistic models using REGARDS data and performed both internal and external validation. Internal validation was accomplished through 10-fold cross-validation, and external validation was performed using ARIC data. We used measures to assess the predictive performance, including area under the curve (AUC), mean squared error (average squared difference between observed and fitted responses), and misclassification (proportion of wrong predicted). We also reported estimates of each individual risk factor in fitted logistic models as odds ratios (ORs) and 95% CIs.

We generated a calibration plot—overall and by race—to assess the model's accuracy in estimating risk and determine whether the model's predicted values align with observed values. We also included a classification table grouped into deciles based on participants' predicted MACE risk as well as clinically meaningful risk groups based on 10-year CVD risk. We then calculated a calibration *P* value using a modified Hosmer-Lemeshow chi-squared statistic.

For sensitivity analysis, we compared the models using completed data and imputed clinical value data. We employed multiple imputations to handle missing clinical data in the REGARDS dataset. This imputation was performed using fully conditional specification (ie, chained equations) with the R package mice.[33] Age, gender, race, and lab values (BMI, glucose, systolic blood pressure, diastolic blood pressure, HDL-c, non-HDL-c, triglycerides) were included in the imputation model, and the number of imputations were chosen based on the highest percent of missing data. Imputed datasets were analyzed separately, and results were combined using Rubin's rule. We also compared our model to other methods, such as the generalized additive model and lasso regression. Statistical analysis was performed using R software (version 4.0.3). The Bayesian model fitting and predictive evaluations were implemented using R function bglm and cv.bh in BhGLM package version 1.1.0. We fitted GAMs and lasso using R packages, mgcv and glmnet, respectively.

RESULTS

DESCRIPTIVE RESULTS.

A total of 20,234 REGARDS participants with a baseline visit were identified for analyses (Figure 1). Baseline characteristics of study participants are described in Table 2. REGARDS participants had a mean age of 64 years (SD 9.3), were mostly female (58%), 41% were non-Hispanic Black, and 18% had diabetes. Across a median 10-year follow-up, there was a MACE incidence of 2,695 events (13.3%). A total of 12,935 ARIC participants were available for validation who, compared with the REGARDS sample, were 10 years younger at baseline and had lower MACE incidence (6.2%) during follow-up (mean age 54 ± 5.7 years; 26% Black; 9% T2D).

Comparing characteristics of REGARDS participants with and without cardiovascular outcomes (ie, MACE), participants were generally more likely to experience an adverse outcome who were older, male, had elevated values of blood glucose, systolic blood pressure, and triglycerides, and were more likely to have diabetes, hypertension medication use, and a smoking history at baseline (Table 3).

FITTED MODELS AND PREDICTIVE VALUES.

Table 4 shows predictive performance of the development and validation CMDS models for composite MACE and individual component outcomes. The REGARDS development model for MACE had an AUC of 0.721. The models including interaction terms (AUC 0.722) and waist circumference (AUC 0.722) did not substantially increase predictive ability ($P > 0.05$). Likewise, models that included LDL-c instead of non-HDL-c did not produce marked gain in predictive ability for MACE (Supplement Table 1). With respect to MACE components, AUC was greatest for CVD mortality in the REGARDS development model (0.771) with lower values for nonfatal myocardial infarction (0.695) and stroke (0.680). Models including interactions and waist circumference did not result in a significant increase in predictive ability. Supplemental Figure 1 displays a calibration plot assessing agreement between predictive vs observed values in the REGARDS development model for MACE, indicating high internal calibration. Supplemental Figure 2 displays the distribution of risk by race illustrating higher predicted risk probabilities among Blacks. The CMDS slightly overestimated risk overall and by race at the upper and lower bounds of both decile and clinically meaningful risk groups (Supplemental Table 2).

External validation of the model was conducted using data from the ARIC cohort, where the AUC for the MACE outcome was 0.737 (Table 4). Similarly, the model was highly predictive of each MACE component outcome.

Figures 2 and 3 show plotted odds ratios and 95% CI per standard deviation increase for the individual risk factors used to construct the fitted main-effect logistic models for MACE and CVD mortality outcomes. For MACE outcome, all risk factors contributed to increased risk except Black race, diastolic blood pressure, HDL-c, and triglycerides. A similar pattern was observed for CVD mortality. Plotted odds for nonfatal myocardial infarction and stroke can be found in Supplemental Figures 3A and 3B. Based on the fitted main-effect logistic model, we obtained a formula for calculating MACE probability for an individual given values of risk factors (Supplemental Appendix). Since risk can be differentially affected by sex, race, diabetes, and smoking status across the spectrum of risk factor values, we plotted predicted probabilities for each parameter in the CMDS development model for MACE (Supplemental Figures 4 to 7). Risks were greater in males compared with females over a range of values (Supplemental Figure 4), with similar findings among those with diabetes (Supplemental Figure 5) and current smokers (Supplemental Figure 6). Probability of MACE did not substantially differ by race (White vs Black) with worsening risk factors (Supplemental Figure 7).

COMPARISONS TO ALTERNATIVE MODELS.

Figure 4 depicts receiver operating characteristic curves comparing our CMDS model to ACC/AHA PCE[29,30] and Framingham 10-year CHD risk score[31] for predicting MACE outcome using REGARDS cohort data. Our development model performed similarly to the ACC/AHA PCE (AUC 0.721 vs 0.716, DeLong's test, $P = 0.41$) and outperformed the Framingham risk score (AUC 0.673, DeLong's test, $P < 0.001$). Figure 5 shows receiver operating characteristic curves comparing models for CVD mortality, which demonstrates superior performance of CMDS. We also limited the models to match the age ranges used in the ACC/AHA and Framingham models (Supplemental Figure 8) and found similar results.

SENSITIVITY ANALYSIS.

We used multiple imputation to impute n = 639 missing lab values and found negligible differences in predictive performance (Supplemental Table 3) for MACE and component outcomes. We graphically compared distributions of observed and imputed composites and found similar distributions (Supplemental Figure 9). When comparing our Bayesian logistic regression model to other methods, we found that the Bayesian model of CMDS with a weak informative prior outperformed the LASSO regression model and was not improved using the generalized additive model in terms of accuracy and interpretability (Supplemental Table 4).

DISCUSSION

In this study using 2 prospective cohorts, we found that CMDS developed for risk prediction of diabetes and then modified with the addition of non-HDL, smoking status, and hypertension medication use, predicted the onset of major cardiovascular events with good predictive ability (AUC 0.721 for MACE and 0.771 for CVD mortality) and performed similarly or better than 2 commonly known CVD prediction risk tools: the ACC/AHA PCE[29,30] and the Framingham 10-year CHD risk score.[31] The CMDS can robustly predict incident diabetes and is superior in performance to the Framingham diabetes risk score, the American Diabetes Association risk calculator, and an earlier version of CMDS that employs weighted discrete Metabolic Syndrome traits.[19,20] Thus, this study, combined with our prior work, demonstrates that CMDS quantitatively reflects the burden of cardiometabolic disease by predicting risk for both T2D and CVD as assessed by the presence and severity of metabolic syndrome traits using a main effects Bayesian model built with commonly available clinical lab values.

In addition to providing a highly effective risk assessment tool, predictive performance of CMDS for both diabetes and CVD is relevant to the basic underlying pathophysiology and natural history of cardiometabolic disease. The center of cardiometabolic disease is the insulin-resistant state, which incorporates a glucoregulatory defect in insulin action with a systemic state of inflammation, oxidative stress, ectopic fat, and endothelial dysfunction.[34] While subclinical much of the lifespan, the insulin-resistant state is characterized by accelerated atherosclerosis together with dysglycemia, dyslipidemia, and elevated blood pressures beginning early in life. Eventually, many individuals meet criteria for prediabetes, prehypertension, metabolic syndrome, and/or hepatic steatosis. These entities provide

clinical confirmation of the presence of insulin resistance and cardiometabolic disease, which give rise to end-stage manifestations of cardiometabolic disease, namely, T2D, nonalcoholic steatohepatitis, hypertension, CVD events, heart failure with preserved or reduced ejection fraction, and chronic kidney disease.[34] Non-HDL and smoking status were added to CMDS for predicting T2D because these factors augment CVD risk outside of the insulin-resistant state, although insulin resistance increases CVD risk in part via abnormalities in size and particle concentration of LDL-c and very low-density lipoprotein cholesterol.[35] The ability of CMDS to predict both CVD and diabetes underscores the role of the insulin-resistant state as a single pathophysiological process causing both vascular and metabolic disease.

It is also clear that CVD risk is continuous over the range of values for risk factors even when below thresholds assigned for abnormal levels. Insulin-resistant individuals who do not meet criteria for metabolic syndrome traits still display abnormalities in triglycerides, HDL-c, fasting glucose, and LDL-c and very low-density lipoprotein particle size and concentration in relation to insulin-sensitive individuals.[22,35] Further, metabolic syndrome has high specificity but low sensitivity for identifying insulin resistance, as assessed by euglycemic hyperinsulinemic clamp studies.[22] Therefore, presence and absence of prediabetes or metabolic syndrome is not sufficient or adequate in comprehensive assessment of cardiometabolic disease (CMD) risk. In addition, use of statins to manage CVD risk due to elevated LDL-c has become common practice over the last several decades. The plethora of CVD outcome trials indicate statins reduce CVD by approximately 30% leaving the bulk of risk (ie, 70%) as residual risk. Insulin resistance has been independently associated with CVD in multiple studies[6,36] and a meta-analysis using HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) index as a measure of insulin sensitivity,[37] and can explain predominant component of residual risk.[23] Less clinical attention is given to management of this residual risk. One impediment has been lack of a pragmatic way to clinically identify and quantify insulin resistance. By using the continuous range of values for quantitative metabolic syndrome traits, which are inherent to the insulin-resistant state,[21,22,35] CMDS is able to comprehensively quantify CVD risk by addressing factors reflecting residual risk.

CMD and its sequela account for a prodigious and increasing burden of patient suffering and social costs. Unfortunately, medical care for patients with CMD is only initiated once the end-stage manifestations become evident. CMDS can be used to assess the risk of T2D and CVD early in the course of CMD. CMDS can be used to target those at highest risk for more aggressive interventions and enhance the benefit/risk ratio and cost-effectiveness of interventions (Central Illustration). One powerful intervention to prevent progression of CMD is weight loss in patients with CMD and obesity. Weight loss improves insulin resistance and ameliorates the core lesion responsible for CMD.[38] As proof of principle, an earlier version of CMDS[19] was highly predictive of future diabetes among individuals with overweight or obesity, and number-needed-to-treat to prevent 1 case of diabetes was reduced among patients in the high-risk strata at baseline following treatment with phentermine/topiramate extended release.[9] Newer tools of obesity medicine provide an effective therapeutic approach in patients with CMD and improve glycemia, hypertension, hepatic steatosis, dyslipidemia, inflammation, and other CVD risk factors.[9,39,40] Clearly,

CMDS can be used as an aid to clinical decisions in identifying patients with CMD who will most benefit from obesity management.

When examining individual risk factors in the CMDS model, we found that age, male sex, BMI, fasting glucose, blood pressure, non-HDL-c, triglycerides, smoking, and hypertension medication use were associated with higher odds of MACE and CVD mortality outcomes. These clinical parameters have been well established as CVD risk factors, and many but not all are included in the ACC/AHA PCE[29,30] and the Framingham 10-year CHD risk score.[31] For example, CMDS and the ACC/AHA estimator, but not Framingham, consider race, specifically the identification of patients as Black or non-Black. Both the ACC/AHA risk estimator and the Framingham ignore triglycerides and consider only presence and absence of diabetes, while, in contrast, CMDS includes triglycerides and glucose levels as continuous variables. Another important difference is use of BMI, which is not included in the ACC/AHA risk calculator and is used in Framingham only when lipid values are not available; however, a recent investigation using ACC/AHA PCE found that equations overestimated risk of CVD events for individuals in overweight and obesity categories.[41] These distinctions could explain differences in performance when all 3 of the risk tools are applied using the same cohort data and highlight need for further investigation around how including risk factors in prediction models translates into improvements in discrimination and net reclassification.

Although multiple risk scores exist for predicting CVD or T2D, to our knowledge, CMDS is the only specific score applicable to CMD over the spectrum of its natural history that has been developed and validated to predict both vascular (CVD events) and metabolic (diabetes) outcomes. Furthermore, CMDS uses quantitative traits readily available to clinicians in EMRs. In this way, CMDS could prove to be a valuable and inexpensive aid to clinicians who treat and prevent CMD in a variety of treatment venues.

Study and use of CMDS have limitations. Risk assessment tools, including CMDS, are based on population risk, and impact of an identical risk profile may vary among individuals. While CMDS accommodates differences based on sex and race, calibration of the model for CVD and diabetes has not been examined in other ethnicities such as Hispanic and Asian populations. CMDS may be disregarding other factors that could add predictive value, for example, inclusion of social determinants of health, which has been shown to increase the ability of CMDS to predict poor outcomes from COVID-19 infection.[42] The inclusion of hemoglobin A1c (not collected in the REGARDS) will be examined in future work as well since this measures the average blood glucose levels over 3 months, is more readily available than blood glucose in the EMR, and is not sensitive to fasting. It also remains to be seen whether treatment strategies will differ in efficacy as a function of baseline risk scores for CVD prevention, as has been shown for diabetes.

In summary, CMDS uses quantitative clinical parameters commonly accessible in EMRs to provide a 10-year risk score that predicts likelihood of progression to both CVD events and diabetes. When applied to the same cohort studies, CMDS performs similarly or better than the ACC/AHA and Framingham risk calculators of CVD. Future work will explore whether availability of interactive CMDS score read-outs as physician reminders in EMRs can orient

primary care professionals toward more preventive care. Such an application of CMDS that can be applied to EMR data responds to current calls encouraging the use of big data to address population cardiovascular outcomes.[14,17] By identifying higher-risk individuals, these approaches will enhance the efficacy and benefit/risk ratio of interventions for CMD prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

AUC	area under the curve
BMI	body mass index
CHD	coronary heart disease
CMD	cardiometabolic disease
CMDS	cardiometabolic disease staging
CVD	cardiovascular disease
EMR	electronic medical record
HDL-c	high-density lipoprotein cholesterol
LDL-c	low-density lipoprotein cholesterol
MACE	major adverse cardiac events

NASH	nonalcoholic steatohepatitis
T2D	type 2 diabetes

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

The CMDS, originally developed to predict diabetes onset, robustly predicts the risk of myocardial infarction, stroke, or a cardiovascular death over a 10-year period.

COMPETENCY IN PATIENT CARE:

Patients who present with high CMDS scores should be referred to aggressive intervention/prevention efforts to reduce likelihood of developing diabetes or CVD.

TRANSLATIONAL OUTLOOK 1:

Future work will explore integrating CMDS into the EMR to facilitate risk stratification and whether the availability of CMDS score read-outs as physician reminders in electronic medical records can orient primary care professionals towards preventive care.

TRANSLATIONAL OUTLOOK 2:

It remains to be seen whether treatment strategies will differ in efficacy as a function of CMDS baseline risk scores for CVD prevention as has been shown for diabetes.

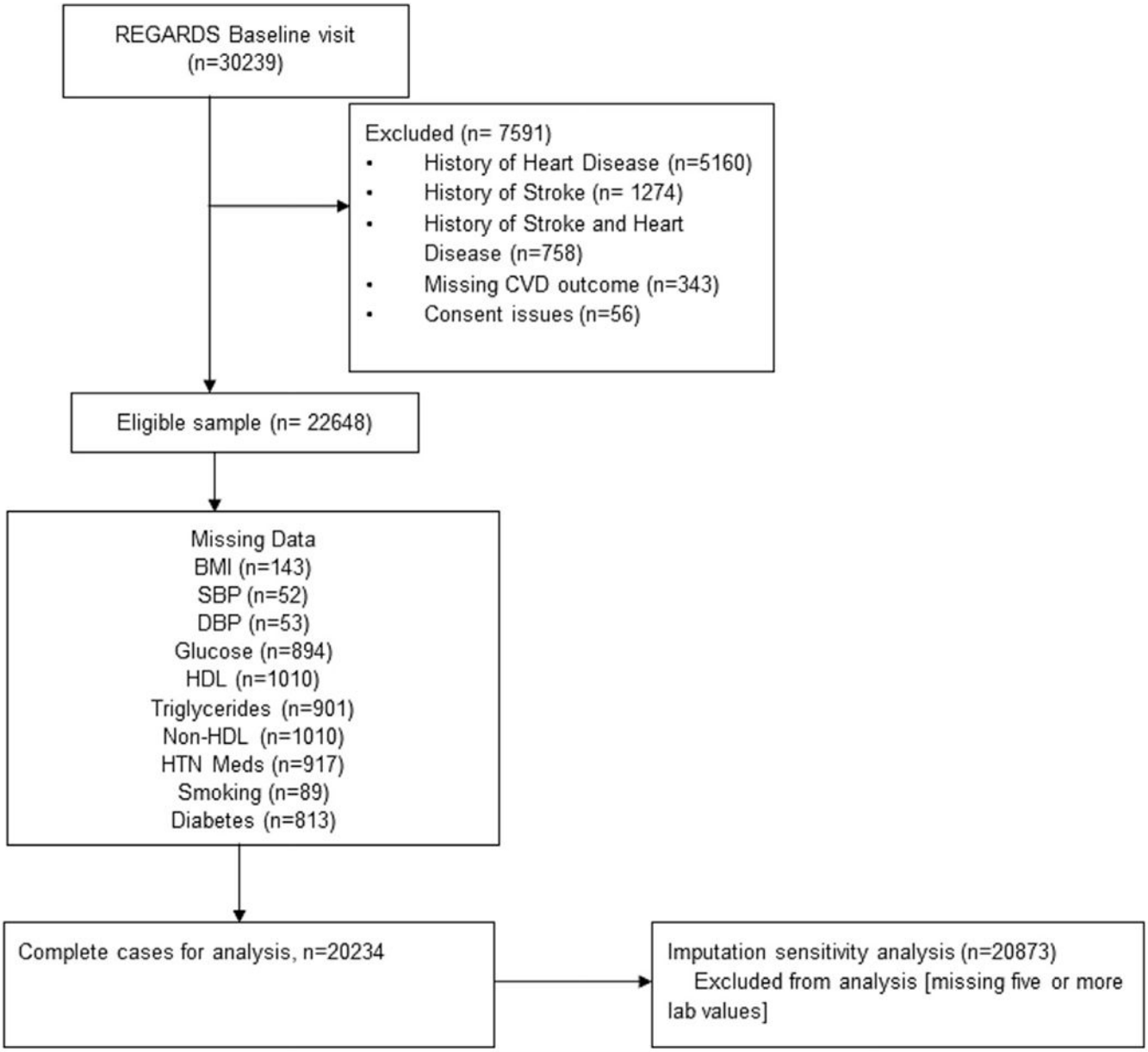


FIGURE 1. Flow of Participant Assessments in the REGARDS Study

After excluding participants with a history of heart disease or stroke, or were missing clinical data, there were N = 20,234 available for analysis. REGARDS = reasons for geographic and racial differences in stroke.

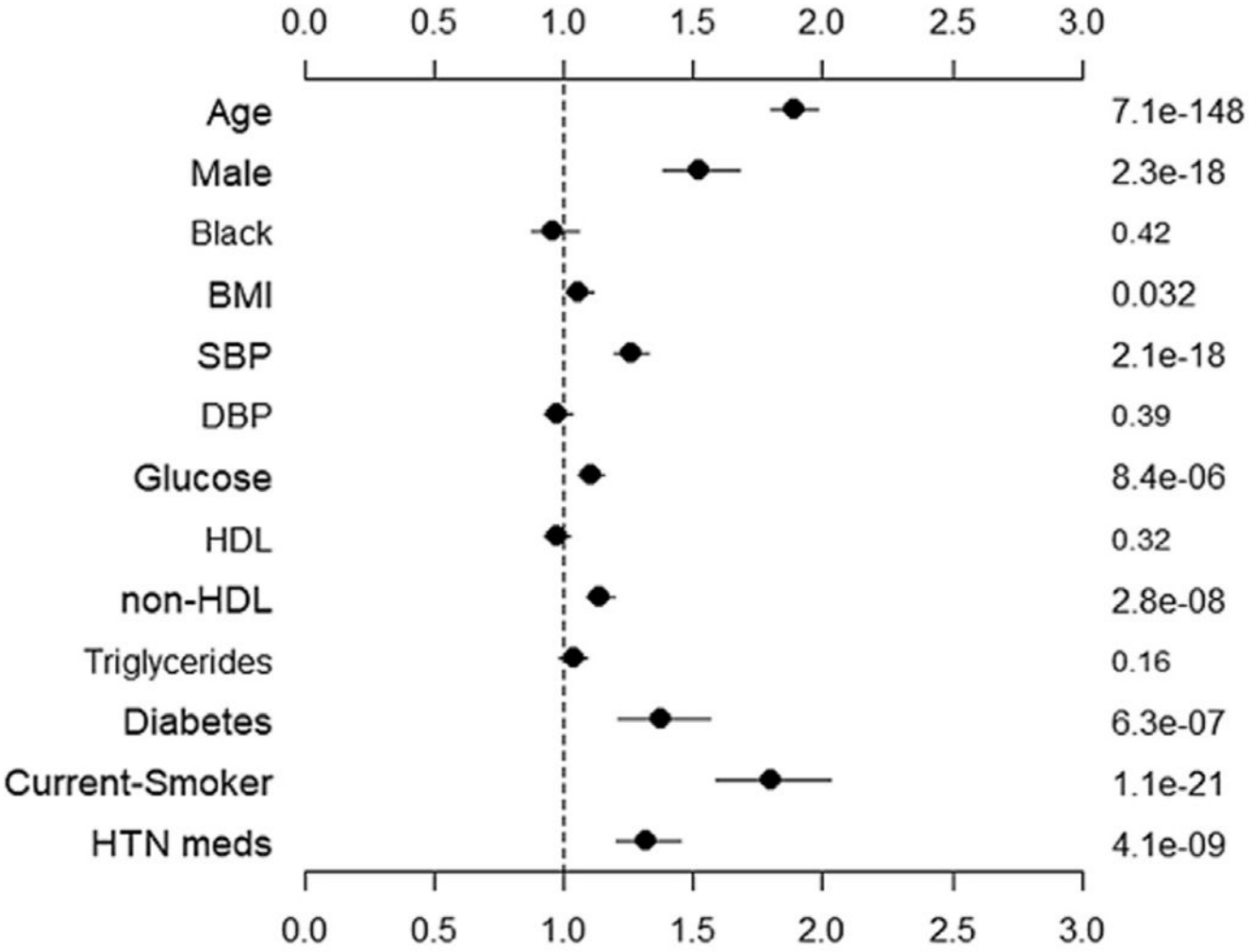


FIGURE 2. Odds Ratio Plots for MACE Outcome

Odds ratio plots per standard deviation increase for Individual risk factors for MACE. The points and lines present the estimated values and 95% CIs, and the values at the right side are *P* values. MACE = major adverse cardiac events.

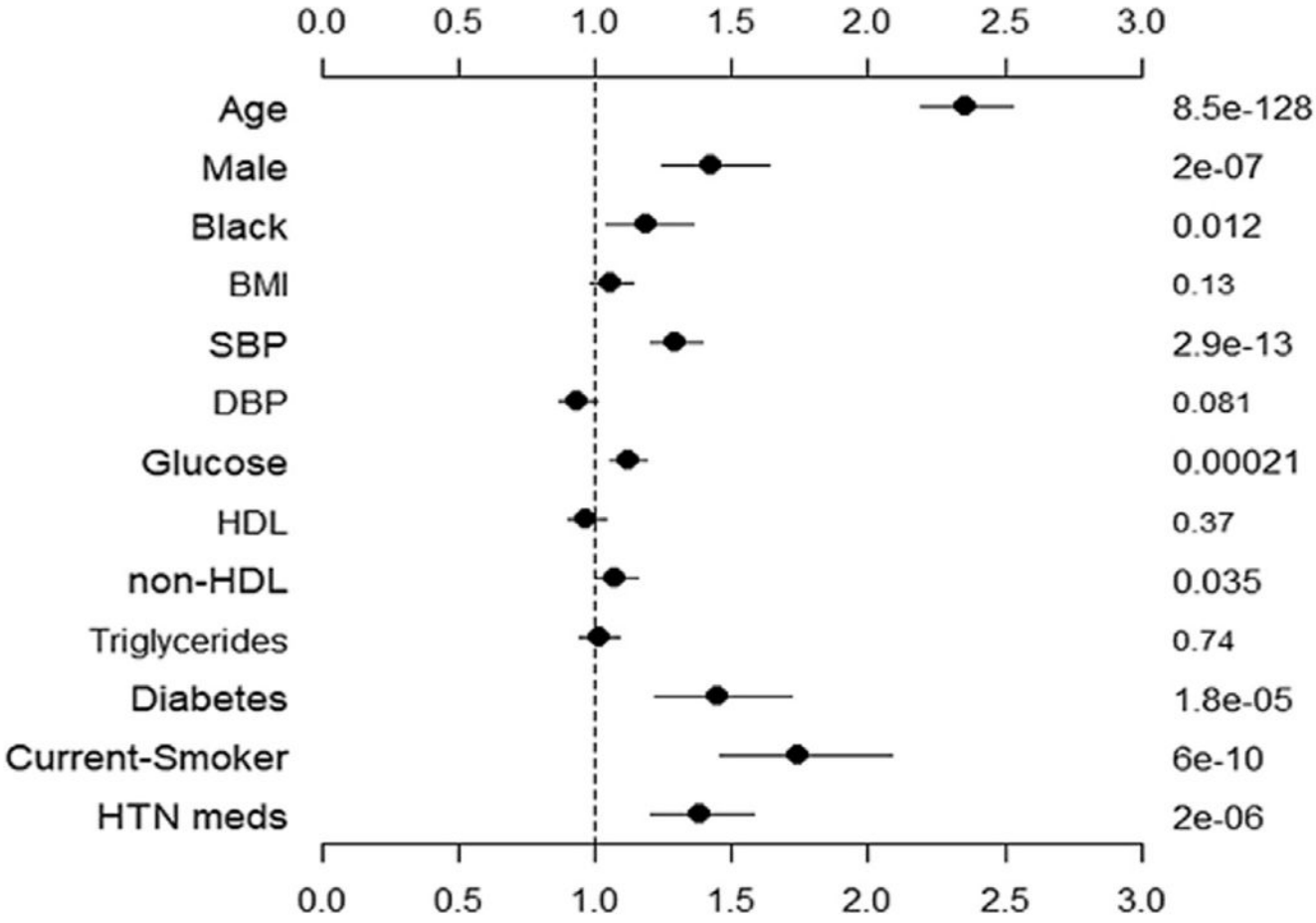


FIGURE 3. Odds Ratio Plots for Cardiovascular Mortality

Odds ratio plots per standard deviation increase for individual risk factors for CVD mortality. The points and lines present the estimated values and 95% CIs and the values at the right side are *P* values. CVD = cardiovascular disease.

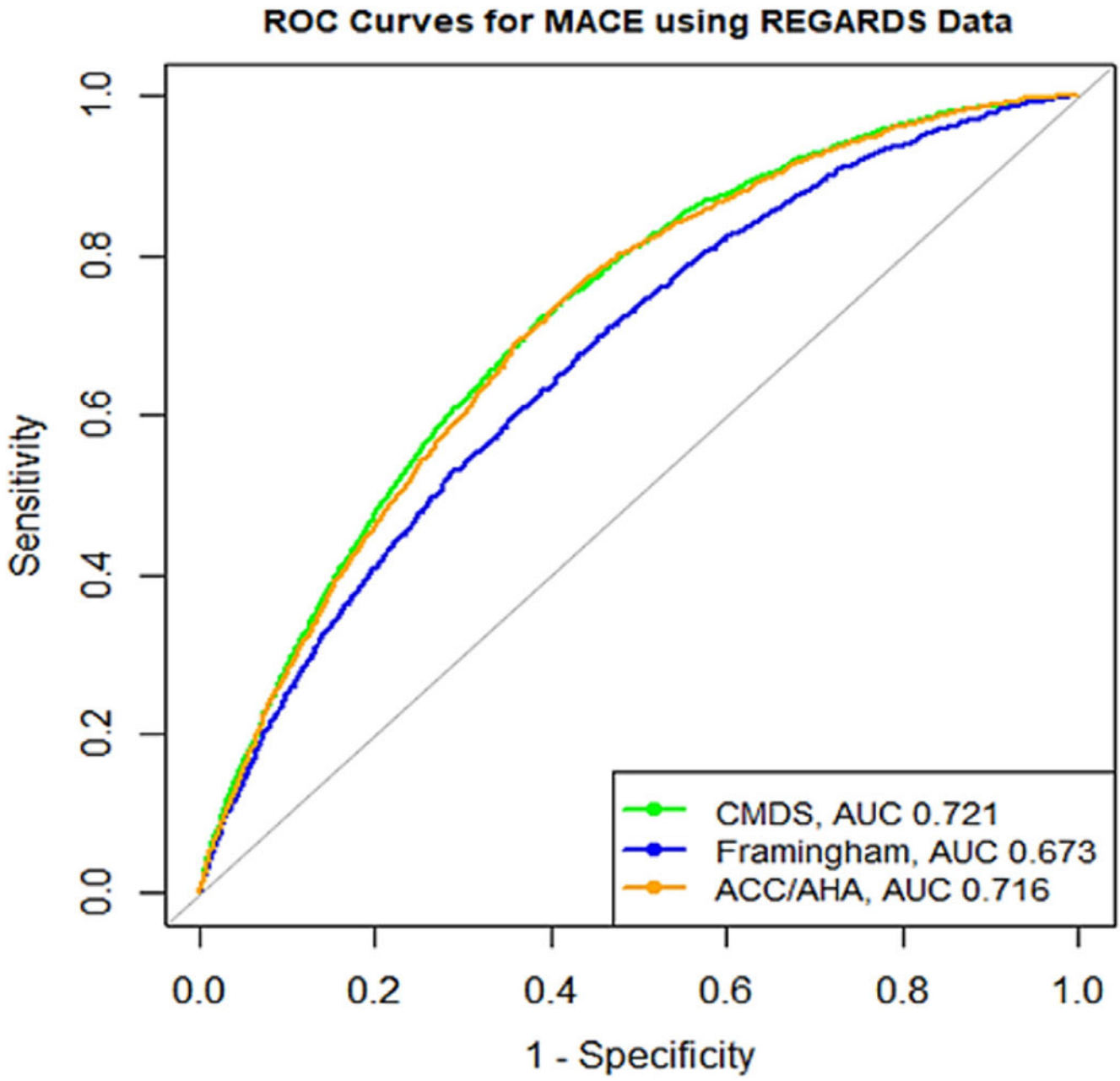


FIGURE 4. Receiver Operating Characteristic Curves for MACE Models

Receiver operating Characteristic curves for CMDS model, ACC/AHA PCE, and the Framingham risk score for MACE outcome using REGARDS data. ACC/AHA = American College of Cardiology/American Heart Association; MACE = major adverse cardiac events; PCE = pooled cohort risk equations; REGARDS = REasons for Geographic And Racial Differences in Stroke.

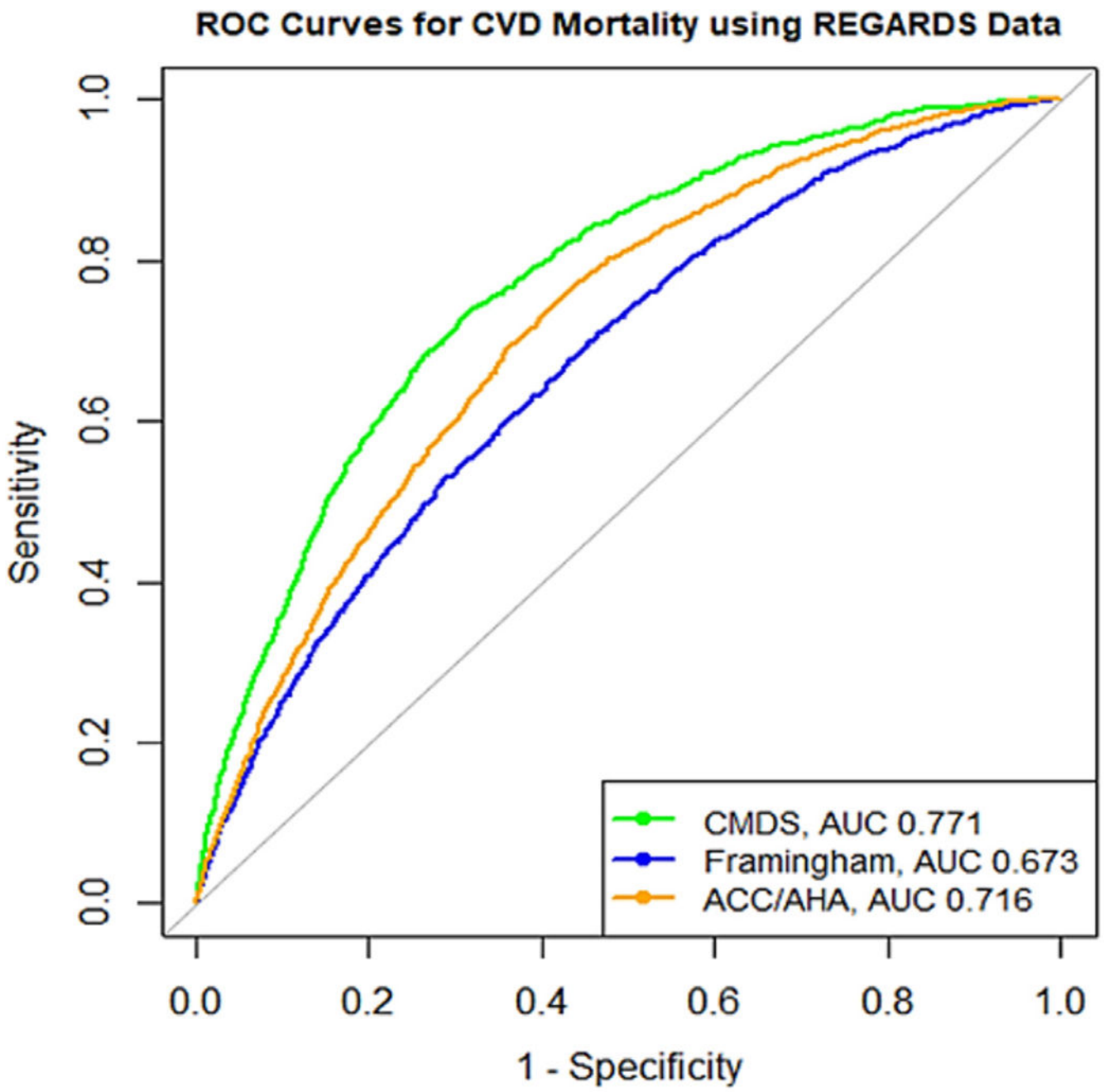
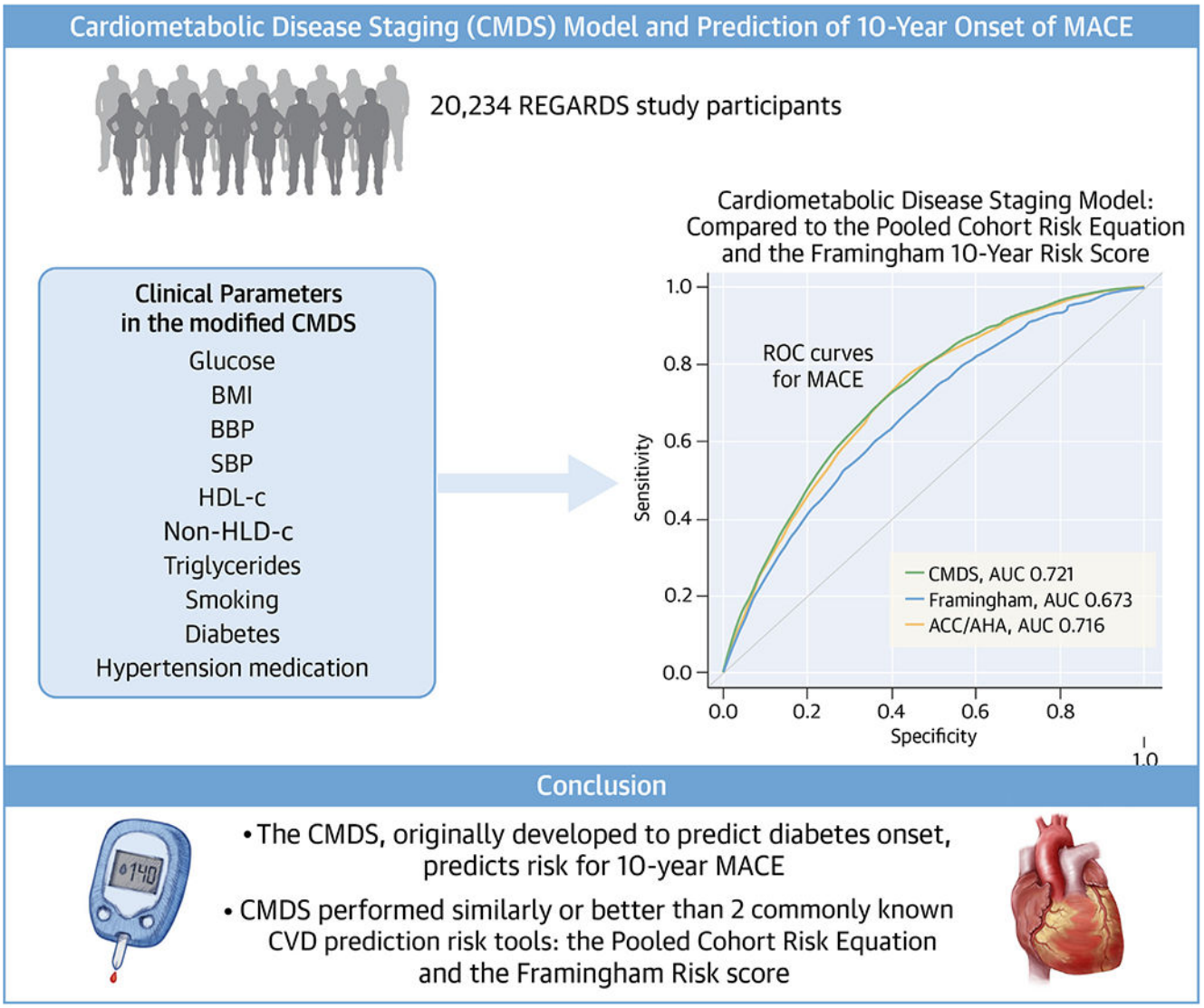


FIGURE 5. Receiver Operating Characteristic Curves for CVD Mortality Models

Receiver operating Characteristic curves for the CMDS model, ACC/AHA PCE, and the Framingham risk score for CVD mortality outcome using REGARDS data.



CENTRAL ILLUSTRATION. Cardiometabolic Staging Predicts Diabetes Incidence and Major Adverse Cardiovascular Events

Cardiometabolic staging (CMDS), originally developed to predict diabetes incidence, robustly predicts the 10-year onset of major adverse cardiovascular events (MACE). The CMDS can be used to risk stratify patients based on risk of developing cardiometabolic disease to aid in the cost/benefit of interventions. Pooled Cohort Risk Equation in the figure refers to the ACC/AHA Pooled Cohort Risk Equations.

TABLE 1

Risk Factors and Covariates Used in Each CMDS Model

Model	Variables in Model
CMDS development model	Age + sex + race + BMI + SBP + DBP + glucose + HDL-c + non-HDL-c + triglycerides + smoking[a] + diabetes status[b] + hypertension medications
CMDS validation model	Same as development model
CMDS model with interactions	Included main effects from development model and interactions between all main effects and diabetes status
CMDS model with waist instead of BMI	Age + sex + race + waist circumference + SBP + DBP + glucose + HDL-c + non-HDL-c + triglycerides + smoking + diabetes status + hypertension medications
CMDS model with LDL-c instead of non-HDL-c	Age + sex + race + BMI + SBP + DBP + glucose + HDL-c + LDL-c + triglycerides + smoking + diabetes status + hypertension medications

[a]Smoking coded as Current vs Not-Current.

[b]Diabetes status at baseline.

BMI = body mass index; CMDS = cardiometabolic disease staging model; DBP = diastolic blood pressure; HDL-c = high density lipoprotein cholesterol; LDL-c = non low density lipoprotein cholesterol; SBP = systolic blood pressure.

TABLE 2

Baseline Characteristics of Included Study Participants

	REGARDS (n = 20,234)	ARIC (n = 12,935)
Age (y)	64.0 ± 9.3	54.0 ± 5.7
Race		
Black	8,354 (41.3)	3,332 (25.8)
White	11,880 (58.7)	9,603 (74.2)
Sex		
Female	11,815 (58.4)	7,278 (56.3)
Male	8,419 (41.6)	5,657 (43.7)
Modified CMDS components		
BMI (kg/m^2)	29.2 ± 6.2	27.6 ± 5.3
Plasma glucose, mg/dL	102.1 ± 32.7	107.3 ± 37.0
Systolic blood pressure, mm Hg	126.5 ± 16.2	120.9 ± 18.8
Diastolic blood pressure, mm Hg	76.5 ± 9.5	73.6 ± 11.2
HDL cholesterol, mg/dL	53.1 ± 16.2	52.3 ± 17.0
Triglycerides, mg/dL	124.3 ± 62.8	123.4 ± 63.9
Non-HDL cholesterol, mg/dL	141.5 ± 37.2	161.5 ± 43.3
LDL cholesterol, mg/dL	116.7 ± 34.1	136.9 ± 39.0
Current smokers	2,774 (13.7)	3,366 (26.0)
Diabetes at baseline	3,577 (17.7)	1,111 (8.6)
Hypertension medication use	9,804 (48.4)	3,534 (27.3)
CVD endpoints		
MACE	2,695 (13.3)	799 (6.2)
CVD death	1,179 (5.8)	127 (0.98)
Nonfatal CVD events	1,028 (5.1)	453 (3.5)
Stroke	1,013 (5.0)	291 (2.2)

Values are mean ± SD or n (%).

ARIC = Atherosclerosis Risk In Communities; BMI = body mass index; CVD = cardiovascular disease; HDL = high density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; MACE = major adverse cardiac events; REGARDS = REasons for Geographic And Racial Differences in Stroke.

TABLE 3

Bivariate Associations Between Model Parameters and Major Adverse Cardiac Events in the REGARDS Participants (N = 20,234)[a]

	MACE[b]			CVD Death			Nonfatal MI			Stroke		
	Yes (n = 2,695)	No (n = 17,539)	*P* Value	Yes (n = 1,179)	No (n = 19,055)	*P* Value	Yes (n = 1,028)	No (n = 19,206)	*P* Value	Yes (n = 1,013)	No (n = 19,221)	*P* Value
Age, y	68.9 ± 9.1	63.2 ± 9.1	<0.0001	71.4 ± 9.3	63.5 ± 9.1	<0.0001	67.5 ± 8.9	63.8 ± 9.3	<0.0001	68.4 ± 8.7	63.8 ± 9.2	<0.0001
Sex												
Male	1,368 (50.8)	7,051 (40.2)	<0.0001	589 (50.0)	7,830 (41.1)	<0.0001	568 (55.2)	7,851 (40.9)	<0.0001	464 (45.8)	7,955 (41.4)	0.0054
Female	1,327 (49.2)	10,488 (59.8)		590 (50.0)	11,225 (58.9)		460 (44.8)	11,355 (59.1)		549 (54.2)	11,266 (58.6)	
Race												
White	1,538 (57.1)	10,342 (59.0)	0.063	613 (52.0)	11,267 (59.1)	<0.0001	652 (63.4)	11,228 (58.5)	0.0016	579 (57.2)	11,301 (58.8)	0.30
Black	1,157 (42.9)	7,197 (41.0)		566 (48.0)	7,788 (40.9)		376 (36.6)	7,978 (41.5)		434 (42.8)	7,920 (41.2)	
CMDS components												
BMI, (kg/m^2)	29.4 ± 6.2	29.2 ± 6.2	0.267	29.2 ± 6.5	29.2 ± 6.1	0.929	29.7 ± 6.3	29.2 ± 6.2	0.008	29.1 ± 5.8	29.2 ± 6.2	0.43
Plasma glucose, mg/dL	109.1 ± 44.2	101.0 ± 30.4	<0.0001	111.0 ± 46.6	101.5 ± 31.5	<0.0001	109.0 ± 41.8	101.7 ± 32.1	<0.0001	109.3 ± 45.2	101.7 ± 31.8	<0.0001
Systolic blood pressure, mm Hg	132.3 ± 17.6	125.6 ± 15.8	<0.0001	133.8 ± 18.6	126.1 ± 16.0	<0.0001	132.3 ± 17.6	126.2 ± 16.1	<0.0001	131.7 ± 16.8	126.2 ± 16.2	<0.0001
Diastolic blood pressure, mm Hg	77.3 ± 10.3	76.4 ± 9.4	<0.0001	76.9 ± 10.5	76.5 ± 9.4	0.153	77.3 ± 10.2	76.5 ± 9.5	0.008	77.7 ± 10.0	76.4 ± 9.5	<0.0001
HDL cholesterol, mg/dL	51.0 ± 15.9	53.5 ± 16.3	<0.0001	51.4 ± 15.8	53.2 ± 16.3	0.0001	49.4 ± 15.2	53.3 ± 16.3	<0.0001	51.8 ± 16.4	53.2 ± 16.2	0.0071
Triglycerides, mg/dL	132.2 ± 66.5	123.0 ± 62.1	<0.0001	128.0 ± 64.3	124.0 ± 62.7	0.036	140.2 ± 70.7	123.4 ± 62.2	<0.0001	131.1 ± 66.9	123.9 ± 62.5	0.0004
Non-HDL cholesterol, mg/dL	143.8 ± 39.0	141.2 ± 36.9	0.0008	140.5 ± 39.0	141.6 ± 37.1	0.343	145.7 ± 40.0	141.3 ± 37.0	0.0003	145.5 ± 38.6	141.3 ± 37.1	0.0004
LDL cholesterol, mg/dL	117.3 ± 35.5	116.6 ± 33.9	0.300	114.9 ± 35.7	116.8 ± 34.0	0.071	117.6 ± 36.5	116.6 ± 34.0	0.37	119.3 ± 35.0	116.5 ± 34.1	0.011
Smoking												
Current	445 (16.5)	2,329 (13.3)	<0.0001	179 (15.2)	2,595 (13.6)	0.13	175 (17.0)	2,599 (13.5)	0.0015	150 (14.8)	2,624 (13.6)	0.30
None	2,250 (83.5)	15,210 (86.7)		1,000 (84.8)	16,460 (86.4)		853 (83.0)	16,607 (86.5)		863 (85.2)	16,597 (86.4)	
Hypertension medication												
Yes	1,613 (59.8)	8,191 (46.7)	<0.0001	757 (64.2)	9,047 (47.5)	<0.0001	600 (58.4)	9,204 (47.9)	<0.0001	616 (60.8)	9,188 (47.8)	<0.0001
No	1,082 (40.2)	9,348 (53.3)		422 (35.8)	10,008 (52.5)		428 (41.6)	10,002 (52.1)		397 (39.2)	10,033 (52.2)	

	MACE[b]			CVD Death			Nonfatal MI			Stroke		
	Yes (n = 2,695)	**No (n = 17,539)**	***P* Value**	**Yes (n = 1,179)**	**No (n = 19,055)**	***P* Value**	**Yes (n = 1,028)**	**No (n = 19,206)**	***P* Value**	**Yes (n = 1,013)**	**No (n = 19,221)**	***P* Value**
Diabetes												
Yes	722 (26.8)	2,855 (16.3)	<0.0001	360 (30.5)	3,217 (16.9)	<0.0001	284 (27.6)	3,293 (17.2)	<0.0001	254 (25.1)	3,323 (17.3)	<0.0001
No	1,973 (73.2)	14,684 (83.7)		819 (69.5)	15,838 (83.1)		744 (72.4)	15,913 (82.8)		759 (74.9)	15,898 (82.7)	

Values are mean ± SD or n (%).

[a]Chi-square was used for categorical variable; 2-sample t-test was used for continuous variable.

[b]MACE is defined as an outcome that includes at least 1 of the following: nonfatal MI, stroke, and/or CV mortality.

CMDS = cardiometabolic disease staging model; CVD = cardiovascular disease; HDL = high density lipoprotein cholesterol; MACE = major adverse cardiac events; MI = myocardial infarction; REGARDS = REasons for Geographic And Racial Differences in Stroke.

TABLE 4

Predictive Power of the Development and Validation CMDS Models for MACE and Individual Components of MACE (CVD Mortality, Nonfatal MI, Events and Stroke)

	AUC	MSE	Misclassification	DeLong's Test *P* Value[c]
MACE outcome				
REGARDS: Development[a]	0.721	0.107	0.134	
ARIC: Validation[a]	0.737	0.064	0.064	
REGARDS with interactions[b]	0.722	0.107	0.134	0.67
REGARDS with Waist instead of BMI[d]	0.722	0.107	0.135	
CVD mortality				
REGARDS: Development	0.771	0.051	0.059	
ARIC: Validation	0.788	0.014	0.011	
REGARDS with interactions	0.772	0.051	0.058	0.829
REGARDS with waist instead of BMI	0.772	0.052	0.059	
Non-fatal MI events				
REGARDS: Development	0.695	0.047	0.051	
ARIC: Validation	0.742	0.033	0.035	
REGARDS with interactions	0.695	0.047	0.051	0.42
REGARDS with waist instead of BMI	0.696	0.047	0.051	
Stroke				
REGARDS: Development	0.680	0.047	0.050	
ARIC: Validation	0.741	0.022	0.022	
REGARDS with interactions	0.680	0.047	0.050	0.45
REGARDS with waist instead of BMI	0.679	0.047	0.050	

[a]Model included age + sex + race + BMI + SBP + DBP + glucose + HDL + non-HDL + triglycerides + smoking + diabetes status + hypertension medication use.

[b]Development model with interaction of main effects with diabetes.

[c]Comparing interaction model to original development model in REGARDS

[d]Model included age + sex + race + waist circumference + SBP + DBP + glucose + HDL + non-LDL + triglycerides + smoking + diabetes status + hypertension medication use.

ARIC = Atherosclerosis Risk In Communities; AUC = area under the curve; BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; HDL = high density lipoprotein cholesterol; MACE = major adverse cardiac events; MSE = mean square error; REGARDS = REasons for Geographic And Racial Differences in Stroke; SBP = systolic blood pressure.