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ORIGINAL RESEARCH ARTICLE

Development and Validation of the American Heart Association's PREVENT Equations

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BACKGROUND: Multivariable equations are recommended by primary prevention guidelines to assess absolute risk of cardiovascular disease (CVD). However, current equations have several limitations. Therefore, we developed and validated the American Heart Association Predicting Risk of CVD EVENTs (PREVENT) equations among US adults 30 to 79 years of age without known CVD.

METHODS: The derivation sample included individual-level participant data from 25 data sets (N=3 281 919) between 1992 and 2017. The primary outcome was CVD (atherosclerotic CVD and heart failure). Predictors included traditional risk factors (smoking status, systolic blood pressure, cholesterol, antihypertensive or statin use, and diabetes) and estimated glomerular filtration rate. Models were sex-specific, race-free, developed on the age scale, and adjusted for competing risk of non-CVD death. Analyses were conducted in each data set and meta-analyzed. Discrimination was assessed using the Harrell C-statistic. Calibration was calculated as the slope of the observed versus predicted risk by decile. Additional equations to predict each CVD subtype (atherosclerotic CVD and heart failure) and include optional predictors (urine albumin-to-creatinine ratio and hemoglobin A1c), and social deprivation index were also developed. External validation was performed in 3 330 085 participants from 21 additional data sets.

RESULTS: Among 6 612 004 adults included, mean±SD age was 53±12 years, and 56% were women. Over a mean±SD follow-up of 4.8±3.1 years, there were 211 515 incident total CVD events. The median C-statistics in external validation for CVD were 0.794 (interquartile interval, 0.763–0.809) in female and 0.757 (0.727–0.778) in male participants. The calibration slopes were 1.03 (interquartile interval, 0.81–1.16) and 0.94 (0.81–1.13) among female and male participants, respectively. Similar estimates for discrimination and calibration were observed for atherosclerotic CVD– and heart failure–specific models. The improvement in discrimination was small but statistically significant when urine albumin-to-creatinine ratio, hemoglobin A1c, and social deprivation index were added together to the base model to total CVD (Δ C-statistic [interquartile interval] 0.004 [0.004–0.005] and 0.005 [0.004–0.007] among female and male participants, respectively). Calibration improved significantly when the urine albumin-to-creatinine ratio was added to the base model among those with marked albuminuria (>300 mg/g; 1.05 [0.84–1.20] versus 1.39 [1.14–1.65]; *P*=0.01).

CONCLUSIONS: PREVENT equations accurately and precisely predicted risk for incident CVD and CVD subtypes in a large, diverse, and contemporary sample of US adults by using routinely available clinical variables.

Key Words: cardiovascular diseases ■ heart failure ■ kidney diseases ■ models, cardiovascular ■ risk assessment ■ social determinants of health

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Clinical Perspective

What Is New?

- We derive and validate novel sex-specific, race-free models to predict risk of total cardiovascular disease (and components of atherosclerotic cardiovascular disease and heart failure) in adults 30 to 79 years of age from a sample of >6 million people.
- The prognostic performance of the risk model demonstrates good discrimination and calibration in the overall population and among demographic and cardiovascular-kidney-metabolic subgroups (eg, obesity, diabetes, and chronic kidney disease).
- The base model includes estimated glomerular filtration rate, and add-on models offer the flexibility to include additional measures of kidney (urine albumin-to-creatinine ratio), metabolic (hemoglobin A1c), and social (social deprivation index) risk.

What Are the Clinical Implications?

- Removal of race from risk prediction and inclusion of a measure of place-based social disadvantage support a more equitable approach to cardiovascular disease prevention.
- Absolute risk assessment for total cardiovascular disease supports more comprehensive clinician-patient risk communication and preventive decision-making.
- Inclusion of predictors for kidney and metabolic health offers support for a holistic approach to screening, risk assessment, and prevention of cardiovascular disease among patients with or at risk for cardiovascular-kidney-metabolic conditions of obesity, diabetes, and chronic kidney disease.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CHD	coronary heart disease
CKD	chronic kidney disease
CKD-PC	Chronic Kidney Disease Prognosis Consortium
CKM	cardiovascular-kidney-metabolic
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
EMR	electronic medical record
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
IQI	interquartile interval
NRI	net reclassification improvement
OLDW	Optum Labs Data Warehouse
PCEs	pooled cohort equations
PCP-HF	Pooled Cohort Equations to Prevent Heart Failure
PREVENT	Predicting Risk of CVD EVENTs
SBP	systolic blood pressure
SDI	social deprivation index
TC	total cholesterol
UACR	urine albumin-to-creatinine ratio

Assessment of absolute risk for cardiovascular disease (CVD) with multivariable risk prediction equations is recommended by multisociety guidelines to guide primary prevention efforts for CVD.[1–3] This conceptual framework of risk-based prevention is defined by matching the intensity of the prevention efforts to the risk of an individual (eg, initiation of lipid-lowering therapy on the basis of estimated 10-year risk of atherosclerotic CVD [ASCVD]).[1,4] Although this paradigm was originally described >2 decades ago at the 1996 Bethesda Conference, models to assess risk for incident CVD have evolved over time in terms of specific predictors included, outcomes ascertained, and populations studied.[5] The American Heart Association (AHA) and the American College of Cardiology (ACC) developed the pooled cohort equations (PCEs) in 2013,[2,6] which are sex- and race-stratified models that estimate risk of ASCVD in White and Black adults. Although the PCEs are currently endorsed by the 2019 AHA/ACC Primary Prevention Guidelines for use in US adults 40 to 79 years of age,[1] the PCEs do not capture the total burden of CVD given the rising prevalence of other CVD subtypes not previously included (eg, heart failure [HF][7,8]). In addition, risk estimated by PCEs may not reflect population-level changes in risk factor prevalence[9] and exposure to preventive treatment in the contemporary era.[10] Furthermore, the PCEs may not be generalizable to individuals of other race and ethnicity groups who were not included in the derivation.[11] Therefore, updated prediction models are needed to assess CVD risk more precisely, accurately, and equitably across diverse populations.

AHA recently convened a science advisory group to address the growing burden of CVD, both ASCVD and HF, related to cardiovascular-kidney-metabolic (CKM) conditions (eg, obesity, diabetes, and chronic kidney disease [CKD]) that often cluster together.[12,13] Poor CKM health is increasing in prevalence, is associated with earlier onset of CVD, and disproportionately affects racial and ethnic minoritized individuals who experience a greater burden of adverse social factors[14–16] (eg, residing in neighborhoods with high social deprivation[17,18]). As such, optimal risk prediction equations are needed that incorporate prediction of total CVD (ASCVD and HF), integrate predictors relevant to CKM risk, and are applicable in younger populations. These efforts are now propelled by the growing armamentarium of novel cardiovascular

and kidney-protective glucose-lowering therapies (eg, glucagon-like peptide 1 agonists and sodium glucose cotransporter-2 inhibitors) that offer unique opportunities to target prevention among individuals identified to be at high risk for CVD.[19]

To address these gaps, we developed and validated the Predicting Risk of CVD EVENTs (PREVENT) equations to estimate risk of total CVD (and CVD subtypes) for US adults 30 to 79 years of age without CVD at baseline. The background and rationale for the development of a modern set of risk prediction equations are reviewed in detail in the 2023 AHA Scientific Statement on "Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health."[20]

METHODS

This study was approved by the institutional review board at the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (No. IRB00003324). Given the use of deidentified data in this analysis, a waiver for informed consent was approved for this analysis.

Study Population

The PREVENT development and validation included multiple data sources. We used data specifically from participants included in a global consortium of observational cohorts with individual-level participant data on CVD risk factors and outcomes: the Chronic Kidney Disease Prognosis Consortium (CKD-PC). Although the CKD-PC infrastructure was developed with a specific interest in participants with CKD, this consortium includes observational data sets derived from both research-based cohorts and health systems without restriction for those with CKD and represents a broadly generalizable sample of adults. Comprehensive details of the origins and infrastructure of the CKD-PC have been previously published.[21] For the current analysis, data sets were eligible for inclusion if they were US-based, had measured data on key risk factors of interest (systolic blood pressure [SBP], total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], body mass index [BMI], and estimated glomerular filtration rate [eGFR]), and a minimum 95th percentile follow-up of 5 years.

In total, 46 cohorts had adequate data and were included. The available sample was divided prospectively into derivation and validation subsets by data set to enhance validity and generalizability of risk prediction equations. To be included as part of the derivation sample, cohorts were required to share deidentified individual-level data with the CKD-PC Data Coordinating Center. Derivation samples included: (1) general population research–based cohorts: the ARIC study (Atherosclerosis Risk in Communities),[22] CARDIA (Coronary Artery Risk Development in Young Adults),[23] CHS (Cardiovascular Health Study),[24] FHS (Framingham Heart Study),[25] JHS (Jackson Heart Study),[26] and MESA (Multi-Ethnic Study of Atherosclerosis)[27]; and (2) real-world, contemporary clinical data that include deidentified administrative claims and electronic medical records (EMRs): Geisinger[28] Health and a random 50% selection of health systems in the Optum Labs Data Warehouse (OLDW).[29] Validation samples included: (1) a general population–based research cohort: REGARDS (Reasons for Geographic and Racial Differences in Stroke),[30] which was primarily focused on factors that account for disparities in stroke outcomes by race and region of residence; a disease-specific research-based cohort: CRIC (Chronic Renal Insufficiency Cohort),[31] which recruited participants with impaired kidney function (half of whom were diagnosed with diabetes); and RBS (Rancho Bernardo Study),[32] which recruited older adult residents of a suburban area of Southern California; and (2) the remaining 50% of health systems from OLDW. None of the validation data sets contributed to the model derivation.

Individual-level participant data were included for adults 30 to 79 years of age without known ASCVD or HF at baseline. Individuals with missing data on predictors or extreme clinical ranges for SBP, TC, HDL-C, or BMI were excluded given the nonlinear association with CVD and non-CVD death or preexisting guideline-based clinical recommendations for treatment at these extreme values. For SBP, TC, and HDL-C, the cutoffs for exclusion were based on those used for development of the PCEs (SBP <90 or >200 mm Hg, TC <130 or >320 mg/dL, and HDL-C <20 or >100 mg/dL). For BMI, the excluded range was based on that used for the development of the Pooled Cohort Equations to Prevent Heart Failure (PCP-HF) models[33] (<18.5 or ≥40.0 kg/m^2).

For research cohort data sets, the baseline visit was selected as the earliest visit on or after January 1, 1992, on the basis of the overall availability of complete risk factor data. For health system data sets, the baseline visit was selected as the earliest eligible date for each participant between January 1, 2008, and December 31, 2017, based on availability of complete risk factor data and required enrollment for at least 1 year. Follow-up was censored at 15 years to optimize short-term risk prediction, given that the majority of data sets had <10 years of follow-up with additional details described in Appendix S1.

Outcome Ascertainment: Total CVD, CVD Subtypes, and Mortality

The primary outcome was incident total CVD, which was defined as a composite of fatal and nonfatal ASCVD and HF events.[2,34] ASCVD included coronary heart disease (CHD: myocardial infarction and fatal CHD) and stroke as a composite outcome similar to the PCEs.[2] Coronary revascularization was not included as part of ASCVD given the significant variability in practice patterns in an approach consistent with that for the development of the PCEs. Other CVD subtypes were considered (specifically peripheral artery disease and atrial fibrillation) but not included given their incomplete ascertainment in available data sets. Deaths from all causes were ascertained and non-CVD deaths were treated as competing events. Details on how each cohort or data set defined incident CVD (including *International Classification of Diseases* codes) and causes of death are summarized in Appendix S1.

Measurement of Traditional and Novel Predictors

Details on the ascertainment of demographics, traditional risk factors, and novel predictors in each cohort and health system are summarized in Appendix S1. Demographic data on age,

sex, and race and ethnicity were included based on self-report in research-based cohorts or as part of clinical care in health system–based data sets. Race and ethnicity variables are social constructs and, thus, were not considered as predictors in risk modeling to eliminate propagation of race-based risk algorithms and clinical care as recommended.[35] Although racial and ethnic differences in the prevalence of CVD risk factors and incidence of CVD are well-described, these largely reflect the downstream effects of differences in social determinants of health among racial and ethnic groups.[15,16] To subsequently ensure there was no systematic under- or overprediction, calibration was assessed across racial and ethnic groups.

Risk factors included in the prediction equations were selected on based on being included in the development of PCEs, as well as being available in derivation data sets, recommended in target populations for screening, and readily ascertained in the primary care clinical setting. Measurements of traditional risk factors and kidney health, including SBP, cholesterol (TC and HDL-C to calculate non–HDL-C), height and weight (to calculate BMI), and estimated glomerular filtration rate (eGFR), were collected according to research or clinical protocols. All available cholesterol levels were used in the analyses, as clinical practice guidelines no longer recommend fasting for measurement of non–HDL-C, given that TC and HDL-C are minimally affected by fasting status, and the prognostic value of fasting and nonfasting values are similar.[4,36] eGFR was newly included as a predictor in the primary or base model on the basis of: (1) a new holistic approach to CKM health as a broader framework for prevention, given novel therapies that simultaneously target cardiovascular and kidney outcomes, (2) statistically significant and clinically meaningful hazard ratios demonstrating the association between eGFR and risk of CVD, (3) routine availability in clinical settings, and (4) examination of model performance improvement with eGFR.[37,38] The rationale for this is further detailed in the 2023 AHA Scientific Statement.[20] In all data sets, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation[39] using standardized or calibrated serum creatinine.[40] Diabetes, current smoking, and use of antihypertensive or statin medications were also included as predictors with detailed descriptions of how these were derived in Appendix S1.

Optional predictors were considered that reflect kidney, metabolic, and social risk and evaluated in additional prediction equations to personalize risk assessment and refine prediction in higher-risk subgroups (eg, CKD and diabetes). Change in model performance was assessed specifically with the addition of each predictor of interest (urine albumin-to-creatinine ratio [UACR], hemoglobin A1c [HbA1c], and social deprivation index [SDI]), and with the addition of all 3 predictors.

UACR was abstracted based on the spot measurement or converted from measured urine protein-to-creatinine ratio based on published equations.[41] Any available UACR values were used, including measured or estimated levels (from proteinuria),[42] regardless of diabetes or CKD status. UACR was considered as a novel predictor, given the available evidence supporting the robust association between UACR and CVD risk and clinical practice recommendations to measure UACR in individuals with CKD (eg, eGFR <60 mL/min per 1.73 m^2) or diabetes.[43–45] However, as UACR is not routinely recommended for screening in the general population, and screening rates in recommended populations are low,[46] it was not included in the primary model and was not a required variable in additional model development (ie, a missing UACR indicator was also included). A similar rationale was applied to HbA1c, whereby any available HbA1c values were used in development, including those in individuals with and without diabetes, as well as a missing indicator.

The SDI was calculated at the zip code level on the basis of 5-year estimates from the American Community Survey (2015–2020) and was linked to individual-level participant data in the OLDW cohorts (detailed in Appendix S1).[47] Given available epidemiological data demonstrating the consistent association between socioeconomic deprivation and risk of CVD, SDI was considered in model development as a widely available social determinant of health.[48–50] Analyses with SDI as a predictor were restricted to available OLDW data sets (36 data sets). SDI integrates information on 7 area-level characteristics: percentage living in poverty, percentage with <12 years of education, percentage of single-parent households, percentage living in rented housing units, percentage living in an overcrowded housing unit, percentage of households without a car, and percentage of unemployed adults <65 years of age.[47] Individual-level social determinants of health (eg, annual household income, highest level of education, and perceived discrimination) were also considered but were not systematically available across data sets and, therefore, were not included in the current model development.

Statistical Analysis

Summary statistics of baseline demographics and risk factor levels were defined using mean±SD or median (interquartile intervals) and frequencies as appropriate. All analyses were performed separately in each cohort and meta-analyzed to pool estimates through random-effects models, consistent with methods used in previous CKD-PC publications.[38,51,52] The base model to predict risk of total CVD included the following predictors: SBP, HDL-C, non–HDL-C, eGFR, smoking status, use of antihypertensive or statin medications, and diabetes. Diabetes and smoking status were dichotomized as yes or no. All other predictors were modeled continuously. A piecewise linear spline was used to examine inflections in slope. On the basis of a priori hypothesized nonlinear associations, SBP, eGFR, and BMI were modeled with a knot. For SBP, coefficients were modeled per 20 mm Hg for <110 mm Hg and ≥110 mm Hg; for eGFR per −15 mL/min per 1.73 m^2 for <60 mL/min per 1.73 m^2 and ≥60 mL/min per 1.73 m^2; for BMI per 5 kg/m^2 for <30 kg/m^2 and ≥30 kg/m^2. Interaction terms for each risk factor with age were also included because associations of risk factors with CVD vary with age,[53] consistent with development of the PCEs. Models were also developed with and without eGFR to examine its additive role in prognostic performance. Additional risk prediction equations were also developed for each CVD subtype: ASCVD (PREVENT-ASCVD) and HF (PREVENT-HF) and for each component of ASCVD (CHD and stroke). Additional or optional risk prediction equations were further developed to evaluate novel predictors of kidney, metabolic, and social risk. Additional equations were specifically developed that included linear terms for UACR (log-transformed), HbA1c, and SDI (decile-based categories of 1–3, 4–6, and 7–10) separately, as well as a set of equations that included all 3 predictors

together. In the development of risk prediction equations with UACR, HbA1c, or SDI, a missing indicator was also modeled to represent when each factor was not available or not clinically indicated to allow for broader implementation and generalizability. In the equations with HbA1c, an interaction term with diabetes status was included. Given observational data demonstrating a robust independent association between obesity and incident HF, but not ASCVD, BMI was included as a predictor only in the HF-specific and death models; in contrast, given the limited association between cholesterol values and incident HF in previous studies, cholesterol was not included as a predictor in HF-specific and death models.[54,55]

For model development, sex-specific associations between risk factors (predictors) and total CVD (and each CVD subtype or outcomes) were estimated using Cox proportional hazards models adjusting for competing risk of non-CVD death. We modeled participant age, rather than calendar time follow-up, as the time scale,[56] because age is the strongest predictor of incident CVD (and CVD subtypes). Thus, this approach obviates the need to model the functional relationship between age and CVD, which is necessary when relying on calendar follow-up time as the time scale.[57,58] Models were additionally adjusted for left truncation (people entering the study at different ages) as recommended in previous publications when age is used as the time scale.[59] Modeling on the age scale allows the estimation of short- and long-term risk of CVD and is consistent with some European risk prediction algorithms (eg, SCORE[60]).

To estimate absolute risk of CVD, age- and sex-specific baseline hazards were estimated from the median of the cohort-specific hazards. In each sex-stratified model, a cubic spline in log age with knots at 35, 55, 65, 75 and 85 years (on the basis of rounded percentiles of 1, 25, 50, 75, and 99) was fit to the log baseline cumulative hazard in each cohort. Age-specific hazards were calculated for each cohort, and their median value was estimated and modeled using a linear regression of log hazard versus age, thus yielding a parametric equation for baseline log hazard. Absolute risk calculations accounting for non-CVD death as a competing cause were subsequently performed by combining the age- and sex-specific hazards of CVD and non-CVD death (each calculated from their baseline hazard, relative hazards, and risk factor levels) to estimate 10-year and 30-year cumulative risk. These time horizons were selected because they were used previously in risk prediction models[1,2] and are currently recommended by the 2019 ACC/AHA Primary Prevention Guidelines[1] to guide clinician-patient discussions.

Model performance, including discrimination and calibration, of PREVENT was assessed separately in each data set in the derivation and validation samples and meta-analyzed using random-effects models. Model discrimination was assessed with the Harrell C-statistic.[61] Change in model discrimination using enhanced risk prediction equations when each novel predictor (UACR, HbA1c, and SDI) was added individually or when all 3 were added together was assessed with the change in C-statistic and categorical net reclassification improvement (NRI; based at event rate), for each data set and then summarized. The NRI at event rate was selected due to its adaptability to outcomes with different incidence rates and optimal statistical properties for assessment of change in predictive utility.[62] Calibration was first assessed visually by plotting deciles of predicted versus observed risk of CVD and second by calculation of a slope of this relationship. A slope of 1.0 indicates optimal calibration, a slope of <1.0 indicates lower observed than predicted risk (eg, overprediction), and a slope of >1.0 indicates higher observed than predicted risk (eg, underprediction).[63] Observed risk was calculated using a cause-specific risk model for each CVD event, competing with non-CVD mortality. Model performance was additionally assessed among key subgroups, including sociodemographic (age, sex, race and ethnicity as a social construct, zip code–level SDI) and CKM conditions of interest (obesity including class III obesity ≥40.0 kg/m^2, diabetes, and CKD).

Several secondary analyses were conducted. We first performed a direct comparison between risk estimates derived from PREVENT and PCEs. We specifically assessed discrimination and calibration statistics of the PCEs in both the derivation and validation samples. We also examined correlations between predicted risk estimates and compared cumulative percentile distribution from the PREVENT and PCE models. Second, we examined potential differences in the magnitude and direction of associations between predictors and outcomes by baseline calendar year to determine if changes in risk factor prevalence, treatment, or period cohort effects may influence estimates. Third, we examined potential differences in the analysis by data set type (research cohort versus health system data set). For these 2 analyses, we estimated the association of the relative hazards for each predictor with CVD (and CVD subtypes) using meta-regression and used Bonferroni-corrected *P* value thresholds to determine statistical significance. Fourth, calibration was also assessed truncating follow-up to 5 years to assess for differences across data sets with limited follow-up.

Simplified regression approximations to estimate risk of CVD and CVD subtypes were calculated (see detailed methods in Appendix S1.2). All analyses were performed using STATA 16 (College Station, TX). A 2-sided *P* value of <0.05 was considered statistically significant unless otherwise noted. We used analytic approaches and reporting standards as recommend by TRIPOD for risk prediction.[64] The study was designed and completed by the AHA CKM Science Advisory Group in collaboration with members of the CKD-PC and representatives of the included cohorts. Data used for the current study are available on reasonable request and approval through direct contact with the individual cohorts according to cohort-specific policies. STATA code for calculation of the PREVENT equations is available on request from the authors, including simplified regression approximations.

Role of the Funding Source

The funders had no role in the study design, data collection, analysis, or interpretation, or the writing of the report. J.C. had full access to all analyses, and all authors had final responsibility for the decision to submit for publication, informed by discussions with collaborators.

Data Sharing Statement

Under agreement with the participating cohorts, CKD-PC cannot share individual data with third parties. Inquiries regarding specific analyses should be made to ckdpc@nyulangone.org. Investigators may approach the original cohorts regarding their

own policies for data sharing (eg, https://aric.cscc.unc.edu/aric9/researchers/Obtain_Submit_Data for the ARIC Study).

RESULTS

Baseline Characteristics

In the derivation sample, there were 1 839 828 female and 1 442 091 male participants from 25 individual data sets with a mean±SD age 53±13 and 52±12 years, respectively (Table 1; details by data set in Table S1). Among female participants, 78% were White, 10% Black, 6.0% Hispanic, and 2.6% Asian; prevalence of diabetes was 10% and the use of antihypertensive and statin medications was 23% and 14%, respectively, among female participants. Among male participants, 80% were White, 8.0% Black, 5.3% Hispanic, and 2.5% Asian; prevalence of diabetes was 12% and the use of antihypertensive and statin medications was 27% and 17%, respectively, among male participants. Mean eGFR was 91 mL/min per 1.73 m^2 in both female and male participants. The median UACR was 8 mg/g for both female and male

Table 1. Individual-Level Participant Baseline Characteristics of Derivation and Validation Samples Stratified by Sex for Prediction of Total Cardiovascular Disease and Cardiovascular Disease Subtypes

	Derivation sample*		Validation sample*	
Baseline characteristics	Female	Male	Female	Male
No. of participants	1 839 828	1 442 091	1 894 882	1 435 203
No. of cohorts	25	25	21	21
Age, years, mean±SD	53±13	52±12	52±13	52±12
Race and ethnicity, %				
White	78	80	78	80
Black	10	8.0	10	8.2
Hispanic	6.0	5.3	4.2	3.7
Asian	2.6	2.5	2.7	2.2
Other or missing	4.1	4.6	4.9	5.5
Cardiovascular risk factors or predictors in PREVENT base model				
Systolic blood pressure, mm Hg	123±16	127±15	123±16	128±15
Total cholesterol, mmol/L	5.0±0.8	4.9±0.8	5.0±0.8	4.9±0.8
Non–high-density lipoprotein cholesterol, mmol/L	3.4±0.8	3.6±0.8	3.5±0.8	3.6±0.8
High-density lipoprotein cholesterol, mmol/L	1.5±0.4	1.2±0.3	1.5±0.4	1.2±0.3
Body mass index, kg/m^2	29±5	29±4	28±5	29±4
Diabetes, %	10	12	11	13
Current smoking, %	5.8	6.2	4.7	4.9
Antihypertensive treatment, %	23	27	24	29
Statin treatment, %	14	17	14	17
Estimated glomerular filtration rate, mean±SD, mL/min per 1.73 m^2	91±19	91±17	91±18	91±17
Add-on risk factors/predictors in optional models				
UACR, median (interquartile interval), mg/g†	8 (8–12)	8 (8–12)	8 (8–12)	8 (8–11)
Hemoglobin A1c among those with diabetes, mean±SD, %‡	7.3±1.8	7.6±1.9	7.2±1.8	7.6±1.9
Hemoglobin A1c among those without diabetes, mean±SD, %‡	5.7±0.8	5.8±0.9	5.5±0.6	5.6±0.8
SDI decile, median (interquartile interval)§	4 (2–7)	3 (2–6)	4 (2–7)	4 (2–6)
Outcomes				
Mean±SD follow-up time	4.8±3.1	4.6±3.0	5.0±3.2	4.8±3.2
Total cardiovascular disease events	53 258	53 403	54 365	50 489
Atherosclerotic cardiovascular disease events	31 812	34 691	33 969	33 933
Heart failure events	30 957	28 393	30 287	25 679
Deaths	84 289	80 897	82 555	76 783

Data are reported as mean±SD except where otherwise noted. PREVENT indicates Predicting Risk of CVD EVENTs; SDI, social deprivation index (nonmissing in 27%–33%); and UACR, urine albumin to creatinine ratio (nonmissing in 40%–46%). Details on missing data are shown in Appendix S1.4. To convert from mmol/L to mg/dL, multiply by 38.67.

*All participants with extreme values were excluded from the sample before analyses.

†UACR was nonmissing when urine protein to creatinine ratio or dipstick allows for conversion to UACR.[42]

‡Hemoglobin A1c was nonmissing in 90% to 94% among those with diabetes and 23% to 27% among those without diabetes.

§SDI was only available in the Optum Labs Data Warehouse cohorts.

participants; mean HbA1c was 7.3% and 7.6% in female and male participants, respectively; and the median SDI decile was 4 among female participants and 3 among male participants. The validation sample comprised 1 894 882 female and 1 435 203 male participants from 21 individual data sets with similar distribution of sociodemographic characteristics, traditional cardiovascular risk factor burden, and kidney health as the derivation sample. In addition, median levels of UACR, HbA1c, and SDI were similar in the validation compared with the derivation sample.

Incident CVD Events

In the derivation sample, over a mean follow-up time of 4.8 years among female participants, 53 258 total incident CVD events occurred. Over a mean follow-up time of 4.6 years among male participants, 53 403 total incident CVD events occurred. The number of ASCVD and HF events is shown in Table 1. Incident CVD, ASCVD, and HF events in each data set are detailed in Table S1.

Associations Between Predictors and CVD Events

Associations between predictors and each outcome (total CVD and CVD subtypes [ASCVD and HF]) in the derivation sample are displayed in Table 2 for the primary base model that includes traditional CVD risk factors, eGFR, and age–risk factor interactions. Hazard ratios for predictors in the base model were similar in the model with eGFR excluded, as well as when novel predictors (UACR, HbA1c, and SDI) were added to the base model individually (Tables S2 through S4) or all together (Table 3).

Table 2. Meta-Analyzed Sex-Specific Hazard Ratios (95% CIs) of Traditional Cardiovascular Risk Predictors for Total Cardiovascular Disease and Cardiovascular Disease Subtypes in Derivation Samples

	Total CVD		ASCVD		Heart failure	
Risk factor	Female N=1 839 828	Male N=1 442 091	Female N=1 839 828	Male N=1 442 091	Female N=1 839 828	Male N=1 442 091
Cardiovascular disease risk factors in the PREVENT-CVD primary model						
Non–HDL-C per 1 mmol/L	1.03 (0.99–1.07)	1.07 (1.03–1.11)	1.12 (1.07–1.17)	1.17 (1.13–1.21)	*	*
HDL-C per 0.3 mmol/L	0.85 (0.84–0.87)	0.91 (0.89–0.93)	0.86 (0.85–0.88)	0.89 (0.87–0.92)	*	*
SBP <110 per 20 mm Hg	0.78 (0.69–0.88)	0.63 (0.54–0.72)	0.91 (0.80–1.04)	0.73 (0.61–0.86)	0.63 (0.56–0.71)	0.49 (0.44–0.56)
SBP ≥110 per 20 mm Hg	1.43 (1.37–1.50)	1.40 (1.35–1.45)	1.44 (1.38–1.50)	1.39 (1.34–1.44)	1.44 (1.37–1.51)	1.45 (1.39–1.50)
Diabetes	2.39 (2.31–2.48)	2.18 (2.08–2.29)	2.35 (2.23–2.47)	2.10 (1.98–2.23)	2.86 (2.72–3.01)	2.56 (2.41–2.71)
Current smoking	1.74 (1.55–1.96)	1.59 (1.43–1.76)	1.67 (1.46–1.91)	1.53 (1.38–1.70)	1.84 (1.60–2.12)	1.70 (1.48–1.95)
BMI <30, per 5 kg/m^2	*	*	*	*	0.98 (0.94–1.03)	0.93 (0.88–0.99)
BMI ≥30, per 5 kg/m^2	*	*	*	*	1.35 (1.28–1.41)	1.46 (1.38–1.54)
eGFR <60, per −15 mL/min per 1.73 m^2	1.94 (1.86–2.03)	1.86 (1.78–1.94)	1.75 (1.66–1.84)	1.59 (1.53–1.66)	2.26 (2.16–2.36)	2.19 (2.03–2.36)
eGFR ≥60, per −15 mL/min per 1.73 m^2	1.04 (1.01–1.07)	1.01 (0.99–1.03)	1.04 (1.01–1.07)	1.01 (0.99–1.03)	1.05 (1.01–1.09)	1.02 (0.98–1.06)
Cardiovascular disease risk factor treatment status						
Antihypertensive use	1.37 (1.20–1.55)	1.34 (1.20–1.49)	1.26 (1.11–1.42)	1.23 (1.11–1.37)	1.42 (1.21–1.67)	1.35 (1.16–1.57)
Statin use	0.86 (0.81–0.91)	0.86 (0.81–0.91)	0.93 (0.87–1.00)	0.90 (0.84–0.96)	*	*
Treated SBP ≥110 mm Hg per 20 mm Hg	0.93 (0.90–0.97)	0.95 (0.92–0.98)	0.96 (0.92–1.00)	0.96 (0.93–1.00)	0.90 (0.87–0.94)	0.95 (0.92–0.98)
Treated non–HDL-C per 1 mmol/L	1.12 (1.08–1.17)	1.16 (1.10–1.23)	1.09 (1.03–1.15)	1.12 (1.06–1.19)	*	*
Age–risk factor interactions per 10 y older						
Age* non–HDL-C per 1 mmol/L	0.92 (0.91–0.94)	0.95 (0.94–0.96)	0.95 (0.93–0.96)	0.97 (0.95–0.98)	*	*
Age* HDL-C per 0.3 mmol/L	1.03 (1.02–1.05)	1.02 (1.01–1.04)	1.04 (1.02–1.05)	1.03 (1.01–1.04)	*	*
Age* SBP ≥110 mm Hg per 20 mm Hg	0.91 (0.90–0.93)	0.90 (0.89–0.91)	0.91 (0.89–0.92)	0.91 (0.90–0.93)	0.91 (0.90–0.93)	0.88 (0.86–0.90)
Age* diabetes	0.77 (0.75–0.79)	0.81 (0.78–0.83)	0.79 (0.77–0.82)	0.83 (0.81–0.85)	0.71 (0.68–0.73)	0.75 (0.71–0.78)
Age* current smoking	0.93 (0.90–0.97)	0.92 (0.89–0.96)	0.93 (0.88–0.99)	0.92 (0.88–0.96)	0.90 (0.85–0.95)	0.88 (0.84–0.92)
Age* ≥BMI 30 per 5 kg/m^2	*	*	*	*	0.99 (0.96–1.02)	1.00 (0.98–1.03)
Age* eGFR <60, per −15 mL/min per 1.73 m^2	0.87 (0.85–0.89)	0.89 (0.87–0.91)	0.87 (0.85–0.89)	0.92 (0.90–0.94)	0.85 (0.83–0.87)	0.87 (0.83–0.90)

Hazard ratios are for the units quoted for linear terms (eg, non–HDL-C per 1 mmol/L) and piecewise linear splines (eg, SBP ≥110 per 20 mm Hg). Models are centered at 55 years of age, non–HDL-C 3.5 mmol/L, HDL-C 1.3 mmol/L, and SBP 130 mm Hg. ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; PREVENT, Predicting Risk of CVD EVENTs; and SBP, systolic blood pressure.

*Not applicable to model development for specific outcome.

Table 3. Meta-Analyzed Sex-Specific Adjusted Hazard Ratios (95% CIs) of the Base Model Adding All Novel Cardiovascular Risk Predictors for Total Cardiovascular Disease and Cardiovascular Disease Subtypes in Derivation Samples

Risk factor	Total CVD		ASCVD		Heart failure	
	Female N=1 734 246	Male N=1 356 397	Female N=1 734 246	Male N=1 356 397	Female N=1 734 246	Male N=1 356 397
Cardiovascular disease risk factors in the PREVENT-CVD primary model						
Non–HDL-C per 1 mmol/L	1.00 (0.97–1.04)	1.05 (1.01–1.09)	1.09 (1.05–1.14)	1.15 (1.10–1.20)	*	*
HDL-C per 0.3 mmol/L	0.86 (0.84–0.88)	0.92 (0.90–0.94)	0.87 (0.86–0.88)	0.90 (0.88–0.92)	*	*
SBP <110 per 20 mm Hg	0.82 (0.72–0.93)	0.59 (0.52–0.67)	0.97 (0.84–1.11)	0.68 (0.59–0.80)	0.65 (0.58–0.74)	0.49 (0.43–0.56)
SBP ≥110 per 20 mm Hg	1.36 (1.30–1.42)	1.35 (1.31–1.39)	1.37 (1.32–1.42)	1.35 (1.30–1.41)	1.36 (1.28–1.43)	1.37 (1.33–1.42)
Diabetes	1.65 (1.52–1.79)	1.58 (1.46–1.70)	1.63 (1.49–1.79)	1.51 (1.38–1.65)	1.87 (1.71–2.05)	1.75 (1.59–1.93)
Current smoking	1.62 (1.44–1.82)	1.48 (1.33–1.65)	1.54 (1.36–1.73)	1.44 (1.30–1.59)	1.75 (1.52–2.01)	1.58 (1.38–1.80)
BMI <30, per 5 kg/m^2	*	*	*	*	0.97 (0.92–1.02)	0.89 (0.85–0.94)
BMI ≥30, per 5 kg/m^2	*	*	*	*	1.32 (1.26–1.38)	1.43 (1.36–1.51)
eGFR <60, −15 mL/min per 1.73 m^2	1.72 (1.64–1.81)	1.61 (1.53–1.69)	1.58 (1.48–1.69)	1.42 (1.36–1.49)	1.96 (1.85–2.07)	1.83 (1.69–1.97)
eGFR ≥60, −15 mL/min per 1.73 m^2	1.05 (1.02–1.08)	1.00 (0.98–1.02)	1.05 (1.02–1.08)	1.01 (0.99–1.02)	1.06 (1.03–1.10)	1.01 (0.97–1.04)
Cardiovascular disease risk factor treatment status						
Antihypertensive use	1.35 (1.16–1.57)	1.29 (1.13–1.46)	1.24 (1.08–1.43)	1.19 (1.06–1.34)	1.39 (1.15–1.68)	1.29 (1.09–1.54)
Statin use	0.85 (0.79–0.91)	0.84 (0.79–0.90)	0.92 (0.86–0.99)	0.88 (0.82–0.94)	*	*
Treated SBP ≥110 mm Hg per 20 mm Hg	0.93 (0.89–0.97)	0.95 (0.92–0.97)	0.95 (0.91–1.00)	0.96 (0.92–0.99)	0.90 (0.86–0.95)	0.94 (0.91–0.97)
Treated non–HDL-C per 1 mmol/L	1.11 (1.08–1.14)	1.15 (1.08–1.23)	1.08 (1.03–1.14)	1.11 (1.05–1.19)	*	*
Age–risk factor interactions per 10 y older						
Age* non–HDL-C per 1 mmol/L	0.93 (0.91–0.95)	0.95 (0.94–0.97)	0.95 (0.93–0.97)	0.97 (0.96–0.99)	*	*
Age* HDL-C per 0.3 mmol/L	1.03 (1.02–1.04)	1.02 (1.01–1.04)	1.03 (1.02–1.04)	1.03 (1.02–1.05)	*	*
Age* SBP ≥110 mm Hg per 20 mm Hg	0.92 (0.90–0.94)	0.90 (0.89–0.92)	0.91 (0.90–0.93)	0.92 (0.90–0.93)	0.93 (0.91–0.94)	0.89 (0.87–0.91)
Age* diabetes	0.80 (0.78–0.83)	0.85 (0.83–0.87)	0.83 (0.80–0.86)	0.88 (0.85–0.90)	0.75 (0.72–0.78)	0.80 (0.76–0.84)
Age* current smoking	0.94 (0.91–0.97)	0.94 (0.91–0.97)	0.95 (0.90–1.00)	0.93 (0.89–0.98)	0.90 (0.86–0.95)	0.91 (0.86–0.95)
Age* BMI ≥30 per 5 kg/m^2	*	*	*	*	0.99 (0.97–1.02)	1.00 (0.98–1.02)
Age* eGFR <60, per −15 mL/min per 1.73 m^2	0.89 (0.87–0.91)	0.91 (0.89–0.93)	0.89 (0.87–0.91)	0.93 (0.91–0.95)	0.87 (0.85–0.90)	0.89 (0.86–0.92)
Kidney function						
Ln UACR, mg/g, per 1 ln unit	1.19 (1.17–1.22)	1.21 (1.20–1.23)	1.16 (1.14–1.19)	1.17 (1.15–1.19)	1.23 (1.21–1.26)	1.27 (1.24–1.29)
No UACR available†	1.02 (0.98–1.07)	1.12 (1.07–1.18)	1.01 (0.96–1.05)	1.07 (1.02–1.13)	1.04 (0.98–1.11)	1.19 (1.13–1.25)
Glycemic status						
HbA1c in diabetes, per 1%	1.14 (1.06–1.23)	1.13 (1.07–1.19)	1.14 (1.05–1.23)	1.11 (1.05–1.18)	1.20 (1.12–1.28)	1.17 (1.10–1.24)
HbA1c no diabetes, per 1%	1.15 (1.14–1.16)	1.11 (1.10–1.12)	1.15 (1.14–1.17)	1.12 (1.10–1.14)	1.18 (1.16–1.20)	1.13 (1.12–1.15)
No HbA1c available†	0.99 (0.94–1.05)	0.97 (0.93–1.02)	1.00 (0.95–1.06)	0.99 (0.94–1.03)	1.00 (0.94–1.06)	0.97 (0.91–1.04)
SDI‡ decile categories						
SDI 1–3	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
SDI 4–6	1.15 (1.07–1.24)	1.09 (1.00–1.20)	1.16 (1.08–1.24)	1.08 (0.97–1.20)	1.14 (1.02–1.26)	1.13 (1.02–1.25)
SDI 7–10	1.26 (1.15–1.38)	1.33 (1.23–1.43)	1.26 (1.16–1.38)	1.32 (1.23–1.43)	1.27 (1.15–1.40)	1.42 (1.26–1.59)
No SDI available†	1.20 (1.13–1.27)	1.16 (1.10–1.24)	1.18 (1.12–1.24)	1.16 (1.09–1.23)	1.20 (1.12–1.29)	1.19 (1.10–1.29)

Hazard ratios are for the units quoted for linear terms (eg, non–HDL-C per 1 mmol/L) and piecewise linear splines (eg, SBP ≥110 per 20 mm Hg). Models centered at 55 years of age, non–HDL-C 3.5 mmol/L, HDL-C 1.3 mmol/L, SBP 130 mm Hg, BMI 25 kg/m^2, eGFR 90 mL/min per 1.73 m^2, no diabetes, nonsmoker, no medication used, SDI decile 1–3, ACR 1 mg/g, and HbA1c 5.3%. Smaller models with one set of novel risk factors at a time added to the base model are shown in Tables S2–S4. ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Ln, natural log; PREVENT, Predicting Risk of CVD EVENTs; Ref., reference; SBP, systolic blood pressure; SDI, social deprivation index; and UACR, urinary albumin-to-creatinine ratio.

*Not applicable to model development for specific outcome.

†No available data when measurement of the novel risk factor is not indicated or not done for another reason.

‡SDI is only available in the Optum Labs Data Warehouse cohorts.

PREVENT Model Performance Characteristics

Model performance, including discrimination and calibration for prediction of total CVD and CVD subtypes (ASCVD and HF) for derivation data sets and validation data sets are displayed in Table S5A and Table 4. The primary PREVENT model (base model) for prediction of total CVD that included traditional CVD risk factors

Table 4. Meta-Analyzed Discrimination, Calibration, and Net Reclassification Statistics of Model Performance for Prediction of Total Cardiovascular Disease and Cardiovascular Disease Subtypes in Validation Cohorts

	Total CVD		ASCVD		Heart failure	
Models	Female	Male	Female	Male	Female	Male
Base PREVENT model						
No. of cohorts	21	21	21	21	21	21
No. of participants	1 894 882	1 435 203	1 894 882	1 435 203	1 894 882	1 435 203
No. of events	50 324	46 804	31 277	31 328	27 931	23 707
C-statistic (IQI)	0.794 (0.763 to 0.809)	0.757 (0.727 to 0.778)	0.774 (0.743 to 0.788)	0.736 (0.710 to 0.755)	0.830 (0.816 to 0.850)	0.809 (0.777 to 0.827)
Calibration slope (IQI)	1.03 (0.81 to 1.16)	0.94 (0.81 to 1.13)	1.09 (0.93 to 1.33)	1.04 (0.95 to 1.19)	1.00 (0.55 to 1.15)	0.89 (0.49 to 1.07)
Pooled cohort equations*						
C-statistic (IQI)	0.789 (0.746 to 0.802)	0.747 (0.721 to 0.767)	0.772 (0.729 to 0.782)	0.733 (0.701 to 0.751)	0.810 (0.785 to 0.838)	0.791 (0.742 to 0.801)
C-statistic (95% CI)† of PREVENT minus pooled cohort equations	0.009 (0.008 to 0.011)	0.008 (0.007 to 0.009)	0.007 (0.006 to 0.009)	0.005 (0.004 to 0.006)	0.015 (0.013 to 0.017)	0.022 (0.020 to 0.024)
Calibration slope (IQI)	0.84 (0.65 to 1.00)	0.67 (0.60 to 0.81)	0.54 (0.47 to 0.61)	0.50 (0.39 to 0.52)	0.51 (0.28 to 0.61)	0.37 (0.20 to 0.47)
PREVENT model additionally enhanced for kidney-specific risk with urinary albumin-to-creatinine ratio						
No. of cohorts	21	21	21	21	21	21
No. of participants	1 894 882	1 435 203	1 894 882	1 435 203	1 894 882	1 435 203
No. of events	50 324	46 804	31 277	31 328	27 931	23 707
Base model C-statistic (IQI)	0.794 (0.763 to 0.809)	0.757 (0.727 to 0.778)	0.774 (0.743 to 0.788)	0.736 (0.710 to 0.755)	0.830 (0.816 to 0.850)	0.809 (0.777 to 0.827)
Base model enhanced for kidney risk C-statistic (IQI)	0.796 (0.766 to 0.812)	0.759 (0.735 to 0.780)	0.776 (0.746 to 0.790)	0.739 (0.715 to 0.758)	0.833 (0.820 to 0.851)	0.815 (0.786 to 0.830)
ΔC-statistic (95% CI)†	0.002 (0.002 to 0.003)	0.004 (0.003 to 0.004)	0.002 (0.001 to 0.002)	0.002 (0.002 to 0.003)	0.003 (0.002 to 0.003)	0.005 (0.004 to 0.006)
NRI (IQI)	0.011 (−0.009 to 0.023)	0.031 (0.013 to 0.049)	0.022 (0.013 to 0.033)	0.042 (0.023 to 0.065)	0.038 (0.027 to 0.069)	0.130 (0.079 to 0.189)
Calibration slope (IQI)	1.03 (0.83 to 1.17)	0.95 (0.85 to 1.13)	1.10 (0.94 to 1.34)	1.03 (0.93 to 1.20)	0.99 (0.53 to 1.14)	0.89 (0.48 to 1.07)
PREVENT model enhanced for metabolic risk with hemoglobin A1c						
No. of cohorts	19	19	19	19	19	19
No. of participants	1 893 349	1 433 735	1 893 349	1 433 735	1 893 349	1 433 735
No. of events	50 120	46 541	31 149	31 170	27 820	23 555
Base model C-statistic (IQI)	0.795 (0.768 to 0.814)	0.757 (0.734 to 0.778)	0.779 (0.747 to 0.790)	0.739 (0.714 to 0.757)	0.837 (0.817 to 0.850)	0.816 (0.786 to 0.832)
Base model enhanced for metabolic risk C-statistic (IQI)	0.799 (0.771 to 0.815)	0.759 (0.738 to 0.780)	0.787 (0.750 to 0.792)	0.740 (0.719 to 0.760)	0.837** (0.818 to 0.853)	0.818 (0.790 to 0.835)
ΔC-statistic (95% CI)†	0.002 (0.001 to 0.003)	0.003 (0.002 to 0.004)	0.003 (0.002 to 0.004)	0.003 (0.002 to 0.004)	0.001 (0.001 to 0.002)	0.002 (0.002 to 0.003)
NRI (IQI)	0.002 (−0.002 to 0.005)	0.004 (0.001 to 0.010)	0.005 (0.002 to 0.010)	0.003 (−0.002 to 0.007)	0.001 (−0.005 to 0.004)	0.004 (0.003 to 0.008)
Calibration slope (IQI)	1.02 (0.68 to 1.16)	0.95 (0.73 to 1.14)	1.10 (0.91 to 1.35)	1.05 (0.92 to 1.28)	0.99 (0.53 to 1.18)	0.88 (0.48 to 1.08)
PREVENT model enhanced for social risk with social deprivation index‡						
No. of cohorts	18	18	18	18	18	18
No. of participants	606 662	468 195	606 662	468 195	606 662	468 195
No. of events	15 059	14 084	9423	9456	8169	6970
Base model C-statistic (IQI)	0.807 (0.787 to 0.816)	0.774 (0.751 to 0.788)	0.793 (0.761 to 0.800)	0.752 (0.737 to 0.772)	0.835 (0.817 to 0.852)	0.824 (0.790 to 0.836)
Base model enhanced for social risk C-statistic (IQI)	0.810 (0.788 to 0.817)	0.774 (0.757 to 0.789)	0.796 (0.761 to 0.800)	0.753 (0.737 to 0.774)	0.836 (0.818 to 0.853)	0.824 (0.793 to 0.837)
ΔC-statistic (95% CI)†	0.001 (0.001 to 0.002)	0.002 (0.001 to 0.003)	0.001 (0.000 to 0.002)	0.001 (0.000 to 0.002)	0.001 (0.001 to 0.002)	0.002 (0.001 to 0.002)
NRI (IQI)	0.003 (0.000 to 0.009)	0.005 (−0.002 to 0.018)	0.004 (−0.000 to 0.012)	0.004 (−0.009 to 0.013)	0.004 (−0.004 to 0.007)	0.005 (0.001 to 0.016)
Calibration slope (IQI)	1.04 (0.73 to 1.20)	0.94 (0.72 to 1.08)	1.09 (0.96 to 1.41)	1.00 (0.80 to 1.20)	0.97 (0.63 to 1.14)	0.84 (0.61 to 1.02)
PREVENT model enhanced for all novel predictors§						
No. of cohorts	18	18	18	18	18	18
No. of participants	606 662	468 195	606 662	468 195	606 662	468 195

(*Continued*)

Table 4. Continued

Models	Total CVD		ASCVD		Heart failure	
	Female	Male	Female	Male	Female	Male
No. of events	15059	14084	9423	9456	8169	6970
Base model C-statistic (IQI)	0.807 (0.787 to 0.816)	0.774 (0.751 to 0.788)	0.793 (0.761 to 0.800)	0.752 (0.737 to 0.772)	0.835 (0.817 to 0.852)	0.824 (0.790 to 0.836)
Base model enhanced for all novel predictors C-statistic (IQI)	0.813 (0.794 to 0.820)	0.776 (0.762 to 0.793)	0.799 (0.767 to 0.804)	0.755 (0.742 to 0.776)	0.841 (0.828 to 0.858)	0.830 (0.799 to 0.843)
ΔC-statistic (95% CI)†	0.004 (0.004 to 0.005)	0.005 (0.004 to 0.007)	0.004 (0.003 to 0.005)	0.004 (0.002 to 0.006)	0.005 (0.004 to 0.006)	0.007 (0.006 to 0.009)
NRI (IQI)	0.005 (–0.000 to 0.018)	0.006 (0.000 to 0.021)	0.009 (0.001 to 0.023)	0.008 (–0.009 to 0.015)	0.007 (0.004 to 0.015)	0.014 (0.012 to 0.030)
Calibration slope (IQI)	1.05 (0.73 to 1.20)	0.95 (0.72 to 1.10)	1.11 (0.96 to 1.41)	1.01 (0.83 to 1.18)	0.96 (0.62 to 1.14)	0.81 (0.65 to 1.06)

ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular disease; IQI, interquartile interval; NRI, net reclassification improvement; and PREVENT, Predicting Risk of CVD EVENTs.

*Same sample as evaluated for the base PREVENT model.

† Δ C-statistic is meta-analyzed using the Δ within each cohort weighted inversely to its standard error. Therefore, the meta-analyzed mean Δ C-statistic may not equal the difference of between the 2 median C-statistics of the models being compared.

‡Social deprivation index is only available in the Optum Labs Data Warehouse cohorts.

§Same sample as PREVENT model + social deprivation index.

and eGFR had a median C-statistic (interquartile interval [IQI]: 25th–75th percentile of cohorts) of 0.789 (0.778–0.810) in the derivation sample and 0.794 (0.763–0.809) in the validation sample among female participants. Among male participants, the median C-statistic (IQI) was 0.745 (0.734–0.760) and 0.757 (0.727–0.778) in the derivation and validation samples, respectively. Discrimination was similar for PREVENT when ASCVD (PREVENT-ASCVD) and HF (PREVENT-HF) were each modeled as secondary outcomes. Specifically in the validation samples, among female participants, the median C-statistic (IQI) was 0.774 (0.743–0.788) and 0.830 (0.816–0.850) for ASCVD and HF, respectively. Among male participants, the median C-statistic (IQI) was 0.736 (0.710–0.755) and 0.809 (0.777–0.827) for prediction of ASCVD and HF, respectively, in the validation samples. Similar estimates of discrimination were observed among race and ethnicity subgroups in the derivation and validation data sets (Table S5B). Black individuals specifically had similar C-statistics compared with White individuals for total CVD, ASCVD, and HF. When comparing model performance with versus without eGFR, there was statistically significant but minimal improvement in discrimination (Δ C-statistic [95% CI]) among female participants (0.005 [0.004–0.006]) and male participants (0.004 [0.003–0.005]) for prediction of total CVD in the validation samples, with similar results in derivation samples (Table S5C).

Calibration plots of the base model (observed versus predicted risk deciles) in the validation samples are displayed in Figure 1 (derivation samples in Figure S1). Among female participants in the validation samples, the calibration slope median (IQI) was 1.03 (0.81–1.16), 1.09 (0.93–1.33), and 1.00 (0.55–1.15) for total CVD, ASCVD, and HF, respectively. Among male participants in the validation sample, the calibration slope was 0.94 (0.81–1.13), 1.04 (0.95–1.19), and 0.89 (0.49–1.07), respectively. Similar calibration slopes were observed among race and ethnicity subgroups: Black individuals (1.11 [0.79–1.24]), Asian individuals (0.87 [0.73–0.97]), non-Hispanic White individuals (1.01 [0.82–1.14]), and Hispanic individuals (0.94 [0.80–1.05]) for total CVD in the validation data sets (Table S6). Calibration estimates for ASCVD- and HF-specific models in the validation data sets and in the derivation data sets by sex and other subgroups (Tables S7 and S8) were similar. Supplemental analyses among people with a BMI >40 kg/m^2 demonstrated modest underestimation of risk (calibration slope 1.30 [0.96–1.47]). When follow-up was restricted to 5 years, calibration was similar, with slopes 0.94 (0.84–1.13), 1.08 (0.89–1.33), and 0.93 (0.40–1.05) for total CVD, ASCVD, and HF, respectively, for the PREVENT base model in the validation data sets. Calibration was similar when the model was compared with and without eGFR in the overall sample and was modestly improved among those with CKD defined as an eGFR <60 mL/min per 1.73 m^2 (1.29 [0.98–1.48]) to (1.02 [0.83, 1.22]) in the validation sample (Table S5D).

Optional PREVENT Equations

Model performance (C-statistic, calibration slope) and change in model performance (Δ C-statistic, NRI at event rate) with addition of novel predictors (UACR, HbA1c, and SDI) individually or together to the base model is displayed in Table 4. There were minimal statistically significant improvements in discrimination (Δ C-statistic [95% CI]) when novel predictors were added among female participants (UACR: 0.002 [0.002–0.003], HbA1c: 0.002 [0.001–0.003], and SDI: 0.001 [0.001–0.002]) for prediction of total CVD in the validation samples. The median NRI at event rate (interquartile range [IQI] across cohorts) for UACR added to the base model was 0.011 (–0.009 to 0.023), for HbA1c added to the base model

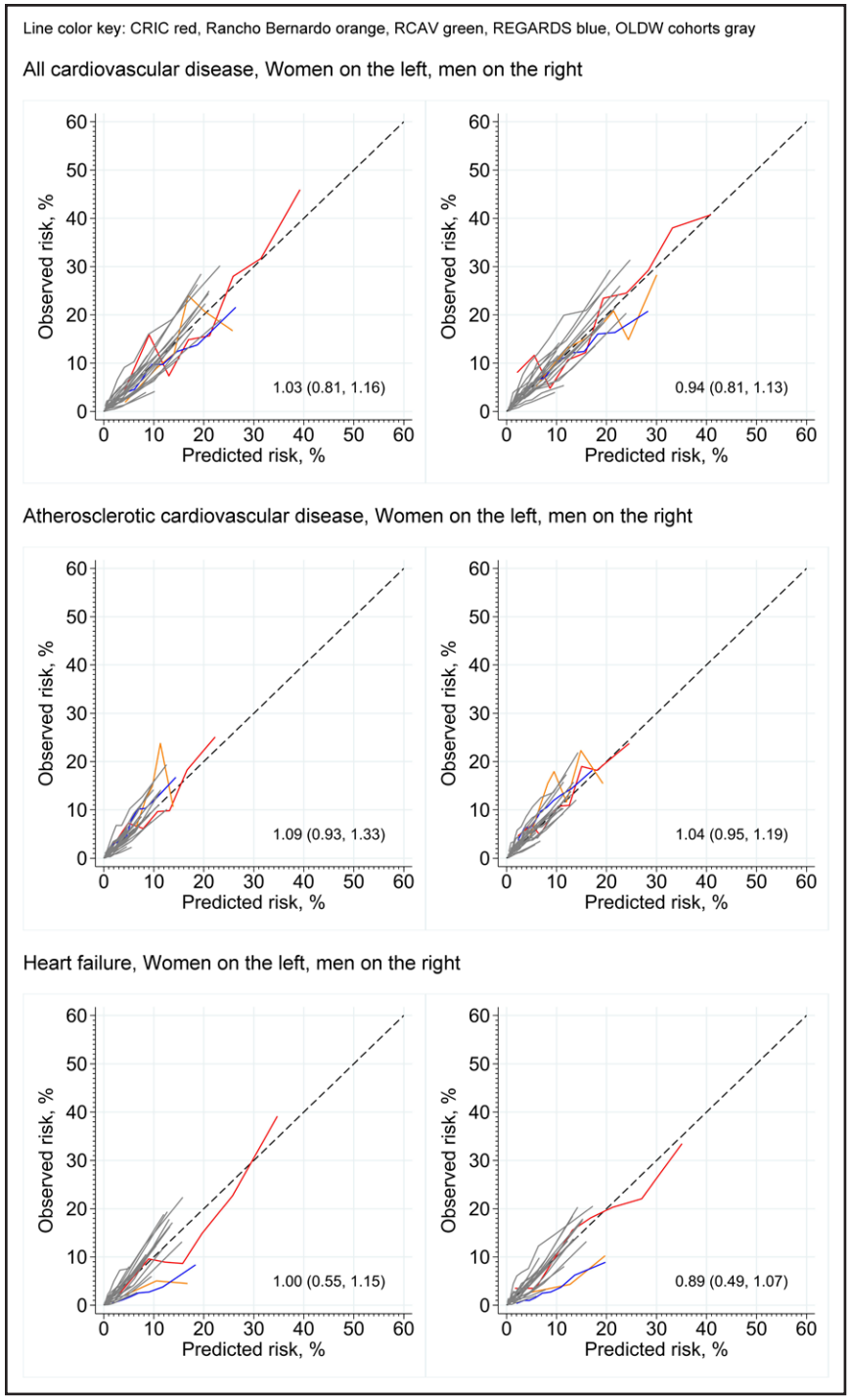

Figure 1. Sex-specific calibration plots in the validation sample for the PREVENT base model for total cardiovascular disease, atherosclerotic cardiovascular disease, and heart failure.
Predicted vs observed risk by decile within each validation cohort (Optum Labs Data Warehouse cohorts are shown in gray). PREVENT indicates Predicting Risk of CVD EVENTs.

was 0.002 (−0.002 to 0.005), and for SDI added to the base model was 0.003 (0.000 to 0.009) among female participants for the prediction of total CVD. Among male participants, the Δ C-statistic (95% CI) for addition of UACR, HbA1c, and SDI was 0.004 (0.003–0.004), 0.003 (0.002–0.004), and 0.002 (0.001–0.003), respectively, for total CVD. The median NRI at event rate (IQI across cohorts) was 0.031 (0.013–0.049) when UACR was added to the base model, 0.004 (0.001–0.010) when HbA1c was added to the base model, and was 0.005 (−0.002 to 0.018) when SDI was added to the base model among male participants for prediction of total CVD. Similar results were observed for change in model discrimination when ASCVD and HF were considered as end points.

In higher-risk subgroups, calibration was assessed in additional models predicting total CVD (Table S6). When UACR was added to the base model in CKD subgroups, calibration in the validation sample was 1.05 (0.84–1.20) among individuals with UACR >300 mg/g, which was

significantly improved compared with the base model without UACR (P=0.01). When HbA1c was added to the base model, calibration in the validation sample was 1.00 (0.66–1.14) among individuals with diabetes, which was similar to the model without HbA1c. When SDI was added, calibration in the validation sample was 0.96 (0.72–1.11), which was similar to the model without SDI.

Similar findings of good to excellent discrimination and calibration were observed for ASCVD- and HF-specific models when additional predictors (UACR, HbA1c, and SDI) were added to the base model (Table 4; Tables S5, S7, and S8). When CHD and stroke were examined as individual end points, the magnitude of association for cholesterol (non–HDL-C and HDL-C) was greater for CHD than for stroke, as expected (Tables S9 and S10). Model discrimination and calibration were good to excellent when developed for each subtype of ASCVD (MI and stroke) as displayed in Tables S5 and S11. Correlation between predicted risk of ASCVD and HF model was also high (median [IQI] of 0.899 [0.883–0.909]).

Predicted 10- and 30-Year CVD Risk

Estimates for 10-year (Figure 2) and 30-year (Figure 3) predicted risk on the basis of PREVENT are displayed using the primary base model for each outcome (total CVD, ASCVD, and HF). The predicted risk for a given age and combination of optimal to suboptimal risk factors varied substantially with a higher estimate with older age and a dose-dependent relationship with a greater number of elevated risk factor levels. Regression models were developed for translation and implementation of each of the models to estimate 10- and 30-year predicted risk for each outcome, which provided excellent approximations of predicted risk of CVD (R^2≥0.99 for 10-year risk estimates and ≥0.97 for 30-year risk estimates; Table S12A through S12J; and implemented on the AHA website at https://professional.heart.org/prevent). For example, the estimated 10-year CVD, ASCVD, and HF risk for a 50-year-old woman with the risk factor profile TC of 240 mg/dL, HDL-C of 55 mg/dL, no statin use, treated SBP of 160 mm Hg, no diabetes, no smoking, BMI of 35 kg/m^2, and eGFR 90 mL/min per 1.73 m^2 was 5.4%, 3.6%, and 2.5%, respectively; if smoking, the predicted risk was estimated at 9.3%, 6.0%, and 4.7%, respectively. The estimated 30-year CVD, ASCVD, and HF risk for the same individual was >3-fold higher at 31%, 20%, and 19%, respectively; if smoking, the predicted risk was estimated at 40%, 26%, and 26%, respectively.

Secondary Analyses

Model performance of the PCEs in the validation data sets was directly compared with PREVENT. Model discrimination of the PCEs was good at 0.772 (0.729–0.782) for female participants and 0.733 (0.701–0.751) for male participants (Table 4). The PREVENT model discrimination was marginally but statistically better, with a Δ C-statistic (95% CI) 0.007 (0.006–0.009) and 0.005 (0.004–0.006) for female and male participants, respectively. Calibration of the PCEs demonstrated overestimation of ASCVD risk that was significantly lower than the calibration slopes obtained with PREVENT (PCEs median [IQI] of 0.54 [0.47–0.61] and 0.50 [0.39–0.52] in female and male participants, respectively; P<0.001 for both). Similar results were obtained in the derivation data sets for discrimination (Table S13) and calibration (overall and across subgroups; Table S14). Correlations between predicted 10-year risk of ASCVD estimated for the new base model and the PCEs were high (Table S15). Based on a PCE risk estimate of 7.5%, the median PREVENT risk estimate was 8.4 (7.7–9.0) and 5.9 (5.7–6.3) for total CVD and 4.9 (4.4–5.3) and 3.7 (3.6–4.0) for ASCVD among female and male participants, respectively.

Coefficients for the association between predictors and outcomes were similar in research and health system–based data sets, with no statistically significant differences after Bonferroni adjustment for multiple comparisons (Table S16). There were also no statistically significant differences by baseline examination year despite significant differences across epochs in baseline statin treatment (<7% in those with baseline year <2000; 21% between 2000 and 2009; and 15% in ≥2009; Table S17A and S17B).

DISCUSSION

Based on data from >6 million individuals from 46 data sets, we derived and validated the PREVENT equations, a suite of sex-specific, race-free models to predict short- and long-term risk for incident CVD (and CVD subtypes) among US adults 30 to 79 years of age by using variables routinely available in the clinical setting. These newly developed models offer several conceptual and methodological advances for CVD risk prediction, particularly in the context of CKM health, as summarized in Figure 4 and as outlined in the 2023 AHA Scientific Statement that details the need for novel approaches to risk prediction.[20] First, the models remove race from risk prediction to support more equitable care in CVD prevention because race is a social construct and not a biological predictor.[35,65] Second, we vastly expand the sample size used in derivation and validation, leveraging data from contemporary cohorts and health system data sets, which resulted in broad generalizability with good to excellent discrimination and calibration across subgroups, including by race and ethnicity. This also resulted in significantly improved calibration for PREVENT compared with the PCEs. This was demonstrated by a slope of observed to predicted risk of close to 1 for PREVENT, indicating a well-calibrated model. In contrast, the slope of the PCEs ranged from 0.50 to 0.54 for ASCVD, which

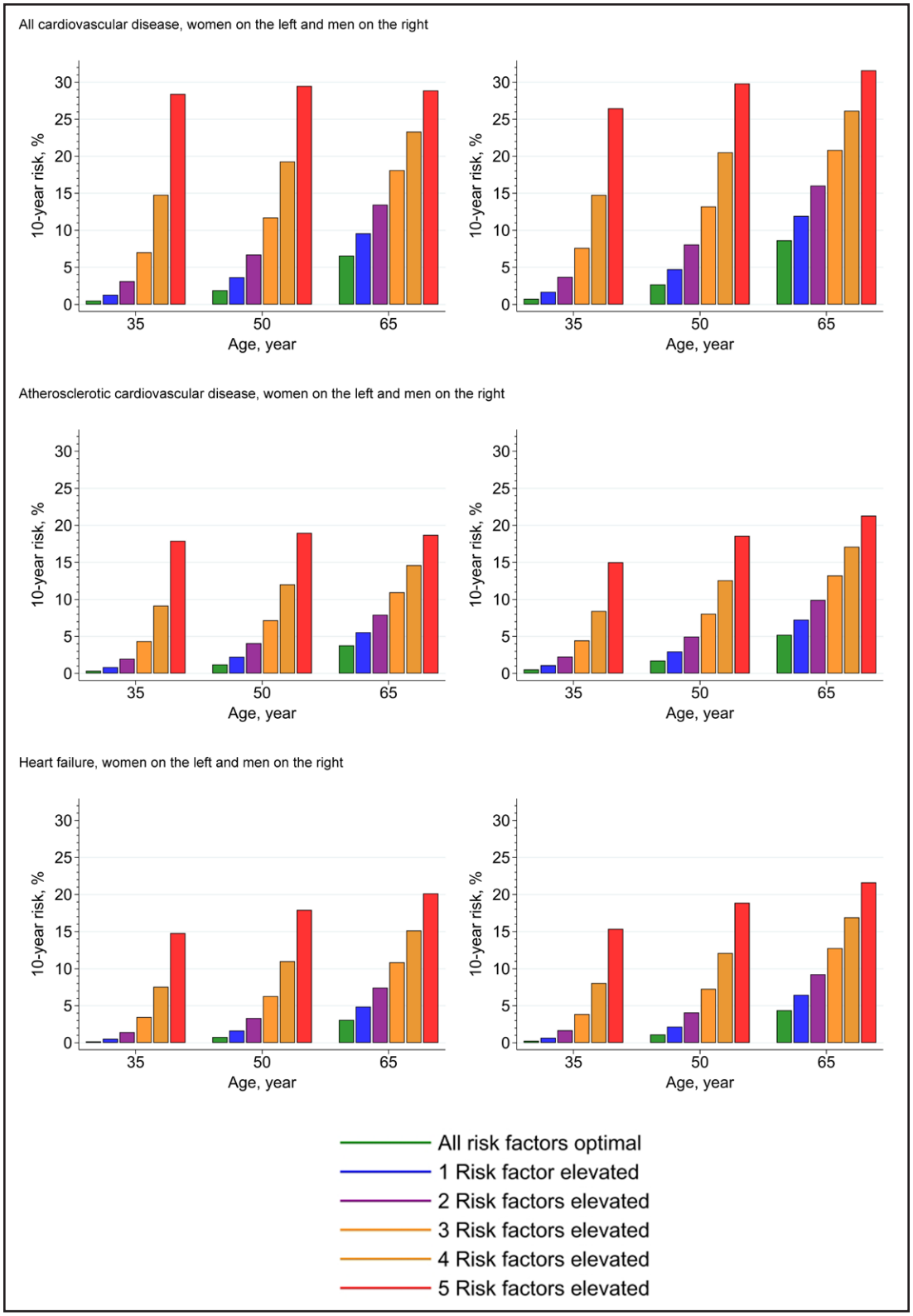

Figure 2. Estimated 10-year risk of total cardiovascular disease, atherosclerotic cardiovascular disease, and heart failure stratified by sex (women on the left and men on the right for each outcome) at varying ages (35, 50, and 65 years) according to the number of elevated risk factors (from 0 to 5) adjusted for competing risks of non–cardiovascular disease death.
Optimal risk factor levels are defined as non–high-density lipoprotein cholesterol (3.5 mmol/L; 135 mg/dL), high-density lipoprotein cholesterol (1.5 mmol/L, 58 mg/dL), systolic blood pressure 120 mm Hg, no diabetes, no smoking, no hypertension medications, no statin use, and estimated glomerular filtration rate 90 mL/min per 1.73 m^2. Elevated risk factor levels included non–high-density lipoprotein cholesterol (5.5 mmol/L; 213 mg/dL), systolic blood pressure 150 mm Hg, diabetes, or smoking and estimated glomerular filtration rate 45 mL/min per 1.73 m^2. For multiple elevated risk factors, the risk shown is the average risk of all combinations.

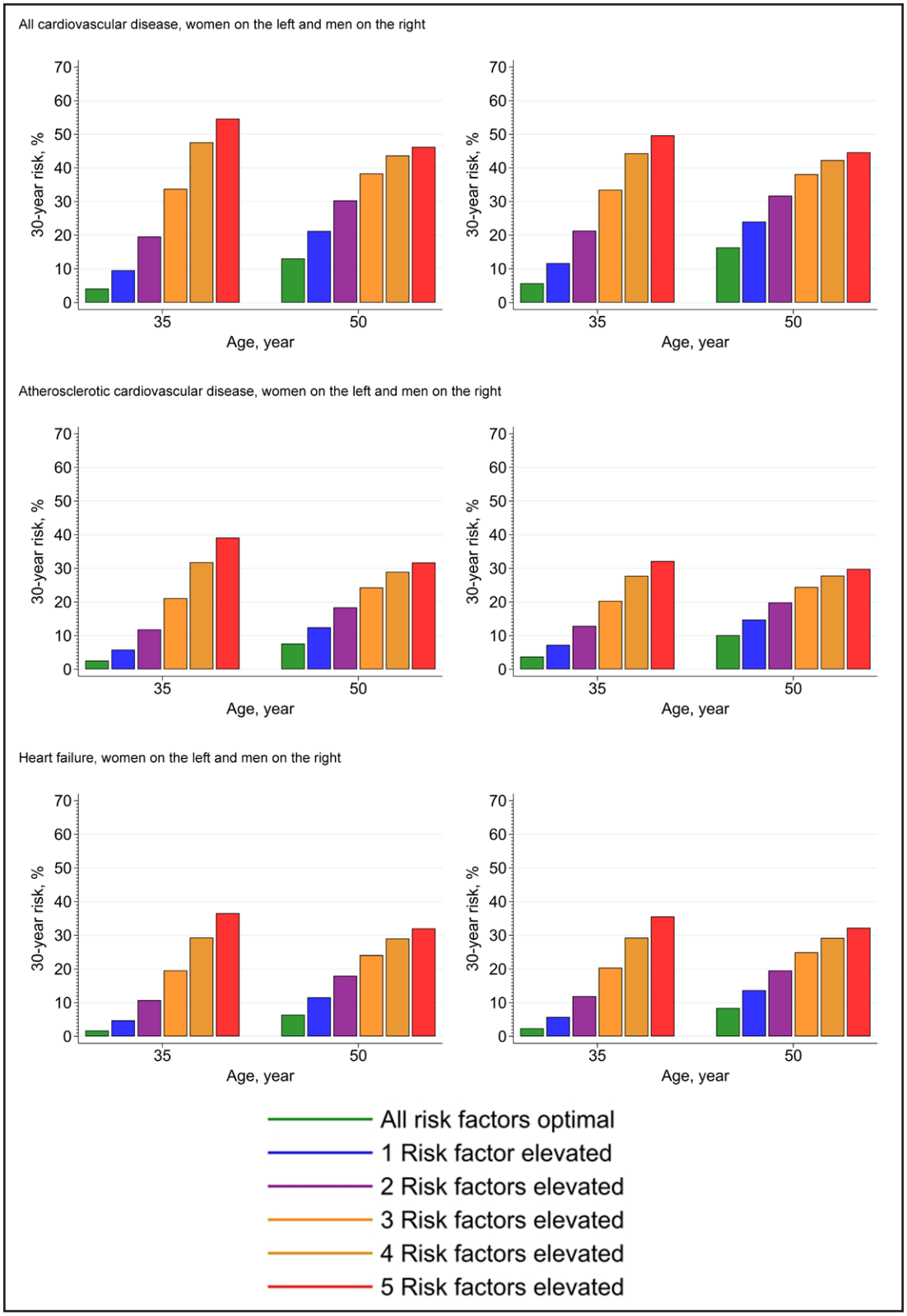

Figure 3. Estimated 30-year risk of total cardiovascular disease, atherosclerotic cardiovascular disease, and heart failure stratified by sex (women on the left and men on the right for each outcome) at varying ages (35, 50, and 65 years) according to the number of elevated risk factors (from 0 to 5) adjusted for competing risks of non–cardiovascular disease death.
Optimal risk factor levels are non–high-density lipoprotein cholesterol (3.5 mmol/L; 135 mg/dL), high-density lipoprotein cholesterol (1.5 mmol/L, 58 mg/dL), systolic blood pressure 120 mm Hg, no diabetes, no smoking, no hypertension medications, and no statins, and an estimated glomerular filtration rate of 90 mL/min per 1.73 m^2. Elevated risk factor levels considered are non–high-density lipoprotein cholesterol (5.5 mmol/L; 213 mg/dL), systolic blood pressure 150 mm Hg, diabetes, or smoking, and an estimated glomerular filtration rate of 45 mL/min per 1.73 m^2. For multiple elevated risk factors, the risk shown is the average risk of all combinations.

Key Takeaways of the AHA PREVENT Equations
1. Include a large, contemporary, and diverse sample of US adults for derivation and external validation
2. Predict the risk of total or global CVD as a composite of atherosclerotic cardiovascular disease and heart failure as well as for each CVD subtype separately
3. Broaden the outcome to include prediction of heart failure
4. Remove race from risk prediction acknowledging that race is a social construct and not a biological predictor
5. Lower the age to begin risk prediction as early as age 30 years and capture a greater proportion of the adult life course
6. Provide risk estimates for CVD over a 10-year and 30-year time span
7. Offer optional models that incorporate add-on measures of kidney and metabolic health when indicated given the growing burden of cardiovascular-kidney-metabolic (CKM) syndrome
8. Include a measure of place-based social disadvantage (social deprivation index [SDI]) to acknowledge the role of social determinants of health in cardiovascular disease risk

Figure 4. Key takeaways of the American Heart Association PREVENT equations.
The AHA PREVENT equations offer several key conceptual and methodological advances in the approach used to estimate CVD risk. CVD indicates cardiovascular disease; and PREVENT, Predicting Risk of CVD EVENTs.

represents overestimation of risk by ≈50%. Third, the outcome of interest was broadened to include HF both as part of a composite of total CVD, as well as individually with separate risk estimates for ASCVD and HF. Fourth, models were developed to include adults starting at 30 years of age and predict short- (10-year) and long-term (30-year) risk estimates. This was accomplished by using age as a time scale, which enables flexible modeling of risk for different age and time horizons even when individual data sets have limited follow-up and obviates the need for historical and outdated data from >30 years ago. In addition, competing risk of non-CVD death was accounted for, which is particularly relevant when estimating lifetime or longer-term risk. Fifth, the models newly include eGFR as a predictor in the base model and offer a set of optional add-on predictors of kidney and metabolic health to allow personalization of risk assessment among higher-risk subgroups with CKM (eg, use of UACR with CKD). This offers the opportunity to comprehensively assess risk in the context of often co-occurring comorbidities in patients with obesity, diabetes, or CKD who are at high risk for CVD.

The inclusion of HF in PREVENT is a timely and clinically important end point given the significant increases in HF-related mortality[7] and HF hospitalizations[66] in recent years and the availability of new classes of medications that prevent incident HF.[67] The PREVENT models build on existing multivariable models that each predict risk separately for ASCVD (eg, PCEs[2]) and HF (eg, PCP-HF[33]). However, the multiplicity of these algorithms may be a critical barrier to clinical implementation of these distinct models, whereas PREVENT offers a singular and comprehensive risk framework to estimate risk for total CVD, as well as for ASCVD and HF. The present work builds on previous risk prediction efforts to predict total CVD, such as the multimodality model developed by de Lemos et al,[68] which included variables from ECG (left ventricular hypertrophy), coronary artery calcium, N-terminal pro B-type natriuretic peptide, high-sensitivity troponin T, and high-sensitivity C-reactive protein, with an improvement in C-statistic from 0.74 to 0.79, which is larger than the differences observed here. However, this prediction model was derived in a single cohort that may not be representative of the US population, and the use of a multimodality strategy, including biomarkers and imaging not routinely performed in clinical care, may limit its utility and implementation on a population scale. The growing burden supports the utility of including HF as an outcome in CVD risk prediction, but it is possible that the heterogeneity of HF and its distinct pathophysiology compared with ASCVD may result in suboptimal risk prediction for each outcome. To address this, the PREVENT models separately modeled and developed risk equations for total CVD, ASCVD, and HF. Estimates for each CVD subtype are important because a clinician may target risk assessment and preventive measures for each specific end point (eg, lipid-lowering therapy to reduce risk of ASCVD[1,4] or sodium glucose cotransporter-2 inhibitors to reduce risk of HF[69]). Use of multivariable risk models to predict risk for HF for primary prevention was also recently endorsed, for the first time, in the 2022 AHA/ACC/Heart Failure Society of America Guideline for the Management of Heart Failure as a class IIa recommendation.[69] Although it is well-established that risk

factors for ASCVD and HF overlap,[70] and those with multiple risk factors have higher absolute risk of ASCVD and HF events,[3] PREVENT refines the estimation for each CVD subtype, as well as inclusion of BMI, as a predictor for HF for a more comprehensive assessment of risk.[71]

The PREVENT models further account for CVD risk associated with impaired CKM health with the addition of eGFR for prediction of CVD, which directly addresses the call for action outlined in the 2023 CKM Presidential Advisory and Scientific Statements to prioritize and promote CKM health.[12,13] The inclusion of eGFR is also aligned with the 2019 Primary Prevention Guidelines that included CKD as a risk-enhancing factor based on the robust evidence base for the dose-dependent association of kidney function and CVD; markers of kidney function (eg, eGFR or UACR) were not incorporated into the PCEs.[1] Other investigations have previously incorporated kidney measures in risk prediction but have demonstrated their predictive utility separately for ASCVD and HF in the general population and among people with CKD.[38,51,72] The add-on PREVENT models consider UACR when clinically indicated and available.[41] Although the changes in risk discrimination with the addition of eGFR and UACR were minimal, they were statistically significant. Furthermore, the improvement in calibration among individuals with CKD suggests that their utility may be important in this high-risk group. In addition, their inclusion in risk prediction can offer a potential platform for future implementation research to determine whether inclusion of guideline-recommended predictors in risk models can improve the uptake of appropriate screening for risk markers, such as UACR or HbA1c, among individuals with CKD or diabetes.[46,73] Future research should also evaluate the effect of the inclusion of these predictors in the uptake of guideline-recommended therapies that are both cardio-protective and kidney-protective, with the combined benefit of CVD risk reduction and promotion of kidney health (eg, renin-angiotensin system antagonists, sodium glucose cotransporter-2 inhibitors, and nonsteroidal mineralocorticoid antagonists).[74–76]

The PREVENT models account for competing risk of non-CVD death to prevent overestimation of CVD risk and overestimation of the benefit of treatment. This is particularly relevant among subgroups (eg, poor CKM health) in which competing risk for non-CVD death is high.[77–79] The burden of poor CKM health is growing in the United States.[80] Age-adjusted prevalence for obesity is estimated to exceed 40% (and for diabetes, 10%) in the US adult population based on contemporary data from population-based samples (National Health and Nutrition Examination Survey: 2017–2020).[8] The prevalence of CKD (defined as eGFR <60 mL/min per 1.73 m^2 or UACR ≥30 mg/g) is nearly 15%.[8] It is important to note that the presence of any of these CKM risk factors is associated not only with higher risk of CVD, but also with higher risk of non-CVD death.[8] In addition, poor CKM health is associated with earlier onset of CVD.[81–83] Therefore, the approach in the PREVENT models incorporate age as a time scale, which also allows estimation of longer-term risk (eg, 30-year time horizon) and targeted prevention earlier in the life course. Thus, PREVENT addresses the fact that risk for CVD is not able to be calculated for those <40 years of age and is underestimated among younger individuals when relying only on short-term risk. This gap has been highlighted recently by federal funding agencies as a key area in which prevention trials are needed in risk-enriched subsets of the young adult population.[84,85]

Limitations

There are several limitations to note. We derived risk prediction models in a sample of primary prevention adults from 46 data sets, including 36 EMR-based data sets, after excluding those with extreme clinical values for SBP, TC, HDL-C, or BMI. EMR data are obtained for clinical care and, therefore, may be limited by the lack of research-based measurements of predictors, lack of adjudication of outcomes, and potential for nonrandom missingness of data. However, secondary analyses demonstrated consistent risk associations between risk factors and CVD across research cohorts and EMR data sets. Furthermore, the use of large, contemporary, and diverse samples from EMR data covering all US census region sources add to the real-world representativeness of the PREVENT equations with more generalizable risk estimates for CVD. Second, the baseline for the included data sets spanned >3 decades, which may lead to differences in risk factor prevalence, treatment, and period effects. However, secondary analyses demonstrated no clinically meaningful differences in the directionality and magnitude of hazard ratios between predictors and outcomes per decade. This is also consistent with recent analyses that demonstrate no difference in the association between treated and untreated cholesterol levels and CVD risk in research cohorts and clinical samples.[86,87] Third, models were developed using age as the time scale. Although this enables the flexibility of modeling longer-term estimates without requiring all data sets to have long-term follow-up, this may result in overestimation of 30-year risk. However, we modeled the risk of CVD using risk factor levels at baseline and adjusted for competing risk of non-CVD death to address potential overestimation of risk. Alternative approaches requiring at least 30 years of follow-up would limit available data sets for prediction and result in the use of historical data that are not generalizable to a contemporary US population. Fourth, individual-level social determinants of health were not routinely available in all data sets, and thus were not included in the development of PREVENT.[88] Zip code–level SDI was selected as a widely available measure of area-based deprivation that may be implemented

while health systems continue to evolve data collection on broader measures of social determinants of health, which has been recommended by the Centers for Medicare & Medicaid Services and will become mandatory by 2024. However, SDI was only available in the health system data sets from OLDW, and the addition of SDI only minimally improved discrimination. This may, in part, be a result of the inherent limitations of a zip code–based measure, which incompletely assesses the broader context of multilevel social drivers of health. Therefore, the approach in PREVENT is a first step, but future models should account for individual-level and area-based social determinants of health that more comprehensively reflect aspects of the lived experience. Fifth, biomarkers representing target-organ damage (eg, high-sensitivity troponin or brain natriuretic peptide), inflammation (eg, high-sensitivity C-reactive protein), or subclinical disease (eg, coronary artery calcium) were considered but not included in PREVENT model development. These biomarkers are not routinely recommended for screening in primary prevention samples by guidelines, and data on these were limited in clinical data sets and not consistently present in all research data sets. Previous models have used these biomarkers in risk prediction (eg, Astro-CHARM,[89] de Lemos et al,[68] and others[90]), but these models were developed in smaller sample sizes on the basis of limited data sets with comprehensive ascertainment of these biomarkers. Given that high-sensitivity troponin and brain natriuretic peptide are clinically available, these should be considered in future risk models and more widely incorporated into risk assessment frameworks for the general population. Thus, the current PREVENT approach is aligned with current clinical practice guidelines,[1] which suggests a Bayesian sequential approach that allows for qualitative consideration of these predictors as risk-enhancing factors after an initial risk estimate is calculated. Finally, total CVD and its components, including ASCVD, heart failure, CHD, and stroke, were each modeled separately. An individual may develop 1 or more of these outcomes. Therefore, the predicted risk for each composite outcome (eg, CVD, ASCVD) is less than the sum of its components. Future research may also consider the quantitative incorporation of additional risk factors through add-on methodologies (eg, patch) as has been previously applied to the PCEs.[72] This is also discussed in greater detail in the AHA Scientific Statement on "Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health."[20]

In conclusion, the PREVENT models represent a novel set of sex-specific, race-free, prediction equations to assess risk of total CVD and CVD subtypes. The PREVENT models were well-calibrated across racial, ethnic, and higher-risk subgroups (eg, CKD and diabetes), which support their broad generalizability in a diverse sample of primary prevention adults. Thus, PREVENT can be successfully implemented in clinical care to guide short- and long-term risk communication in the general primary prevention population with or without CKD or diabetes. The developed models accurately discriminate risk of CVD with routinely available clinical variables and leverage optional models with add-on predictors that may further personalize risk estimation.

ARTICLE INFORMATION

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Supplemental Material

Appendices S1–S4
Figure S1
Tables S18–S25
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