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Development and Validation of the American Heart Association Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) Equations

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Abstract

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 AHA Predicting Risk of CVD EVENTs (PREVENT) equations among US adults aged 30-79 years without known CVD.

Methods: The derivation sample included individual-level participant data from 25 datasets (N=3,281,919) between 1992-2017. The primary outcome was CVD (atherosclerotic CVD [ASCVD] and heart failure [HF]). Predictors included traditional risk factors (smoking status, systolic blood pressure, cholesterol, anti-hypertensive or statin use, diabetes) and estimated glomerular filtration rate [eGFR]. 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 dataset and meta-analyzed. Discrimination was assessed using Harrell's C-statistic. Calibration was calculated as the slope of the observed vs. predicted risk by decile. Additional equations to predict each CVD subtype (ASCVD, HF) and include optional predictors (urine albumin-to-creatinine ratio [UACR], hemoglobin A1c [HbA1c]), and social deprivation index [SDI]) were also developed. External validation was performed in 3,330,085 participants from 21 additional datasets.

Results: Among 6,612,004 adults included, mean (SD) age was 53 (12) years and 56% were female. 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 [IQI]: 0.763-0.809) in female and 0.757 (0.727-0.778) in male participants. The calibration slopes were 1.03 (IQI 0.81 -1.16) and 0.94 (0.81-1.13) among females and males, respectively. Similar estimates for discrimination and calibration were observed for ASCVD- and HF-specific models. The improvement in discrimination was small but statistically significant when UACR, HbA1c, and SDI were added together to the base model to total CVD (ΔC-statistic [IQI] 0.004 [0.004, 0.005] and 0.005 [0.004, 0.007] among females and males, respectively). Calibration improved significantly when UACR was added to the base model among those with marked albuminuria (>300mg/g) (1.05 [0.84-1.20] vs. 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 using routinely available clinical variables.

Keywords

risk assessment; models; cardiovascular; cardiovascular diseases; heart failure; kidney diseases; social determinants of health

Introduction

Assessment of absolute risk for cardiovascular disease (CVD) with multivariable risk prediction equations is recommended by multi-society 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 (e.g., initiation of lipid-lowering therapy based on estimated ten-year risk of atherosclerotic CVD [ASCVD]).[1, 4] While this paradigm was originally described more than two 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. While the PCEs are currently endorsed by the 2019 AHA/ACC Primary Prevention Guidelines for use in US adults aged 40-79 years,[1] the PCEs do not capture the total burden of CVD given the rising prevalence of other CVD subtypes not previously included (e.g., 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] Further, 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.

The 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 (e.g., obesity, diabetes, chronic kidney disease [CKD]), which 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] (e.g., 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 (e.g., glucagon-like peptide 1 agonists [GLP-1RA] and sodium glucose co-transporter 2-inhibitors [SGLT2i]) 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 aged 30-79 years 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, Maryland, USA (#IRB00003324). Given the use of de-identified 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. Specifically, we used data 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). While the CKD-PC infrastructure was developed with a specific interest in people with CKD, this consortium includes observational datasets

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, datasets 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 dataset to enhance validity and generalizability of risk prediction equations. In order to be included as part of the derivation sample, cohorts were required to share de-identified individual-level data with the CKD-PC Data Coordinating Center. Derivation samples included: (1) general population research-based cohorts: Atherosclerosis Risk in Communities (ARIC) Study,[22] Coronary Artery Risk Development in Young Adults (CARDIA),[23] Cardiovascular Health Study (CHS),[24] Framingham Heart Study (FHS),[25] Jackson Heart Study (JHS),[26] and the Multi-Ethnic Study of Atherosclerosis (MESA)[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: Reasons for Geographic and Racial Differences in Stroke (REGARDS),[30] which was primarily focused on factors that account for disparities in stroke outcomes by race and region of residence; disease-specific research-based cohort: Chronic Renal Insufficiency Cohort (CRIC),[31] which recruited participants with impaired kidney function (half of whom were diagnosed with diabetes); and the Rancho Bernardo Study (RBS),[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 datasets contributed to the model derivation.

Individual-level participant data were included for adults aged 30 to 79 years 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 non-linear association with CVD and non-CVD death or pre-existing guideline-based clinical recommendations for treatment at these extreme values. For SBP, TC, and HDL-C, the cutoffs for exclusion were based on those utilized for the 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 utilized 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 datasets, the baseline visit was selected as the earliest visit on or after January 1, 1992, based on overall availability of complete risk factor data. For health system datasets, the baseline visit was selected as the earliest eligible date for each participant between January 1, 2008, until December 31, 2017, based on availability of complete risk factor data and required enrollment for at least one year. Follow-up was censored at 15 years to optimize short-term risk prediction given the majority of datasets had <10 years of follow-up with additional details described in Supplemental Appendix 1.

Outcome Ascertainment: Total CVD, CVD Subtypes, and Mortality

The primary outcome was incident total CVD, which was defined as a composite of fatal and non-fatal 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 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 datasets. Deaths from all causes were ascertained and non-CVD deaths were treated as competing events. Details on how each cohort or dataset defined incident CVD (including International Classification of Diseases [ICD] codes) and causes of death are summarized in Supplemental Appendix 1.

Measurement of Traditional and Novel Predictors

Details on ascertainment of demographics, traditional risk factors, and novel predictors in each cohort and health system are summarized in Supplemental Appendix 1. 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 datasets. 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] While 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 not systematic under- or over-prediction, calibration was assessed across racial and ethnic groups.

Risk factors included in the prediction equations were selected based on being included in the development of PCEs as well as being available in derivation datasets, 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 prognostic value of fasting and non-fasting 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 datasets, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 creatinine equation,[39] using standardized or calibrated serum creatinine.[40] Diabetes, current

smoking, and use of anti-hypertensive or statin medications were also included as predictors with detailed descriptions of how these were derived in Supplemental Appendix 1.

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 (e.g., CKD, diabetes). Specifically, change in model performance was assessed 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 three predictors.

UACR was abstracted based on 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 available evidence supporting the robust association between UACR and CVD risk and clinical practice recommendations to measure UACR in individuals with CKD (e.g., eGFR <60 ml/min/1.73m^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 (i.e., a missing UACR indicator was also included). A similar rationale was applied to HbA1c whereby any available HbA1c values were utilized 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 based on 5-year estimates from the American Community Survey (2015-2019) and was linked to individual-level participant data in the OLDW cohorts (detailed in Supplemental Appendix 1).[47] Given available epidemiologic 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 datasets (36 datasets). SDI integrates information on seven area-level characteristics: percent living in poverty, percent with <12 years of education, percent single-parent households, percent living in rented housing units, percent living in the overcrowded housing unit, percent of households without a car, and percent unemployed adults <65 years of age.[47] Individual-level social determinants of health (e.g., annual household income, highest level of education, perceived discrimination) were also considered but were not systematically available across datasets 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 (standard deviation) or median (interquartile intervals) and frequencies, as appropriate. All analyses were performed separately in each cohort and meta-analyzed to pool estimates via random-effects models, consistent with methods utilized in prior 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 anti-hypertensive or statin medications, and diabetes. Diabetes and smoking status were dichotomized as yes/no. All other predictors were modeled continuously. A piece-wise linear spline was used to examine inflections

in slope. On the basis of a priori hypothesized non-linear associations, SBP, eGFR, and BMI were modeled with a knot. For SBP, coefficients were modeled per 20 mm Hg for < and ≥110 mm Hg; for eGFR per -15 mL/min/1.73 m^2 for < and ≥ 60 mL/min/1.73 m^2; for BMI per 5 kg/m^2 for < and ≥ 30 kg/m^2. Interaction terms for each risk factor with age were also included since 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. Specifically, additional equations were developed that included linear terms for UACR (log-transformed), HbA1c, and SDI (decile-based categories of 1-3, 4-6, 7-10) separately as well as a set of equations that included all three 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 prior 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). This approach, thus, 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 prior publications when age is utilized as the time-scale.[59] Modeling on the age-scale allows estimation of short- and long-term risk of CVD and is consistent with some European risk prediction algorithms (e.g., 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 (based on 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 vs. 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 as they have been employed previously in risk prediction models[1, 2]

and are currently recommended by the 2019 AHA/AHA Primary Prevention Guidelines[1] to guide clinician-patient discussions.

Model performance, including discrimination and calibration, of PREVENT was assessed separately in each dataset 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 three were added together was assessed with the change in C-statistic and categorical net reclassification improvement (NRI) (based at event rate), for each dataset 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 less than 1.0 indicates lower observed than predicted risk (e.g., over-prediction), and a slope of greater than 1.0 indicates higher observed than predicted risk (e.g., under-prediction).[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, CKD).

Several secondary analyses were conducted. We first performed a direct comparison between risk estimates derived from PREVENT and PCEs. Specifically, we 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 dataset type (research cohort vs. health system dataset). For these two 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 datasets with limited follow-up.

Simplified regression approximations to estimate risk of CVD and CVD subtypes were calculated (see detailed methods in Supplemental Appendix 1.2). All analyses were performed using STATA 16 (College Station, TX). A two-sided p-value of <0.05 was considered statistically significant unless otherwise noted. We utilized 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 upon reasonable request and approval through direct contact with the individual cohorts according to cohort-specific policies. STATA code for calculation of

the PREVENT equations are available upon 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, data interpretation, or writing of the report. JC 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 (e.g., https://aric.cscc.unc.edu/aric9/researchers/Obtain_Submit_Data for the Atherosclerosis Risk in Communities Study).

Results

Baseline Characteristics

In the derivation sample, there were 1,839,828 female and 1,442,091 male participants from 25 individual datasets with mean (SD) age 53 (13) and 52 (12) years, respectively (Table 1; **details by dataset in** Supplemental Table S1). Among female participants, 78% were White, 10% Black, 6.0% Hispanic, and 2.6% Asian; prevalence of diabetes was 10% and use of anti-hypertensive and statin medications were 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 use of anti-hypertensive and statin medications were 27% and 17%, respectively, among male participants. Mean eGFR was 91 mL/min/1.73m^2 in both female and male participants. The median UACR was 8 mg/g in both females and males; mean HbA1c was 7.3% and 7.6% in females and males, respectively; and the median SDI decile was 4 among female participants and 3 among male participants. The validation sample comprised of 1,894,882 female and 1,435,203 male participants from 21 individual datasets 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 to 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 dataset are detailed in Supplemental Table S1.

Associations between Predictors and CVD Events

Associations between predictors and each outcome (total CVD and CVD subtypes [ASCVD, 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, SDI) were added to the base model individually (Supplemental Tables S2–S4) or all together (Table 3).

PREVENT Model Performance Characteristics

Model performance, including discrimination and calibration for prediction of total CVD and CVD subtypes (ASCVD, HF) for derivation datasets and validation datasets are displayed in Supplemental Table S5A and Table 4. The primary PREVENT model (base model) for prediction of total CVD that included traditional CVD risk factors and eGFR had a median C-statistic (interquartile interval [IQI]: 25^{th}, 75^{th} percentile of cohorts) of 0.789 (0.7778, 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 females, 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 males, 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 datasets (Supplemental Table 5B). Specifically, Black individuals had similar C-statistics when compared with White individuals for total CVD, ASCVD, and HF. When comparing model performance with vs. without eGFR, there were statistically significant but minimal improvement in discrimination (ΔC-statistic [95% CI]) among females (0.005 [0.004-0.006]) and males (0.004 [0.003-0.005) for prediction of total CVD in the validation samples with similar results in derivation samples (Supplemental Table S5C).

Calibration plots of the base model (observed vs. predicted risk deciles) in the validation samples are displayed in Figure 1 (derivation samples in Supplemental Figure S1). Among females 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 males 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 datasets (Supplemental Table S6). Calibration estimates for ASCVD- and HF-specific models in the validation datasets and in the derivation datasets by sex and other subgroups (Supplemental Tables S7–8) was similar. Supplemental analyses among people with BMI greater than 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 datasets. 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/1.73 m^2 (1.29 [0.98, 1.48] to 1.02 [0.83, 1.22]) in the validation sample (Supplemental Table S5D).

Optional PREVENT Equations

Model performance (C-statistic, calibration slope) and change in model performance (ΔC-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 (ΔC-statistic [95% CI]) when novel predictors were added among females (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, 0.023), for HbA1c added to the base model was 0.002 (-0.002, 0.005), and for SDI added to the base model was 0.003 (0.000, 0.009) among females for prediction of total CVD. Among males, the ΔC-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, was 0.004 (0.001, 0.010) when HbA1c was added to the base model, and was 0.005 (-0.002, 0.018) when SDI was added to the base model among males for prediction of total CVD. Similar results were observed for change in model discrimination when ASCVD and HF were considered as endpoints.

In higher-risk subgroups, calibration was assessed in additional models predicting total CVD (Supplemental 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, SDI) were added to the base model (Table 4, Table S5, Supplemental Tables S7–8). When CHD and stroke were examined as individual endpoints, the magnitude of association for cholesterol (non-HDL-C and HDL-C) was greater for CHD compared with stroke, as expected (Supplemental Tables S9–S10). Model discrimination and calibration were good to excellent when developed for each subtype of ASCVD (MI and stroke) as displayed in Supplemental Table 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 ten-year (Figure 2) and thirty-year (Figure 3) predicted risk based on 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 ($R^2 \geq 0.99$ for 10-year risk estimates and ≥0.97 for 30-year risk estimates) (Supplemental Table S12, A–J; 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 following risk factor profile (TC of 240 mg/dL, HDL-C of 55 mg/dL, no statin use, treated SBP of 160 mmHg, no diabetes, no smoking, BMI of 35 kg/m^2, and eGFR 90 ml/min/1.73m^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 more than 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 datasets was directly compared with PREVENT. Model discrimination of the PCEs was good at 0.772 (0.729-0.782) for females and 0.733 (0.701-0.751) for males (Table 4). The PREVENT model discrimination was marginally but statistically better with a ΔC-statistic (95% CI) 0.007 (0.006-0.009) and 0.005 (0.004-0.006) for females and males, respectively. Calibration of the PCEs demonstrated over-estimation 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 females and males, respectively, $p<0.0001$ for both). Similar results were obtained in the derivation datasets for discrimination (Supplemental Table S13) and calibration (overall and across subgroups: Supplemental Table S14). Correlations between predicted ten-year risk of ASCVD estimated for the new base model and the PCEs were high (Supplemental 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 was 4.9 (4.4-5.3) and 3.7 (3.6-4.0) for ASCVD among females and males, respectively.

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

Discussion

Based on data from more than 6 million individuals from 46 datasets, 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 aged 30-79 years 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 datasets, 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 when 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 0.50-0.54 for ASCVD, which represents overestimation of risk by about 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 age 30 years 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 datasets 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 (e.g., 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, CKD who are at high-risk for CVD.

The inclusion of HF in PREVENT is a timely and clinically important endpoint given 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 upon existing multivariable models that each predict risk separately for ASCVD (e.g., PCEs[2]) and HF (e.g., 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 upon prior risk prediction efforts to predict total CVD, such as the multi-modality model developed by de Lemos et. al., that included variables from electrocardiogram (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.[68] However, this prediction model was derived in a single cohort that may not be representative of the US population and the use of a multi-modality 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 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 endpoint (e.g., lipid-lowering therapy to reduce risk of ASCVD[1, 4] or SGLT2i 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] While 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 2019 Primary Prevention Guidelines 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 (e.g., 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] While the changes in risk discrimination with the addition of eGFR and UACR were minimal, they were statistically significant. Further, the improvement in calibration among individuals with CKD suggest 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 if inclusion of guideline-recommended predictors in risk models can improve 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 impact of inclusion of these predictors in the uptake of guideline-recommended therapies that are both cardio- and kidney-protective with the combined benefit of CVD risk reduction and promotion of kidney health (e.g., renin-angiotensin system antagonists, SGLT2i and non-steroidal mineralocorticoid antagonists).[74–76]

The PREVENT models account for competing risk of non-CVD death to prevent over-estimation of CVD risk and over-estimation of benefit of treatment. This is particularly relevant among subgroups (e.g., poor CKM health) where competing risk for non-CVD death is high.[77–79] The burden of poor CKM health is growing in the US.[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/1.73m^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 with not only with higher risk of CVD but also 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 to incorporate age as a time scale, which also allows estimation of longer term risk (e.g., 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 in those <40 years and is under-estimated among younger individuals when relying only on short-term risk. This gap has been highlighted recently by federal funding agencies as a key area where 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 datasets, including 36 EMR-based datasets, after excluding those with extreme clinical values for SBP, TV, 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 non-random missingness of data. However, secondary analyses demonstrated consistent risk associations between risk factors and CVD across research cohorts and EMR datasets. Further, the use of a large, contemporary, and diverse sample from EMR data covering all US census regions sources add to the real-world representativeness of the PREVENT equations with more generalizable risk estimates for CVD. Second, the baseline for the included datasets 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 HRs 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. While this enables the flexibility of modeling longer-term estimates without requiring all datasets to have long-term follow-up, this may result in over-estimation of 30-year risk. However, we modeled the risk of CVD utilizing risk factor levels at baseline and adjusted for competing risk of non-CVD death to address potential over-estimation of risk. Alternative approaches requiring at least 30-years of follow-up would limit available datasets for prediction and result in 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 datasets, 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 recommend by CMS and will become mandatory by 2024. However, SDI was only available in the health system datasets 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 multi-level 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 (e.g., high sensitivity troponin [hsTn], brain natriuretic peptide [BNP]), inflammation (e.g., high sensitivity c-reactive protein), or subclinical disease (e.g., 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 datasets and not consistently present in all research datasets. Prior models have utilized these biomarkers in risk prediction (e.g., 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 datasets with comprehensive ascertainment of these biomarkers. Given that hsTn and BNP are clinically available, these should be considered in future risk models when 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 suggest 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 one or more of these outcomes. Therefore, the predicted risk for each composite outcome (e.g., 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 (e.g., 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 and ethnic and higher-risk subgroups (e.g., CKD, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard 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-PC	Chronic Kidney Disease Prognosis Consortium
CKM	Cardiovascular-Kidney-Metabolic
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
EMR	electronic medical records
GLP-1RA	glucagon-like peptide 1 agonists
HbA1c	hemoglobin A1c
HDL-C	High density lipoprotein-cholesterol
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
SGLT2i	sodium glucose co-transporter 2-inhibitors
TC	Total cholesterol
UACR	urine albumin-to-creatinine ratio

References

1. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Munoz D, Smith SC Jr, Virani SS, Williams KA Sr., Yeboah J and Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140:e596–e646. [PubMed: 30879355]
2. Goff DC Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr., Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr. and Tomaselli GF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49–73. [PubMed: 24222018]
3. Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC Jr., Sperling LS, Virani SS and Blumenthal RS. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Special Report From the American Heart Association and American College of Cardiology. Circulation. 2019;139:e1162–e1177. [PubMed: 30586766]

4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS and Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082–e1143. [PubMed: 30586774]
5. Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. Circulation. 2010;121:1768–77. [PubMed: 20404268]
6. Karmali KN, Goff DC Jr, Ning H and Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014;64:959–68. [PubMed: 25190228]
7. Shah NS, Molsberry R, Rana JS, Sidney S, Capewell S, O'Flaherty M, Carnethon M, Lloyd-Jones DM and Khan SS. Heterogeneous trends in burden of heart disease mortality by subtypes in the United States, 1999-2018: observational analysis of vital statistics. BMJ. 2020;370:m2688. [PubMed: 32816805]
8. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Fugar S, Generoso G, Heard DG, Hiremath S, Ho JE, Kalani R, Kazi DS, Ko D, Levine DA, Liu J, Ma J, Magnani JW, Michos ED, Mussolino ME, Navaneethan SD, Parikh NI, Poudel R, Rezk-Hanna M, Roth GA, Shah NS, St-Onge MP, Thacker EL, Virani SS, Voeks JH, Wang NY, Wong ND, Wong SS, Yaffe K, Martin SS, American Heart Association Council on E, Prevention Statistics C and Stroke Statistics S. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. 2023;147:e93–e621. [PubMed: 36695182]
9. Lloyd-Jones DM, Ning H, Labarthe D, Brewer L, Sharma G, Rosamond W, Foraker RE, Black T, Grandner MA and Allen NB. Status of cardiovascular health in US adults and children using the American Heart Association's new "Life's Essential 8" metrics: prevalence estimates from the National Health and Nutrition Examination Survey (NHANES), 2013 through 2018. Circulation. 2022;146:822–835. [PubMed: 35766033]
10. Bucholz EM, Rodday AM, Kolor K, Khoury MJ and de Ferranti SD. Prevalence and predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia (1999–2014). Circulation. 2018;137:2218–2230. [PubMed: 29581125]
11. Diaz CL, Shah NS, Lloyd-Jones DM and Khan SS. State of the Nation's Cardiovascular Health and Targeting Health Equity in the United States: A Narrative Review. JAMA Cardiol. 2021;6:963–970. [PubMed: 34009231]
12. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, Coresh J, Baker-Smith CM, Carnethon MR and Després J-P. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2023;10.1161/CIR.0000000000001186.
13. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, Coresh J, Mathew RO, Baker-Smith CM and Carnethon MR. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. Circulation. 2023;10.1161/CIR.0000000000001184.
14. Colantonio LD, Gamboa CM, Richman JS, Levitan EB, Soliman EZ, Howard G and Safford MM. Black-White Differences in Incident Fatal, Nonfatal, and Total Coronary Heart Disease. Circulation. 2017;136:152–166. [PubMed: 28696265]
15. Shah NS, Huang X, Petito LC, Bancks MP, Ning H, Cameron NA, Kershaw KN, Kandula NR, Carnethon MR, Lloyd-Jones DM and Khan SS. Social and Psychosocial Determinants of Racial and Ethnic Differences in Cardiovascular Health in the United States Population. Circulation. 2023;147:190–200. [PubMed: 36334260]
16. Shah NS, Ning H, Petito LC, Kershaw KN, Bancks MP, Reis JP, Rana JS, Sidney S, Jacobs DR Jr., Kiefe CI, Carnethon MR, Lloyd-Jones DM, Allen NB and Khan SS. Associations of Clinical and Social Risk Factors With Racial Differences in Premature Cardiovascular Disease. Circulation. 2022;146:201–210. [PubMed: 35607988]

17. Mentias A, Mujahid MS, Sumarsono A, Nelson RK, Madron JM, Powell-Wiley TM, Essien UR, Keshvani N, Girotra S, Morris AA, Sims M, Capers QT, Yancy C, Desai MY, Menon V, Rao S and Pandey A. Historical Redlining, Socioeconomic Distress, and Risk of Heart Failure Among Medicare Beneficiaries. Circulation. 2023;148:210–219. [PubMed: 37459409]

18. Khan SU, Javed Z, Lone AN, Dani SS, Amin Z, Al-Kindi SG, Virani SS, Sharma G, Blankstein R, Blaha MJ, Cainzos-Achirica M and Nasir K. Social Vulnerability and Premature Cardiovascular Mortality Among US Counties, 2014 to 2018. Circulation. 2021;144:1272–1279. [PubMed: 34662161]

19. Nelson AJ, Pagidipati NJ, Aroda VR, Cavender MA, Green JB, Lopes RD, Al-Khalidi H, Gaynor T, Kaltenbach LA and Kirk JK. Incorporating SGLT2i and GLP-1RA for cardiovascular and kidney disease risk reduction: call for action to the cardiology community. Circulation. 2021;144:74–84. [PubMed: 34228476]

20. Khan SS, Coresh J, Pencina MJ, Ndumele CE, Rangaswami J, Chow SL, Palaniappan L, Sperling L, Virani SS, Ho JE, Neeland IJ, Tuttle K, Rajgopal Singh R, Elkind MSV, Lloyd-Jones D and AMerican Heart Association. Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health: A Scientific Statement From the American Heart Association. Circulation. in press;DOI: 10.1161/CIR.0000000000001191.

21. Matsushita K, Ballew SH, Astor BC, Jong PE, Gansevoort RT, Hemmelgarn BR, Levey AS, Levin A, Wen CP, Woodward M and Coresh J. Cohort Profile: The Chronic Kidney Disease Prognosis Consortium. Int J Epidemiol. 2013;42:1660–1668. [PubMed: 23243116]

22. Wright JD, Folsom AR, Coresh J, Sharrett AR, Couper D, Wagenknecht LE, Mosley TH Jr, Ballantyne CM, Boerwinkle EA, Rosamond WD and Heiss G. The ARIC (Atherosclerosis Risk In Communities) Study: JACC Focus Seminar 3/8. J Am Coll Cardiol. 2021;77:2939–2959. [PubMed: 34112321]

23. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr., Liu K and Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988;41:1105–16. [PubMed: 3204420]

24. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, OLeary DH, Psaty B, Rautaharju P, Tracy RP and Weiler PG. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. 1991;1:263–76. [PubMed: 1669507]

25. Dawber TR, Meadors GF and Moore FE Jr., Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health. 1951;41:279–81. [PubMed: 14819398]

26. Taylor HA Jr. The Jackson Heart Study: an overview. Ethn Dis. 2005;15:S6–1-3.

27. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M and Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002;156:871–81. [PubMed: 12397006]

28. Perkins RM, Bucaloiu ID, Kirchner HL, Ashouian N, Hartle JE and Yahya T. GFR decline and mortality risk among patients with chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:1879–86. [PubMed: 21685022]

29. Labs Optum. Optum Labs and OptumLabs Data Warehouse (OLDW) Descriptions and Citation. March 2023;PDF. Reproduced with permission from OptumLabs.

30. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, Graham A, Moy CS and Howard G. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005;25:135–43. [PubMed: 15990444]

31. Denker M, Boyle S, Anderson AH, Appel LJ, Chen J, Fink JC, Flack J, Go AS, Horwitz E, Hsu CY, Kusek JW, Lash JP, Navaneethan S, Ojo AO, Rahman M, Steigerwalt SP, Townsend RR, Feldman HI and Chronic Renal Insufficiency Cohort Study I. Chronic Renal Insufficiency Cohort Study (CRIC): Overview and Summary of Selected Findings. Clin J Am Soc Nephrol. 2015;10:2073–83. [PubMed: 26265715]

32. Criqui MH, Barrett-Connor E and Austin M. Differences between respondents and non-respondents in a population-based cardiovascular disease study. Am J Epidemiol. 1978;108:367–72. [PubMed: 727205]

33. Khan SS, Ning H, Shah SJ, Yancy CW, Carnethon M, Berry JD, Mentz RJ, O'Brien E, Correa A, Suthahar N, de Boer RA, Wilkins JT and Lloyd-Jones DM. 10-Year Risk Equations for Incident Heart Failure in the General Population. J Am Coll Cardiol. 2019;73:2388–2397. [PubMed: 31097157]
34. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM and group obotSp. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987–1003. [PubMed: 12788299]
35. Vyas DA, Eisenstein LG and Jones DS. Hidden in Plain Sight - Reconsidering the Use of Race Correction in Clinical Algorithms. N Engl J Med. 2020;383:874–882. [PubMed: 32853499]
36. Langsted A, Freiberg JJ and Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation. 2008;118:2047–2056. [PubMed: 18955664]
37. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, Polkinghorne KR, Shankar A, Smith DH, Tonelli M, Warnock DG, Wen CP, Coresh J, Gansevoort RT, Hemmelgarn BR and Levey AS. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA. 2012;307:1941–51. [PubMed: 22570462]
38. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, Roderick P, Sairenchi T, Schottker B, Shankar A, Shlipak M, Tonelli M, Townend J, van Zuilen A, Yamagishi K, Yamashita K, Gansevoort R, Sarnak M, Warnock DG, Woodward M, Arnlov J and CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3:514–525. [PubMed: 26028594]
39. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, Grams ME, Greene T, Grubb A, Gudnason V, Gutierrez OM, Kalil R, Karger AB, Mauer M, Navis G, Nelson RG, Poggio ED, Rodby R, Rossing P, Rule AD, Selvin E, Seegmiller JC, Shlipak MG, Torres VE, Yang W, Ballew SH, Couture SJ, Powe NR, Levey AS and Chronic Kidney Disease Epidemiology C. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385:1737–1749. [PubMed: 34554658]
40. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F and Collaboration fCKDE. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Clin Chem. 2007;53:766–772. [PubMed: 17332152]
41. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter, Suppl. 2013;3:1–150.
42. Sumida K, Nadkarni GN, Grams ME, Sang Y, Ballew SH, Coresh J, Matsushita K, Surapaneni A, Brunskill N, Chadban SJ, Chang AR, Cirillo M, Daratha KB, Gansevoort RT, Garg AX, Iacoviello L, Kayama T, Konta T, Kovesdy CP, Lash J, Lee BJ, Major RW, Metzger M, Miura K, Naimark DMJ, Nelson RG, Sawhney S, Stempniewicz N, Tang M, Townsend RR, Traynor JP, Valdivielso JM, Wetzels J, Polkinghorne KR and Heerspink HJL. Conversion of Urine Protein-Creatinine Ratio or Urine Dipstick Protein to Urine Albumin-Creatinine Ratio for Use in Chronic Kidney Disease Screening and Prognosis : An Individual Participant-Based Meta-analysis. Ann Intern Med. 2020;173:426–435. [PubMed: 32658569]
43. Fangel MV, Nielsen PB, Kristensen JK, Larsen TB, Overvad TF, Lip GY and Jensen MB. Albuminuria and Risk of Cardiovascular Events and Mortality in a General Population of Patients with Type 2 Diabetes Without Cardiovascular Disease: A Danish Cohort Study. Am J Med. 2020;133:e269–e279. [PubMed: 32205071]
44. Lees JS, Welsh CE, Celis-Morales CA, Mackay D, Lewsey J, Gray SR, Lyall DM, Cleland JG, Gill JMR, Jhund PS, Pell J, Sattar N, Welsh P and Mark PB. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. Nat Med. 2019;25:1753–1760. [PubMed: 31700174]

45. Khan MS, Shahid I, Anker SD, Fonarow GC, Fudim M, Hall ME, Hernandez A, Morris AA, Shafi T, Weir MR, Zannad F, Bakris GL and Butler J. Albuminuria and Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2023;81:270–282. [PubMed: 36653095]
46. Stempniewicz N, Vassalotti JA, Cuddeback JK, Ciemins E, Storfer-Isser A, Sang Y, Matsushita K, Ballew SH, Chang AR, Levey AS, Bailey RA, Fishman J and Coresh J. Chronic Kidney Disease Testing Among Primary Care Patients With Type 2 Diabetes Across 24 U.S. Health Care Organizations. Diabetes Care. 2021;44:2000–2009. [PubMed: 34233925]
47. Robert Graham Center - Policy Studies in Family Medicine & Primary Care. (2018 November 5). Social deprivation index (SDI). 2023.
48. Kimenai DM, Pirondini L, Gregson J, Prieto D, Pocock SJ, Perel P, Hamilton T, Welsh P, Campbell A, Porteous DJ, Hayward C, Sattar N, Mills NL and Shah ASV. Socioeconomic Deprivation: An Important, Largely Unrecognized Risk Factor in Primary Prevention of Cardiovascular Disease. Circulation. 2022;146:240–248. [PubMed: 35748241]
49. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, Quyyumi AA, Taylor HA, Gulati M, Harold JG, Mieres JH, Ferdinand KC, Mensah GA and Sperling LS. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. Circulation. 2018;137:2166–2178. [PubMed: 29760227]
50. Yeager R, Riggs DW, DeJarnett N, Tollerud DJ, Wilson J, Conklin DJ, O'Toole TE, McCracken J, Lorkiewicz P, Xie Z, Zafar N, Krishnasamy SS, Srivastava S, Finch J, Keith RJ, DeFilippis A, Rai SN, Liu G and Bhatnagar A. Association Between Residential Greenness and Cardiovascular Disease Risk. J Am Heart Assoc. 2018;7:e009117. [PubMed: 30561265]
51. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J and Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–2081. [PubMed: 20483451]
52. Appel LJ, Grams M, Woodward M, Harris K, Arima H, Chalmers J, Yatsuya H, Tamakoshi K, Li Y and Coresh J. Estimated Glomerular Filtration Rate, Albuminuria, and Adverse Outcomes: An Individual-Participant Data Meta-Analysis. JAMA. 2023;330:1266–1277. [PubMed: 37787795]
53. Who CVD Risk Chart Working Group. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Health. 2019;7:e1332–e1345. [PubMed: 31488387]
54. Sinha A, Ning H, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM and Khan SS. Race- and sex-specific population attributable fractions of incident heart failure: a population-based cohort study from the lifetime risk pooling project. Circulation: Heart Failure. 2021;14:e008113. [PubMed: 33761754]
55. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P and St-Onge MP. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021;143:e984–e1010. [PubMed: 33882682]
56. Korn EL, Graubard BI and Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145:72–80. [PubMed: 8982025]
57. Thiebaut AC and Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med. 2004;23:3803–20. [PubMed: 15580597]
58. Cologne J, Hsu WL, Abbott RD, Ohishi W, Grant EJ, Fujiwara S and Cullings HM. Proportional hazards regression in epidemiologic follow-up studies: an intuitive consideration of primary time scale. Epidemiology. 2012;23:565–73. [PubMed: 22517300]
59. Pencina MJ, Larson MG and D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies. Stat Med. 2007;26:1343–59. [PubMed: 16955538]
60. Score working group and E. S. C. Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42:2439–2454. [PubMed: 34120177]
61. Pencina MJ and D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med. 2004;23:2109–2123. [PubMed: 15211606]

62. Pencina MJ, Steyerberg EW and D'Agostino RB Sr. Net reclassification index at event rate: properties and relationships. Stat Med. 2017;36:4455–4467. [PubMed: 27426413]

63. Woodward M Epidemiology: Study design and data analysis. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC; 2005.

64. Collins GS, Reitsma JB, Altman DG, Moons KG and Group T. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. The TRIPOD Group. Circulation. 2015;131:211–9. [PubMed: 25561516]

65. Quaggin SE and Palevsky PM. Removing race from kidney disease diagnosis. Journal of the American Society of Nephrology: JASN. 2021;32:2987. [PubMed: 34753827]

66. Agarwal MA, Fonarow GC and Ziaeian B. National Trends in Heart Failure Hospitalizations and Readmissions From 2010 to 2017. JAMA Cardiol. 2021;6:952–956. [PubMed: 33566058]

67. Freaney PM, Lloyd-Jones DM and Khan SS. Could flozins be the statins for risk-based primary prevention of heart failure? JAMA cardiology. 2021;6:741–742. [PubMed: 34009240]

68. De Lemos JA, Ayers CR, Levine BD, DeFilippi CR, Wang TJ, Hundley WG, Berry JD, Seliger SL, McGuire DK and Ouyang P. Multimodality strategy for cardiovascular risk assessment: performance in 2 population-based cohorts. Circulation. 2017;135:2119–2132. [PubMed: 28360032]

69. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR and Yancy CW. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e876–e894. [PubMed: 35363500]

70. Sinha A, Ning H, Cameron N, Bancks M, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM and Khan SS. Atherosclerotic Cardiovascular Disease or Heart Failure: First Cardiovascular Event in Adults With Prediabetes and Diabetes. J Card Fail. 2023;29:246–254. [PubMed: 36343785]

71. Hamo CE, Kwak L, Wang D, Florido R, Echouffo-Tcheugui JB, Blumenthal RS, Loehr L, Matsushita K, Nambi V, Ballantyne CM, Selvin E, Folsom AR, Heiss G, Coresh J and Ndumele CE. Heart Failure Risk Associated With Severity of Modifiable Heart Failure Risk Factors: The ARIC Study. J Am Heart Assoc. 2022;11:e021583. [PubMed: 35156388]

72. Matsushita K, Sang Y, Chen J, Ballew SH, Shlipak M, Coresh J, Peralta CA and Woodward M. Novel ″Predictor Patch″ Method for Adding Predictors Using Estimates From Outside Datasets-A Proof-of-Concept Study Adding Kidney Measures to Cardiovascular Mortality Prediction. Circ J. 2019;83:1876–1882. [PubMed: 31327793]

73. O'Brien MJ, Zhang Y, Bailey SC, Khan SS, Ackermann RT, Ali MK, Benoit SR, Imperatore G, Holliday CS and Bullard KM. Screening for prediabetes and diabetes: clinical performance and implications for health equity. Am J Prev Med. 2023;64:814–823. [PubMed: 37171231]

74. Jankowski J, Floege J, Fliser D, Böhm M and Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143:1157–1172. [PubMed: 33720773]

75. Moise N, Cené CW, Tabak RG, Young DR, Mills KT, Essien UR, Anderson CA, Lopez-Jimenez F, Epidemiology AHACo, Prevention, Hypertension Co and Council S. Leveraging implementation science for cardiovascular health equity: a scientific statement from the American Heart Association. Circulation. 2022;146:e260–e278. [PubMed: 36214131]

76. Murray R, Zimmerman T, Agarwal A, Palevsky PM, Quaggin S, Rosas SE and Kramer H. Kidney-related research in the United States: a position statement from the National Kidney Foundation and the American Society of Nephrology. Am J Kidney Dis. 2021;78:161–167. [PubMed: 33984405]

77. Khan SS, Ning H, Sinha A, Wilkins J, Allen NB, Vu THT, Berry JD, Lloyd-Jones DM and Sweis R. Cigarette Smoking and Competing Risks for Fatal and Nonfatal Cardiovascular Disease Subtypes Across the Life Course. J Am Heart Assoc. 2021;10:e021751. [PubMed: 34787470]

78. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP and Lloyd-Jones DM. Lifetime risks of cardiovascular disease. N Engl J Med. 2012;366:321–9. [PubMed: 22276822]

79. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN and Lloyd-Jones DM. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity. JAMA Cardiol. 2018;3:280–287. [PubMed: 29490333]

80. Rangaswami J and Mathew RO. Mitigating Cardiovascular Disease Risk in Patients With Type 2 Diabetes and Chronic Kidney Disease-An Unmet Need With Promising Solutions. JAMA Cardiol. 2023;8:742–743. [PubMed: 37314793]

81. Wannamethee SG, Shaper AG, Whincup PH, Lennon L and Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. Arch Intern Med. 2011;171:404–10. [PubMed: 21403036]

82. Lu Y, Li SX, Liu Y, Rodriguez F, Watson KE, Dreyer RP, Khera R, Murugiah K, D'Onofrio G, Spatz ES, Nasir K, Masoudi FA and Krumholz HM. Sex-Specific Risk Factors Associated With First Acute Myocardial Infarction in Young Adults. JAMA Netw Open. 2022;5:e229953. [PubMed: 35503221]

83. Tromp J, Paniagua SMA, Lau ES, Allen NB, Blaha MJ, Gansevoort RT, Hillege HL, Lee DE, Levy D, Vasan RS, van der Harst P, van Gilst WH, Larson MG, Shah SJ, de Boer RA, Lam CSP and Ho JE. Age dependent associations of risk factors with heart failure: pooled population based cohort study. BMJ. 2021;372:n461. [PubMed: 33758001]

84. Navar AM, Fine LJ, Ambrosius WT, Brown A, Douglas PS, Johnson K, Khera AV, Lloyd-Jones D, Michos ED, Mujahid M, Munoz D, Nasir K, Redmond N, Ridker PM, Robinson J, Schopfer D, Tate DF and Lewis CE. Earlier treatment in adults with high lifetime risk of cardiovascular diseases: What prevention trials are feasible and could change clinical practice? Report of a National Heart, Lung, and Blood Institute (NHLBI) Workshop. American journal of preventive cardiology. 2022;12:100430. [PubMed: 36439649]

85. Stone NJ, Smith SC Jr, Orringer CE, Rigotti NA, Navar AM, Khan SS, Jones DW, Goldberg R, Mora S and Blaha M. Managing atherosclerotic cardiovascular risk in young adults: JACC state-of-the-art review. J Am Coll Cardiol. 2022;79:819–836. [PubMed: 35210038]

86. Liu K, Wilkins JT, Colangelo LA and Lloyd-Jones DM. Does Lowering Low-Density Lipoprotein Cholesterol With Statin Restore Low Risk in Middle-Aged Adults? Analysis of the Observational MESA Study. Journal of the American Heart Association. 2021;10:e019695. [PubMed: 33998284]

87. Medina-Inojosa JR, Somers VK, Garcia M, Thomas RJ, Allison T, Chaudry R, Wood-Wentz CM, Bailey KR, Mulvagh SL and Lopez-Jimenez F. Performance of the ACC/AHA pooled cohort cardiovascular risk equations in clinical practice. J Am Coll Cardiol. 2023;82:1499–1508. [PubMed: 37793746]

88. Ukoha EP, Snavely ME, Hahn MU, Steinauer JE and Bryant AS. Toward the elimination of race-based medicine: replace race with racism as preeclampsia risk factor. Am J Obstet Gynecol. 2022;227:593–596. [PubMed: 35640703]

89. Khera A, Budoff MJ, O'Donnell CJ, Ayers CA, Locke J, de Lemos JA, Massaro JM, McClelland RL, Taylor A and Levine BD. Astronaut cardiovascular health and risk modification (Astro-CHARM) coronary calcium atherosclerotic cardiovascular disease risk calculator. Circulation. 2018;138:1819–1827. [PubMed: 30354651]

90. Gore MO, Ayers CR, Khera A, Defilippi CR, Wang TJ, Seliger SL, Nambi V, Selvin E, Berry JD and Hundley WG. Combining biomarkers and imaging for short-term assessment of cardiovascular disease risk in apparently healthy adults. Journal of the American Heart Association. 2020;9:e015410. [PubMed: 32698652]

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 aged 30-79 years 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 (e.g., 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 CVD 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.

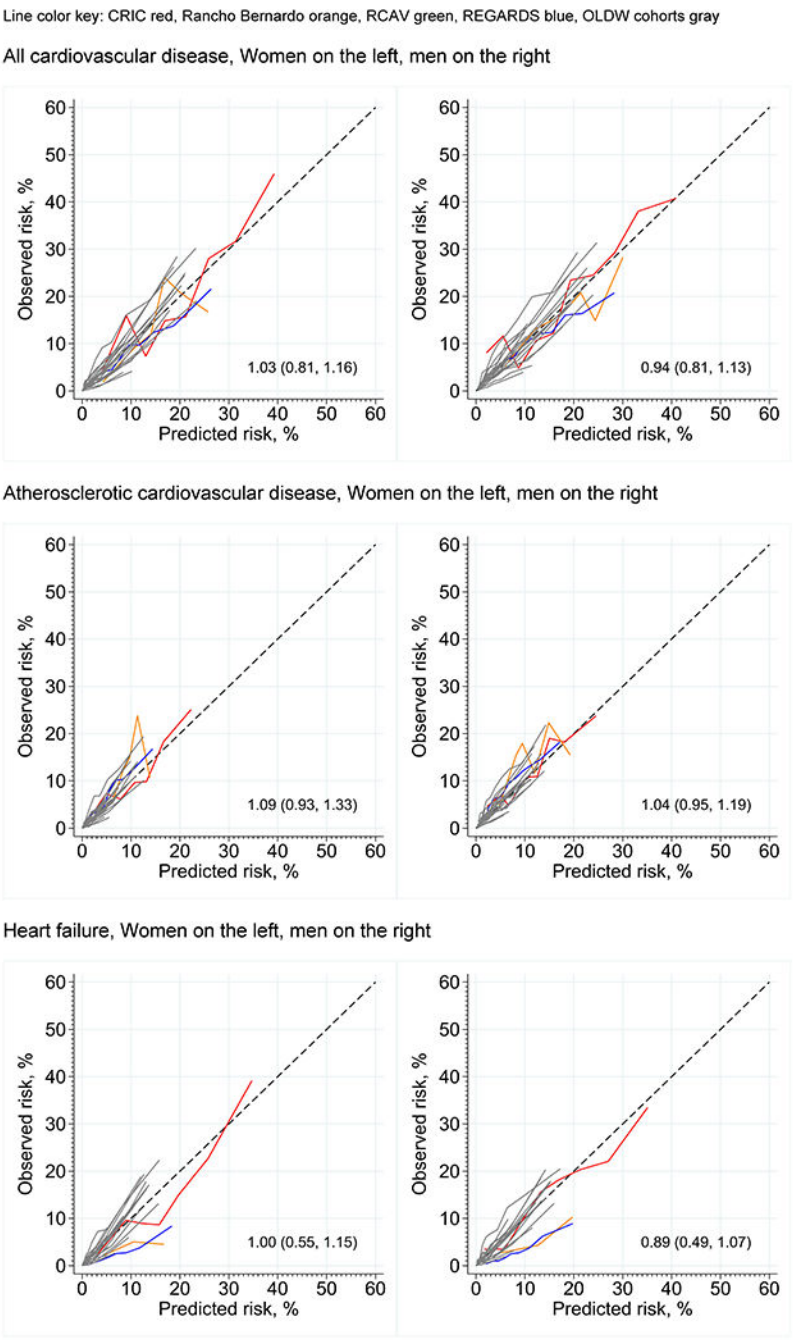
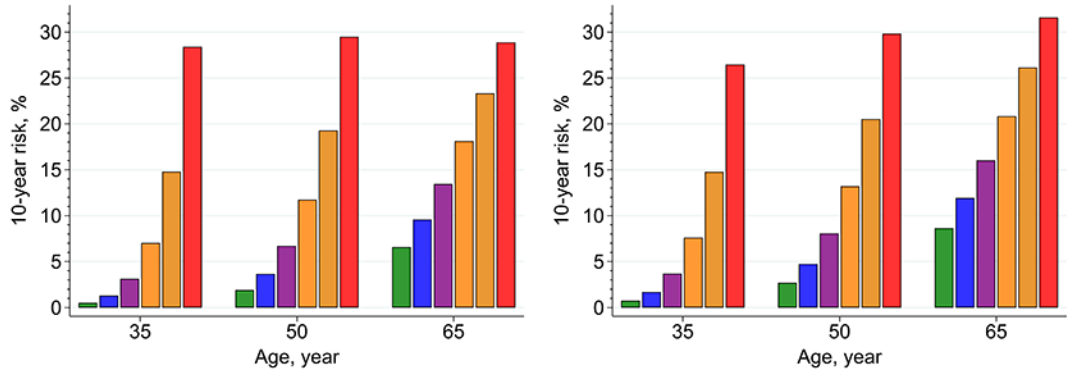


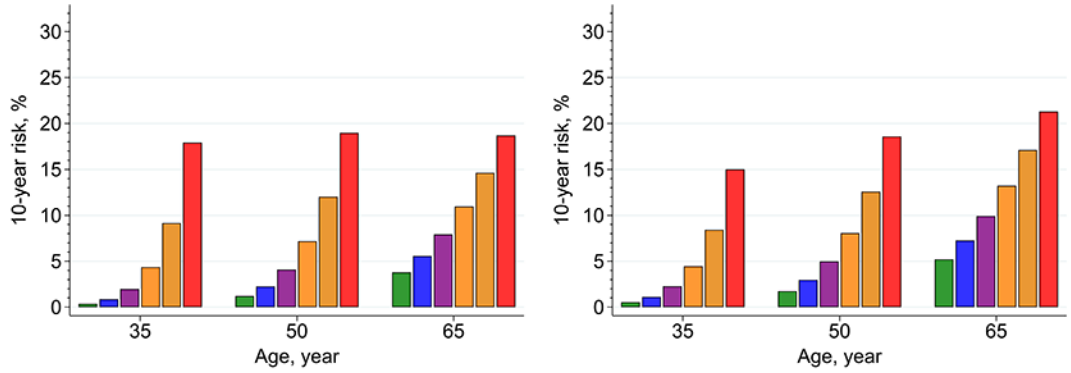
Figure 1.

Sex-specific calibration plots in the validation sample for the PREVENT base model for total CVD, ASCVD and HF. Predicted vs. observed risk by decile within each validation cohort (OLDW cohorts are shown in gray).

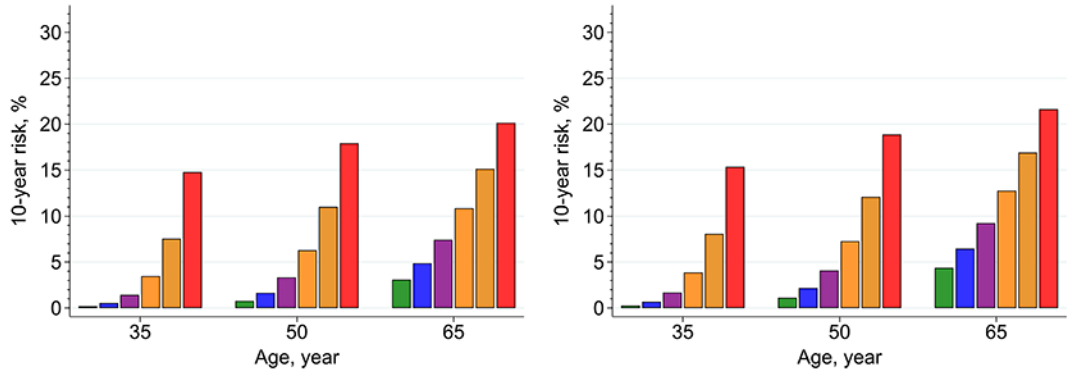
All cardiovascular disease, women on the left and men on the right



Atherosclerotic cardiovascular disease, women on the left and men on the right



Heart failure, women on the left and men on the right



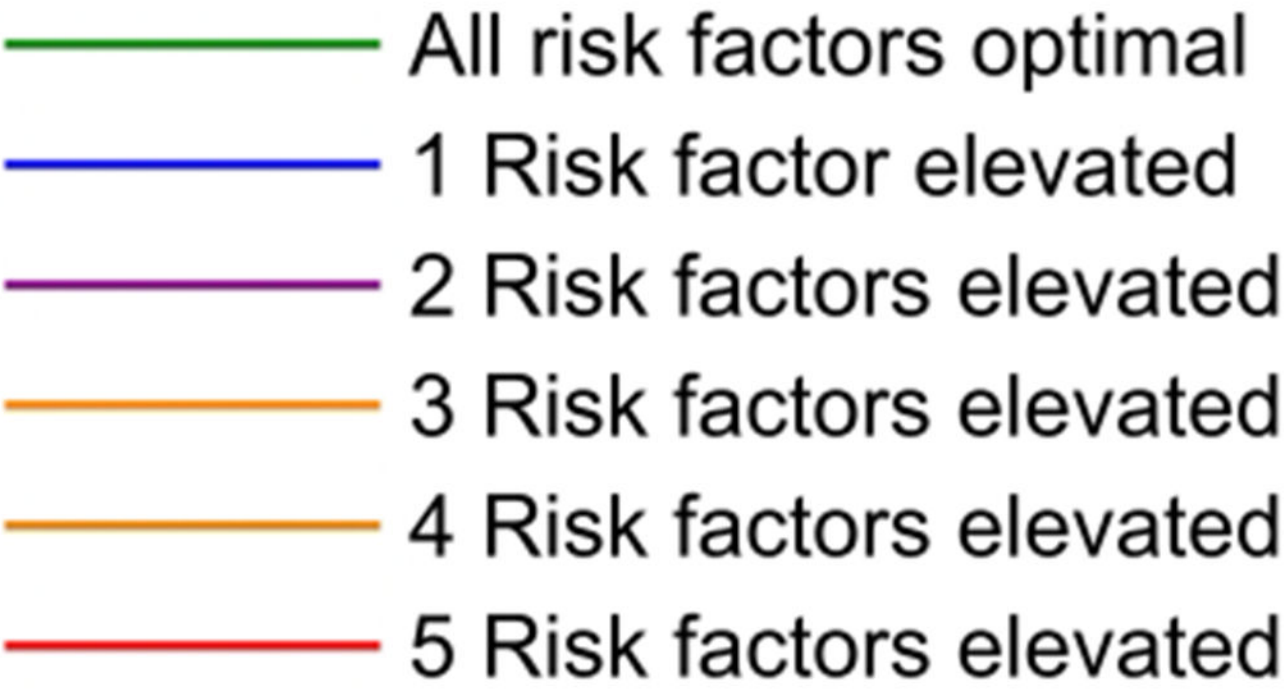
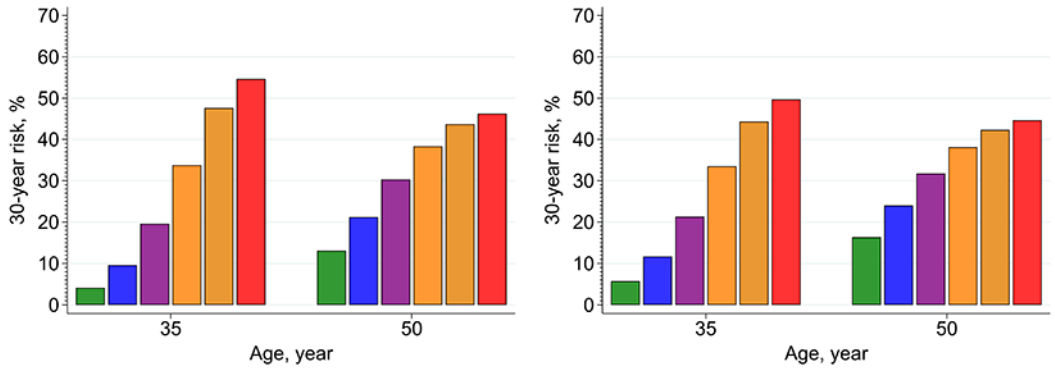


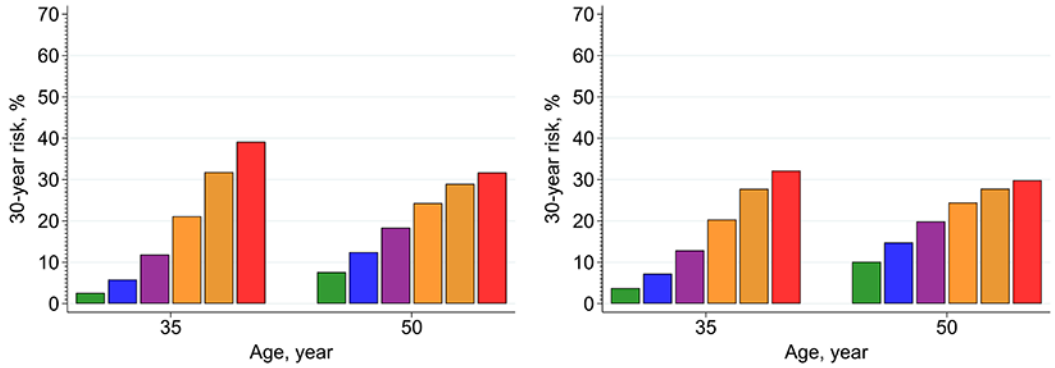
Figure 2.

Estimated 10-year risk of total cardiovascular disease, atherosclerotic cardiovascular disease and heart failure stratified by sex (females on the left and males 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-CVD death. Optimal risk factor levels are defined as non-HDL cholesterol (3.5 mmol/L; 135 mg/dl), high density lipoprotein cholesterol (1.5 mmol/L, 58 mg/dl), SBP 120 mmHg, no diabetes, no smoking, no hypertension medications, no statin use, and eGFR 90 ml/min/1.73m^2. Elevated risk factor levels included non-high density lipoprotein cholesterol (5.5 mmol/L; 213 mg/dl), SBP 150 mmHg, diabetes, or smoking and eGFR 45 ml/min/1.73m^2. For multiple elevated risk factors, the risk shown is the average risk of all combinations.

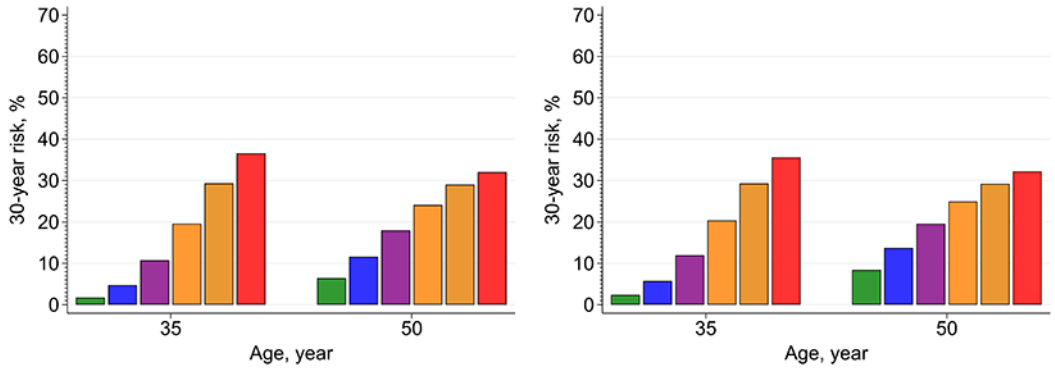
All cardiovascular disease, women on the left and men on the right



Atherosclerotic cardiovascular disease, women on the left and men on the right



Heart failure, women on the left and men on the right



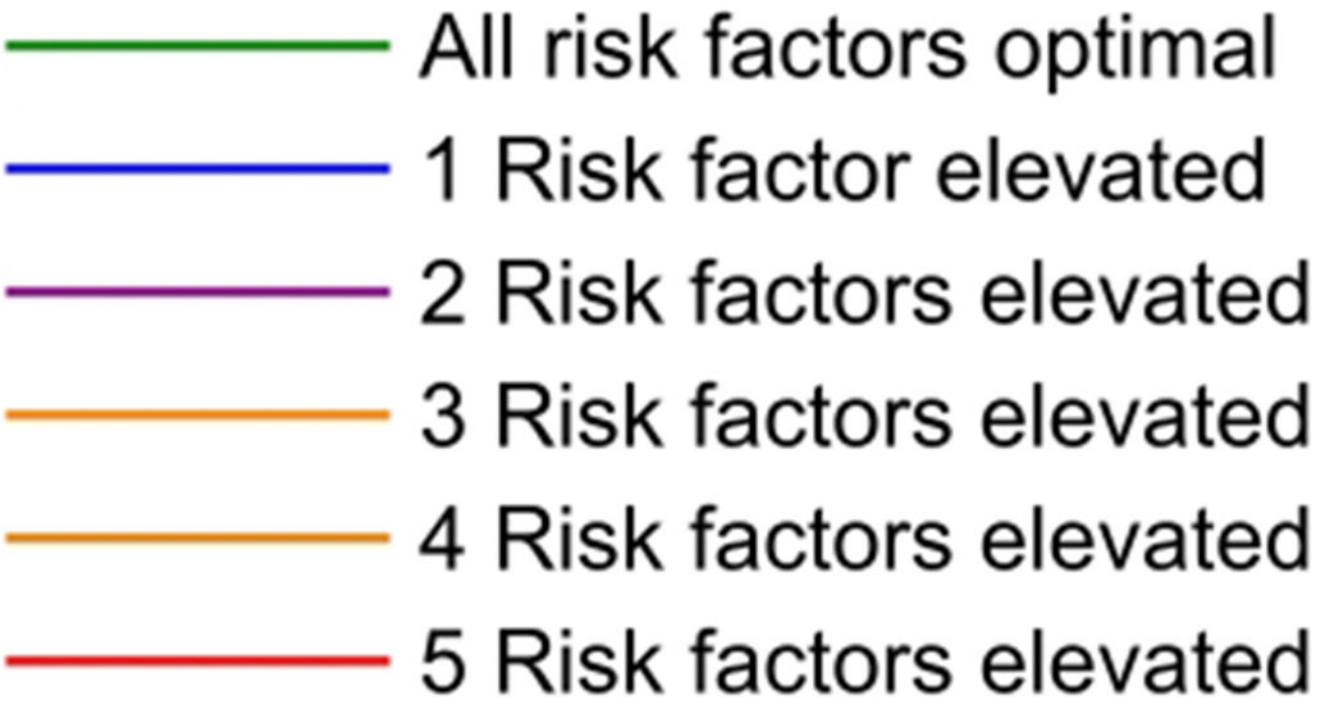


Figure 3.

Estimated 30-year risk of total cardiovascular disease, atherosclerotic cardiovascular disease and heart failure stratified by sex (females on the left and males 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-CVD death. Optimal risk factor levels are non-HDL cholesterol (3.5 mmol/L; 135 mg/dl), high density lipoprotein cholesterol (1.5 mmol/L, 58 mg/dl), SBP 120 mmHg, no diabetes, no smoking, no hypertension medications, and no statins and eGFR 90 ml/min/1.73m^2. Elevated risk factor levels considered are non-high density lipoprotein cholesterol (5.5 mmol/L; 213 mg/dl), SBP 150 mmHg, diabetes, or smoking and eGFR 45 ml/min/1.73m^2. For multiple elevated risk factors, the risk shown is the average risk of all combinations.

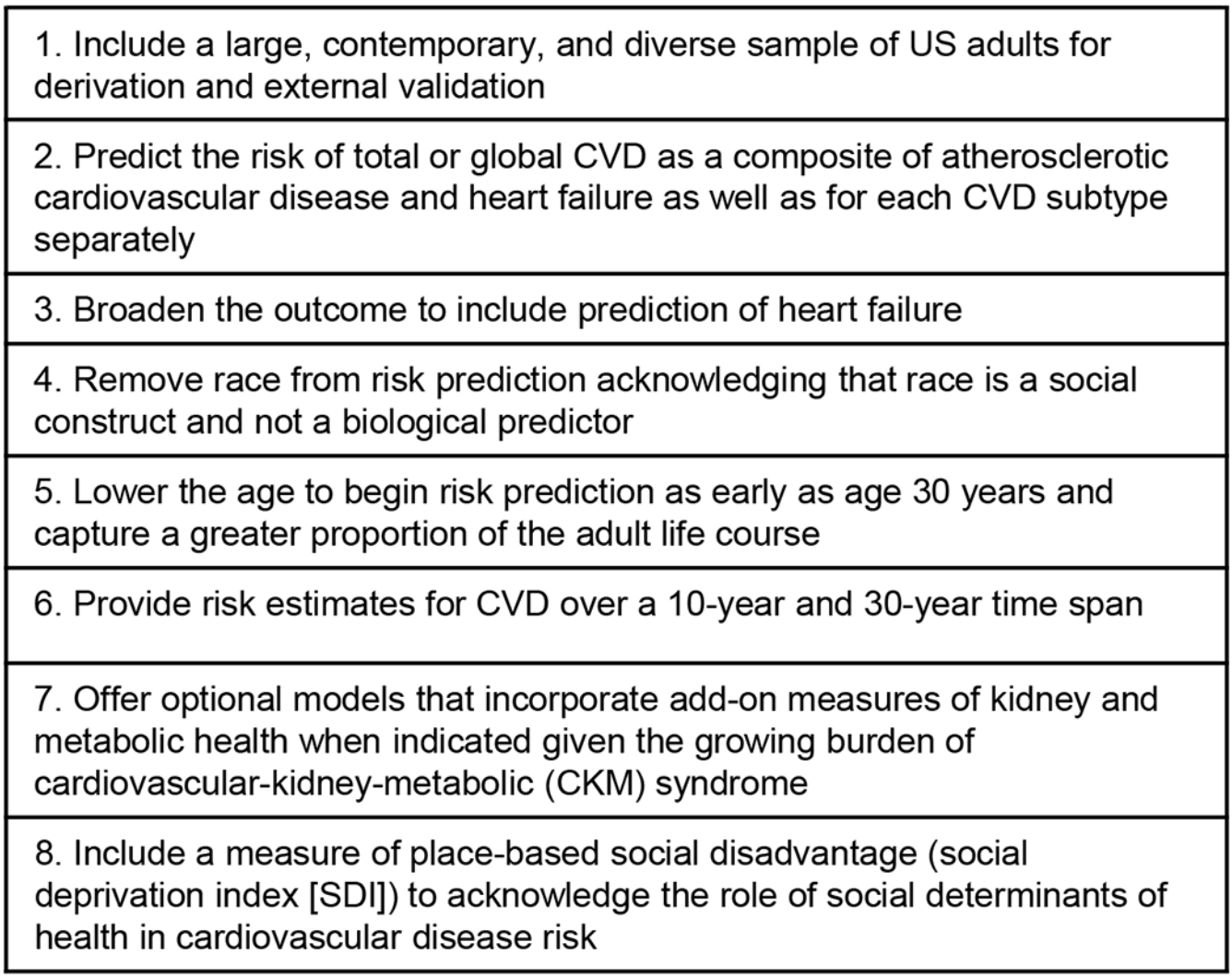


Figure 4.

Key Takeaways of the American Heart Association PREVENT Equations. The AHA PREVENT equations offer several key conceptual and methodological advances in the approach utilized to estimating cardiovascular disease risk.

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*	
	Female	**Male**	**Female**	**Male**
N, participants	**1,839,828**	**1,442,091**	**1,894,882**	**1,435,203**
N, 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/Missing	4.1%	4.6%	4.9%	5.5%
Cardiovascular Risk Factors/Predictors in PREVENT Base Model				
SBP, 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-HDL-C, mmol/L	3.4 (0.8)	3.6 (0.8)	3.5 (0.8)	3.6 (0.8)
HDL-C, mmol/L	1.5 (0.4)	1.2 (0.3)	1.5 (0.4)	1.2 (0.3)
BMI, 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%
Anti-hypertensive treatment, %	23%	27%	24%	29%
Statin treatment, %	14%	17%	14%	17%
eGFR, mean (SD), mL/min/1.73 m^2	91 (19)	91 (17)	91 (18)	91 (17)
Add-on Risk Factors/Predictors in Optional Models				
UACR, median (IQI), mg/g**	8 (8-12)	8 (8-12)	8 (8-12)	8 (8-11)
HbA1c among those with diabetes, mean (SD), %	7.3 (1.8)	7.6 (1.9)	7.2 (1.8)	7.6 (1.9)
HbA1c 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 (IQI)***	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 CVD events	53258	53403	54365	50489
ASCVD events	31812	34691	33969	33933
HF events	30957	28393	30287	25679
Deaths	84289	80897	82555	76783

Data are reported as mean (standard deviation) except where otherwise noted. UACR: urine albumin to creatinine ratio (non-missing in 40% to 46%); eGFR: estimated glomerular filtration rate; IQI interquartile interval; SDI social deprivation index (non-missing in 27% to 33%); SBP systolic blood pressure; HDL high density lipoprotein; BMI body mass index; HbA1c hemoglobin A1c (non-missing in 90% to 94% among those with diabetes and 23% to 27% among those without diabetes); CVD cardiovascular disease; ASCVD atherosclerotic cardiovascular disease; HF heart failure; SD standard deviation. Details on missing data are shown in Appendix 1, section 1.4.

To convert from mmol/L to mg/dl, multiply by 38.67.

*All participants with extreme values were excluded from the sample prior to analyses

**UACR was non-missing when urine protein to creatinine ratio or dipstick allows for conversion to UACR.[42]

***SDI was only available in the OLDW cohorts.

Table 2.

Meta-analyzed sex-specific hazard ratios (95% confidence intervals) of traditional cardiovascular risk predictors for total cardiovascular disease and cardiovascular disease subtypes in derivation samples

	Total CVD		ASCVD		HF	
	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 mmHg	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 mmHg	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/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/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						
Anti-hypertensive 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 years 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 mmHg	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)

	Total CVD		ASCVD		HF	
	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**
Age * eGFR <60, per -15 mL/min/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 (e.g. non-HDL-C per 1 mmol/L) and piece-wise linear splines (e.g. SBP ≥110 per 20 mmHg).

Models centered at age 55 years, non-HDL-C 3.5 mmol/L, HDL-C 1.3 mmol/L, SBP 130 mmHg.

* Not applicable to model development for specific outcome;

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; HF: heart failure; SBP: systolic blood pressure

Table 3.

Meta-analyzed sex-specific adjusted hazard ratios (95% confidence intervals) of the base model adding all novel cardiovascular risk predictors for total cardiovascular disease and cardiovascular disease subtypes in derivation samples.

	Total CVD		ASCVD		HF	
	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 mmHg	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 mmHg	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/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/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						
Anti-hypertensive 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 years 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)

	Total CVD		ASCVD		HF	
	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**
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/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 DM, 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 DM, 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)
Social Deprivation Index (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 (e.g., non-HDL-C per 1 mmol/L) and piece-wise linear splines (e.g., SBP ≥110 per 20 mmHg).

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; HF: heart failure; Ln: natural log; SDI: social deprivation index; SBP: systolic blood pressure; UACR: urinary albumin-to-creatinine ratio.

Models centered at age 55 years, non-HDLC 3.5 mmol/L, HDLC 1.3 mmol/L, SBP 130 mmHg, BMI 25 kg/m^2, eGFR 90 mL/min/1.73 m^2, no DM, non-smoker, no medication used, SDI decile 1-3, ACR 1 mg/g, HbA1c 5.3%

Smaller models with one set of novel risk factors at a time added to the base model are shown in Tables S2–4.

* 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 OLDW cohorts

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		HF	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Base PREVENT Model						
Number of cohorts	21	21	21	21	21	21
Number of participants	1,894,882	1435203	1894882	1435203	1894882	1435203
Number of events	50,324	46,804	31,277	31,328	27,931	23,707
C-statistic (IQI)	0.794 (0.763, 0.809)	0.757 (0.727, 0.778)	0.774 (0.743, 0.788)	0.736 (0.710, 0.755)	0.830 (0.816, 0.850)	0.809 (0.777, 0.827)
Calibration slope (IQI)	1.03 (0.81, 1.16)	0.94 (0.81, 1.13)	1.09 (0.93, 1.33)	1.04 (0.95, 1.19)	1.00 (0.55, 1.15)	0.89 (0.49, 1.07)
Pooled Cohort Equations*						
C-statistic (IQI)	0.789 (0.746, 0.802)	0.747 (0.721, 0.767)	0.772 (0.729, 0.782)	0.733 (0.701, 0.751)	0.810 (0.785, 0.838)	0.791 (0.742, 0.801)
Delta C-statistic (95% CI)**** of PREVENT minus PCEs	0.009 (0.008, 0.011)	0.008 (0.007, 0.009)	0.007 (0.006, 0.009)	0.005 (0.004, 0.006)	0.015 (0.013, 0.017)	0.022 (0.020, 0.024)
Calibration slope (IQI)	0.84 (0.65, 1.00)	0.67 (0.60, 0.81)	0.54 (0.47, 0.61)	0.50 (0.39, 0.52)	0.51 (0.28, 0.61)	0.37 (0.20, 0.47)
PREVENT Model Additionally Enhanced for Kidney-Specific Risk with UACR						
Number of cohorts	21	21	21	21	21	21
Number of participants	1,894,882	1435203	1894882	1435203	1894882	1435203
Number of events	50,324	46,804	31,277	31,328	27,931	23,707
Base model C-statistic (IQI)	0.794 (0.763, 0.809)	0.757 (0.727, 0.778)	0.774 (0.743, 0.788)	0.736 (0.710, 0.755)	0.830 (0.816, 0.850)	0.809 (0.777, 0.827)
Base model enhanced for kidney risk C-statistic (IQI)	0.796 (0.766, 0.812)	0.759 (0.735, 0.780)	0.776 (0.746, 0.790)	0.739 (0.715, 0.758)	0.833 (0.820, 0.851)	0.815 (0.786, 0.830)
Delta C-statistic (95% CI)****	0.002 (0.002, 0.003)	0.004 (0.003, 0.004)	0.002 (0.001, 0.002)	0.002 (0.002, 0.003)	0.003 (0.002, 0.003)	0.005 (0.004, 0.006)
NRI (IQI)	0.011 (−0.009, 0.023)	0.031 (0.013, 0.049)	0.022 (0.013, 0.033)	0.042 (0.023, 0.065)	0.038 (0.027, 0.069)	0.130 (0.079, 0.189)
Calibration slope (IQI)	1.03 (0.83, 1.17)	0.95 (0.85, 1.13)	1.10 (0.94, 1.34)	1.03 (0.93, 1.20)	0.99 (0.53, 1.14)	0.89 (0.48, 1.07)
PREVENT Model Enhanced for Metabolic Risk with HbA1c						
Number of cohorts	19	19	19	19	19	19
Number of participants	1893,349	1,433,735	1,893,349	1,433,735	1,893,349	1,433,735
Number of events	50,120	46,541	31,149	31,170	27,820	23,555

	Total CVD		ASCVD		HF	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Base model C-statistic (IQI)	0.795 (0.768, 0.814)	0.757 (0.734, 0.778)	0.779 (0.747, 0.790)	0.739 (0.714, 0.757)	0.837 (0.817, 0.850)	0.816 (0.786, 0.832)
Base model enhanced for metabolic risk C-statistic (IQI)	0.799 (0.771, 0.815)	0.759 (0.738, 0.780)	0.787 (0.750, 0.792)	0.740 (0.719, 0.760)	0.837 (0.818, 0.853)	0.818 (0.790, 0.835)
Delta C-statistic (95% CI) ****	0.002 (0.001, 0.003)	0.003 (0.002, 0.004)	0.003 (0.002, 0.004)	0.003 (0.002, 0.004)	0.001 (0.001, 0.002)	0.002 (0.002, 0.003)
NRI (IQI)	0.002 (−0.002, 0.005)	0.004 (0.001, 0.010)	0.005 (0.002, 0.010)	0.003 (−0.002, 0.007)	0.001 (−0.005, 0.004)	0.004 (0.003, 0.008)
Calibration slope (IQI)	1.02 (0.68, 1.16)	0.95 (0.73, 1.14)	1.10 (0.91, 1.35)	1.05 (0.92, 1.28)	0.99 (0.53, 1.18)	0.88 (0.48, 1.08)
PREVENT Model Enhanced for Social Risk with SDI **						
Number of cohorts	18	18	18	18	18	18
Number of participants	606,662	468,195	606,662	468,195	606,662	468,195
Number of events	15,059	14,084	9423	9456	8169	6970
Base model C-statistic (IQI)	0.807 (0.787, 0.816)	0.774 (0.751, 0.788)	0.793 (0.761, 0.800)	0.752 (0.737, 0.772)	0.835 (0.817, 0.852)	0.824 (0.790, 0.836)
Base model enhanced for social risk C-statistic (IQI)	0.810 (0.788, 0.817)	0.774 (0.757, 0.789)	0.796 (0.761, 0.800)	0.753 (0.737, 0.774)	0.836 (0.818, 0.853)	0.824 (0.793, 0.837)
Delta C-statistic (95% CI) ****	0.001 (0.001, 0.002)	0.002 (0.001, 0.003)	0.001 (0.000, 0.002)	0.001 (0.000, 0.002)	0.001 (0.001, 0.002)	0.002 (0.001, 0.002)
NRI (IQI)	0.003 (0.000, 0.009)	0.005 (−0.002, 0.018)	0.004 (−0.000, 0.012)	0.004 (−0.009, 0.013)	0.004 (−0.004, 0.007)	0.005 (0.001, 0.016)
Calibration slope (IQI)	1.04 (0.73, 1.20)	0.94 (0.72, 1.08)	1.09 (0.96, 1.41)	1.00 (0.80, 1.20)	0.97 (0.63, 1.14)	0.84 (0.61, 1.02)
PREVENT Model Enhanced for all novel predictors ***						
Number of cohorts	18	18	18	18	18	18
Number of participants	606,662	468,195	606,662	468,195	606,662	468,195
Number of events	15,059	14,084	9423	9456	8169	6970
Base model C-statistic (IQI)	0.807 (0.787, 0.816)	0.774 (0.751, 0.788)	0.793 (0.761, 0.800)	0.752 (0.737, 0.772)	0.835 (0.817, 0.852)	0.824 (0.790, 0.836)
Base model enhanced for all novel predictors C-statistic (IQI)	0.813 (0.794, 0.820)	0.776 (0.762, 0.793)	0.799 (0.767, 0.804)	0.755 (0.742, 0.776)	0.841 (0.828, 0.858)	0.830 (0.799, 0.843)
Delta C-statistic (95% CI) ****	0.004 (0.004, 0.005)	0.005 (0.004, 0.007)	0.004 (0.003, 0.005)	0.004 (0.002, 0.006)	0.005 (0.004, 0.006)	0.007 (0.006, 0.009)
NRI (IQI)	0.005 (−0.000, 0.018)	0.006 (0.000, 0.021)	0.009 (0.001, 0.023)	0.008 (−0.009, 0.015)	0.007 (0.004, 0.015)	0.014 (0.012, 0.030)
Calibration slope (IQI)	1.05 (0.73, 1.20)	0.95 (0.72, 1.10)	1.11 (0.96, 1.41)	1.01 (0.83, 1.18)	0.96 (0.62, 1.14)	0.81 (0.65, 1.06)

ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease; GFR: glomerular filtration rate; HF: heart failure; IQI: interquartile interval; NRI: net reclassification improvement

*Same sample as evaluated for the base PREVENT model

**SDI is only available in the OLDW cohorts

***Same sample as PREVENT model + SDI

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