Supplemental content

Joint Associations of Cardiovascular Health and Polygenic Risk With Incident Cardiovascular Disease Across the CKM Syndrome Continuum: A Prospective Cohort Study

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Reference

eMethods

Assessment of CKM Syndrome Stages[1,2]

Cardiovascular-kidney-metabolic (CKM) syndrome stages were defined among participants in the UK Biobank (UKB) cohort in accordance with the 2023 American Heart Association (AHA) Presidential Advisory on CKM Health. A total of 56 346 participants (11.2%) were excluded due to insufficient data for CKM staging. Definitions of CKM stages were adapted to variables available in the UKB database. Age, sex, race, and ethnicity were self-reported. Comorbidities (e.g., diabetes, hypertension, dyslipidemia) and cardiovascular disease (CVD) history (including coronary heart disease, stroke, atrial fibrillation, heart failure, and peripheral artery disease) were ascertained through primary care records, hospitalization data, death registries, and self-reported medical conditions. Estimated glomerular filtration rate (GFR) was calculated using the race-free CKD-EPI 2021 creatinine equation[3].

CKM Stage 0 was defined as individuals with normal body mass index (BMI; <23 kg/m² for Asian ancestry and <25 kg/m² for other racial/ethnic groups) and normal waist circumference (<80 cm for Asian women and <90 cm for Asian men; <88 cm for women and <102 cm for men of other ancestries), without meeting criteria for advanced stages.

CKM Stage 1 included individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, characterized by elevated BMI (≥23 kg/m² for Asian ancestry and ≥25 kg/m² for other groups), elevated waist circumference (≥80 cm for Asian women and ≥90 cm for Asian men; ≥88 cm for women and ≥102 cm for men of other ancestries), or prediabetes (glycated hemoglobin 5.7% to <6.5% or fasting blood glucose 100 mg/dL to <126 mg/dL), in the absence of additional metabolic

risk factors or chronic kidney disease (CKD).

CKM Stage 2 encompassed individuals with metabolic risk factors or moderate-to-high-risk CKD per Kidney Disease Improving Global Outcomes (KDIGO) criteria. Metabolic risk factors included elevated fasting triglycerides (≥135 mg/dL), hypertension, diabetes, or metabolic syndrome (defined as ≥3 of the following: waist circumference ≥88 cm for women and ≥102 cm for men (≥80 cm for women and ≥90 cm for men of Asian ancestry)[4]; HDL cholesterol <40 mg/dL for men and <50 mg/dL for women; triglycerides ≥150 mg/dL; elevated blood pressure (systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or antihypertensive medication use); or fasting glucose ≥100 mg/dL. Participants with dyslipidemia were also classified into this stage. Due to substantial missing data for urinary albumin-creatinine ratio (available in 38.9% of the cohort), CKD staging primarily relied on eGFR <60 mL/min/1.73 m^2.

CKM Stage 3 was defined by the presence of very-high-risk CKD per KDIGO criteria (GFR categories 4-5 or KDIGO heat map risk stratification) or a 10-year predicted CVD risk ≥20% using the AHA PREVENT equations[5]. The PREVENT equations were applied to adults aged 30-79 years, with participants ≥80 years conservatively assigned an age of 79 years for risk estimation. Variables outside PREVENT-defined ranges (total cholesterol: 130-320 mg/dL; HDL: 20-100 mg/dL; systolic blood pressure: 90-200 mmHg; eGFR: 14-140 mL/min/1.73 m^2) were truncated to boundary values.

CKM Stage 4 identified individuals with established CVD (coronary heart disease, stroke, atrial fibrillation, heart failure, or peripheral artery disease) documented through primary care records, hospitalization data, death registries, or self-reported diagnoses, occurring in the context of excess/dysfunctional adiposity, CKM risk factors, or CKD.

eTable 1. Definitions and UK Biobank Data-Field IDs for Baseline Covariates and Additional CKM Staging Biomarkers

Variable	Definition and Assessment	UK Biobank Data-Field ID
Sociodemographic Factors		
Age (years)	Age of the participant at the time of the baseline assessment center visit.	21003
Sex	Sex of the participant (Male, Female) as derived from NHS registry and/or touchscreen questionnaire.	31
Race and Ethnicity	Self-reported via touchscreen questionnaire (categorized as White British and Others).	21000
Townsend Deprivation Index	A composite score of socioeconomic deprivation based on four aspects (unemployment, non-car ownership, non-home ownership, and household overcrowding). Calculated from the participants' residential postcodes prior to joining the UK Biobank.	189
Education Level	Highest educational qualification achieved, self-reported via touchscreen questionnaire (categorized as Less than high school, High school or equivalent, College or above).	6138
Lifestyle Covariate		
Alcohol Consumption Status	Self-reported alcohol drinking status via touchscreen questionnaire (categorized as Never, Former, Current).	20117
Additional CKM Staging Biomarkers [a]		
Waist Circumference	Measured during the initial Assessment Centre visit using a Seca 200 cm tape measure. Units: cm.	48
Triglycerides	Measured by enzymatic analysis on a Beckman Coulter AU5800. Units: mmol/L.	30870
Systemic Inflammation & Renal Function		
C-Reactive Protein (CRP)	High-sensitivity CRP measured by enzyme immuno-inhibition analysis on a Beckman Coulter AU5800. Units: mg/L.	30710
Estimated Glomerular Filtration Rate (eGFR)	Calculated using the race-free CKD-EPI 2021 creatinine equation.	—
Serum Creatinine	Measured by enzymatic analysis on a Beckman Coulter AU5800.	30700
Genetic Covariates		

Polygenic Risk Score (PRS)	Standardized pre-computed polygenic risk score for cardiovascular disease, extracted from the UK Biobank Research Access Platform.	26201
Genotyping Batch	The batch in which the participant's DNA was genotyped, used to account for potential technical batch effects.	22000
Genetic Principal Components	The first 10 principal components derived from the genetic data, adjusted to account for population stratification.	22009

Abbreviations: CKM, cardiovascular-kidney-metabolic; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; NHS, National Health Service; PRS, polygenic risk score.

Notes: a. Additional biomarkers listed here were utilized specifically for the operationalization of the CKM staging framework (e.g., waist circumference and triglycerides are key components for defining CKM Stage 1 and Stage 2 metabolic risk factors). Definitions and data fields for metrics composing the Cardiovascular Health (Life's Essential 8) score—including physical activity, diet, smoking, sleep, BMI, blood pressure, blood glucose, and non-HDL cholesterol—are extensively detailed in **eTable 2**.

eTable 2. Definition, Measurement, and Scoring Approach for Quantifying CVH in the UK Biobank (Based on AHA Life's Essential 8)[6]

This table outlines the definitions, standardized scoring thresholds based on the latest American Heart Association (AHA) Life's Essential 8 criteria, and the specific Data-Field IDs utilized to derive each cardiovascular health (CVH) metric within the UK Biobank cohort.

CVH Metric	Method of Measurement in UK Biobank	Quantification (Points & Thresholds)	UKB Field ID(s)
Diet ***(DASH-style)***	Self-reported daily intake. DASH-style score derived from 10 food groups: Vegetable, Fruit, Fish, Unprocessed meats, Processed meats, Whole grains, Refined grains, Dairy, Sugar-sweetened beverages, Vegetable oils.	**Quantiles of DASH-style diet adherence:** • 100: ≥95th percentile (top/ideal diet) • 80: 75th–94th percentile • 50: 50th–74th percentile • 25: 25th–49th percentile • 0: 1st–24th percentile (bottom quartile)	**Touchscreen/WebQ:** • Fruit/Veg: 1289, 1299, 1309, 1319 • Meats: 1349, 1369, 1379 • Grains: 1438, 1458 • Oils: 1538 • Detailed WebQ: 100000+
Physical Activity	Self-reported minutes of moderate or vigorous PA per week. Calculated as: (Moderate days/week × mins/day) + 2 × (Vigorous days/week × mins/day).	**Minutes of moderate-(or greater) intensity activity:** • 100: ≥150 minutes • 90: 120–149 minutes • 80: 90–119 minutes • 60: 60–89 minutes • 40: 30–59 minutes • 20: 1–29 minutes • 0: 0 minutes	**Touchscreen:** • Mod days: 884 • Mod duration: 894 • Vig days: 904 • Vig duration: 914
Tobacco/Nicotine Exposure	Self-reported tobacco use (combustible & secondhand). Evaluated by smoking status, time since quitting, and exposure to smokers in the household.	**Combustible tobacco use or inhaled NDS:** • 100: Never smoker • 75: Former smoker, quit ≥5 y • 50: Former smoker, quit 1–<5 y • 25: Former smoker, quit <1 y • 0: Current smoker *(Subtract 20 pts if living with active indoor smoker)*	**Touchscreen:** • Smoking status: 20116 • Age quit: 2897 • Age attended: 21022 • Household smoker: 1259/20115

Sleep Health	Self-reported average hours of sleep per night.	**Sleep hours:** • 100: 7–<9 hours • 90: 9–<10 hours • 70: 6–<7 hours • 40: 5–<6 or ≥10 hours • 20: 4–<5 hours • 0: <4 hours	**Touchscreen:** • Sleep duration: 1160
Body Mass Index	Body mass index was calculated as weight (kg) divided by the square of height (m^2). Directly derived from physical measurements at baseline assessment.	**Body mass index (kg/m^2):** • 100: <25.0 • 70: 25.0–29.9 • 30: 30.0–34.9 • 15: 35.0–39.9 • 0: ≥40.0	**Physical Measures:** • BMI: 21001
Blood Lipids	Non-HDL cholesterol was calculated by total cholesterol minus HDL cholesterol. Serum cholesterol was measured enzymatically.	**Non-HDL cholesterol (mg/dL):** • 100: <130 • 60: 130–159 • 40: 160–189 • 20: 190–219 • 0: ≥220 *(Subtract 20 points if drug-treated)*	**Biomarkers & Meds:** • Chol: 30690 • HDL: 30760 • Meds: 6153 / 6177 / 20003
Blood Glucose	HbA1c was measured by high-performance liquid chromatography methods.	**HbA1c (%):** • 100: No diabetes and HbA1c <5.7% • 60: No diabetes and HbA1c 5.7–6.4% • 40: Diabetes with HbA1c <7.0% • 30: Diabetes with HbA1c 7.0–7.9% • 20: Diabetes with HbA1c 8.0–8.9%	**Biomarkers & Meds:** • HbA1c: 30750 • Diabetes: 2443 • Meds: 6153 / 6177 / 20003

		• 10: Diabetes with HbA1c 9.0–9.9% • 0: Diabetes with HbA1c ≥10.0% *(Subtract 20 points if drug-treated)*	
Blood Pressure	The average of all available automated measurements was used to calculate systolic and diastolic blood pressure.	**SBP and DBP (mmHg):** • 100: <120 / <80 • 75: 120–129 / <80 • 50: 130–139 or 80–89 • 25: 140–159 or 90–99 • 0: ≥160 or ≥100 *(Subtract 20 points if drug-treated)*	**Physical Measures:** • Systolic: 4080 • Diastolic: 4079 • Meds: 6153 / 6177 / 20003

Methodological Notes for Data Harmonization in the UK Biobank:

1. **Unit Conversion for Blood Lipids:** The UK Biobank reports Total Cholesterol (Field 30690) and HDL (Field 30760) in **mmol/L**. To strictly adhere to the AHA criteria (which uses **mg/dL**), the values were multiplied by **38.67** prior to calculating Non-HDL cholesterol and assigning LE8 scores.
2. **Unit Conversion for Blood Glucose (HbA1c):** The UK Biobank measures HbA1c in IFCC standard units (**mmol/mol**, Field 30750). To convert this to the NGSP standard (**%**) used by the AHA LE8 guidelines, the following formula was applied: NGSP (%) = [0.09148 × IFCC (mmol/mol)] + 2.152[7].
3. **Pharmacological Penalty (-20 points):** In alignment with LE8 protocols, a 20-point deduction was rigorously applied to the respective metric score if the target level was achieved through pharmacological intervention. Medication use was ascertained via self-reported medication codes (Data-Coding 4, Field 20003) and verbal interview data (Field 6153 for males and Field 6177 for females). The adjusted score for any metric cannot fall below 0. **For a comprehensive list of specific pharmacological agents and their corresponding numerical identifiers derived from Field 20003, please refer to eTable 3.**
4. **Blood Pressure Stratification:** The final BP tier was determined by the higher (more severe) category of either the systolic or diastolic reading, in accordance with AHA guidelines.

eTable 3. Drug Classification and Data Coding

1. Lipid-lowering medication	20003;6177;6153
Lipid Lowering Drug; Atorvastatin; Velastatin; Rosuvastatin; Simvastatin; Fluvastatin; pravastatin;Eptastatin; lipostat 10mg tablet; Atromid-s 500mg capsule; Modalim 100mg Tablet; crestor 10mg tablet; Bezafibrate; Fenofibrate; Bezafibrate product; Clofibrate; Gemfibrozil; Gemfibrozil product; bezalip; bezalip-mono 400mg m/r tablet; questran 4g/sachet powder; cholestyramine+aspartame 4g/sachet powder; lopid 300 capsule; colestipol; synvinolin; Acipimox; Nicotinic Acid Product; probucol;nicofuranose; lurselle 250mg tablet; colestid 5g/sachet granules; olbetam 250mg capsule; cholestyramine; colestyramine; cholestyramine product;	
1140861922; 1141146234; 1140910654; 1141192410; 1140861958; 1140888594; 1140888648; 1140861970; 1140910632; 140861946;1140862028; 1141192414; 1140861924; 1140861954; 1141157260; 1140861944; 1140861856; 1141157262; 1140861926; 1140861928; 1140861936; 1140861942; 140861858;1140888590;1140910652;1140861868;1140861892;1140861876; 1140861866; 1140861848; 1140861878;1140861894; 1140865576;1140909780; 1141157416;	
2. Antihypertensive medication	20003;6177;6153
capozide 50mg tablets x28; lisinopril ; carace 2.5mg tablet; zestril 2.5mg tablet; quinapril; accuretic tablet; captopril; acepril 12.5mg tablet; capoten 12.5mg tablet; captopril+hydrochlorothiazide 25mg/12.5mg tablet; innovace 2.5mg tablet; innozide tablet; enalapril maleate+hydrochlorothiazide 20mg/12.5mg tablet; coversyl 2mg tablet; ramipril; staril 10mg tablet; cilazapril; vascace 250micrograms tablet; trandolapril; gopten 500 micrograms capsule; odrik 500micrograms capsule; zestoretic 10 tablet; carace 10 plus tablet; lisinopril+hydrochlorothiazide 10mg/12.5mg tablet; indapamide; amlodipine; accupro 5mg tablet; enalapril; fosinopril; perindopril; felodipine; losartan; cozaar half strength 25mg tablet; perdix 7.5mg tablet; valsartan; diovan 40mg capsule; ecopace 12.5mg tablet; kaplon 12.5mg tablet; losartan potassium+hydrochlorothiazide 10mg/12.5mg tablet; cozaar-comp 50mg/12.5mg tablet; irbesartan; aprovel 75mg tablet; tarka 2mg/180mg m/r capsule; trandolapril+verapamil hydrochloride; candesartan cilexetil; amias 2mg tablet; imidapril hydrochloride; tanatril 5mg tablet; felodipine+ramipril; triapin mite 2.5mg/2.5mg tablet; telmisartan; hyteneze 12.5 tablet; tensopril 12.5mg tablet; capto-co 25mg/12.5mg tablet; pralenal 2.5mg tablet; eprosartan; micardis 20mg tablet; irbesartan+hydrochlorothiazide 150mg/12.5mg tablet; coaprovel 150mg/12.5mg tablet; cozaar 25mg tablet; perindopril+indapamide; coversyl plus 4mg/1.25mg tablet; telmisartan+hydrochlorothiazide 40mg/12.5mg tablet; tritace 1.25mg tablet; caralpha 10/12.5mg tablet; Olmesartan; olmetec 10mg tablet;	

lopace 2.5mg capsule; ranace 1.25mg capsule; lisicostad hct 10/12.5mg tablet; valsartan+hydrochlorothiazide 80mg/12.5mg tablet; co-diovan 80mg/12.5mg tablet; centyl 2.5mg tablet; urizide 5mg tablet; enduron 5mg tablet; esidrex k tablet; hygroton k tablet combination pack; navidrex-k tablet; serpasil-esidrex tablet; sotalol hydrochloride+hydrochlorothiazide 80mg/12.5mg tablet; metoprolol tartrate+hydrochlorothiazide 100mg/12.5mg tablet; acebutolol+hydrochlorothiazide 200mg/12.5mg tablet; methyldopa+hydrochlorothiazide 250mg/15mg tablet; quinalapril+hydrochlorothiazide 10mg/12.5mg tablet; bisoprolol fumarate+hydrochlorothiazide 10mg/6.25mg tablet; hydroflumethiazide; hydrenox 50mg tablet; mefruside; baycaron 25mg tablet; metolazone; xuret 500micrograms tablet; xipamide; diurexan 20mg tablet; aprinox 2.5mg tablet; berkozide 2.5mg tablet; neo-naclex 5mg tablet; chlorothiazide; saluric 500mg tablet; hygroton 50mg tablet; cyclopenthiazide; navidrex 500mcg tablet; hydrochlorothiazide; esidrex 25mg tablet; hydrosaluric 25mg tablet; amiloride hcl+cyclopenthiazide 2.5mg/250micrograms tablet; centyl k m/r tablet; neo-naclex k m/r tablet; neo-bendromax 2.5mg tablet; nindaxa 2.5mg tablet; chlortalidone; natramid 2.5mg tablet; opumide 2.5mg tablet; diltiazem hcl+hydrochlorothiazide 150mg/12.5mg m/r capsule; natrilix sr 1.5mg m/r tablet; triamterene+chlortalidone 50mg/50mg tablet; atenolol+chlortalidone; diuril 250mg/5ml oral suspension; Bendroflumethiazide; bendroflumethiazide+potassium 2.5mg/7.7mmol m/r tablet; nadolol+bendroflumethiazide 40mg/5mg tablet; timolol maleate+bendroflumethiazide 10mg/2.5mg tablet; atenolol+Bendroflumethiazide; brinaldix k tablet; diatensec 50mg tablet; laractone 25mg tablet; normetic tablet; synuretic tablet; vasetic co-amilozide 5/50mg tablet; pindolol; pindolol+clopamide 10mg/5mg tablet; timolol maleate+co-amilozide 10mg/2.5mg/25mg tablet; aridil 2.5mg/20mg tablet; spiro-co 25mg tablet; midamor 5mg tablet; berkamil 5mg tablet; spiroctan-m 200mg/10ml injection; spironolactone; aldactone 25mg tablet; lasix 20mg tablet; bumetanide; burinex 1mg tablet; spirospare 25mg tablet; spiretic 25mg tablet; spiroctan 25mg tablet; spirolone 25mg tablet; triamterene+benzthiazide 50mg/25mg capsule; triam-co tablet; triamterene+chlorthalidone 50mg/50mg tablet; triamterene+frusemide 50mg/40mg tablet; lasoride tablet; delvas tablet; navispare tablet; amilmaxco 5/50 tablet; burinex a tablet; triamaxco tablet; triamterene; dytac 50mg capsule; aldactide 25 tablet; amil-co tablet; dyazide tablet; dytide capsule; frumil tablet; kalspare tablet; moduret 25 tablet; fru-co tablet; moduretic tablet; amiloride hydrochloride+bumetanide 5mg/1mg tablet; burinex k m/r tablet; diumide-k continus m/r tablet; lasikal m/r tablet; bumetanide+potassium 500micrograms/7.7mmol m/r tablet; diuretic; amiloride; furosemide; amipramizide; zida-co 5mg/50mg tablet; co-triamterzide; co-amilozide; co-flumactone; co-amilofruse; amilamont 5mg/ml s/f oral solution; frusemek 5mg/40mg tablet; atenolol+co-amilozide; angiotensin ii receptor antagonist+diuretic; froop co 5mg/40mg tablet; komil 5/40 tablet; triamterene+furosemide 50mg/40mg tablet; furosemide+potassium 20mg/10mmol m/r tablet; inspra 25mg tablet; spiroprop tablet; metoros 95mg tablet; bedranol 10mg tablet; totamol 25mg tablet; arbralene 50mg tablet; kerlone 20mg tablet; trandate 50mg tablet; betaloc 50mg tablet; mepranix 50mg tablet; metoprolol; artrate+chlorthalidone 100mg/12.5mg tablet; secadrex tablet; sotazide tablet; penbutolol

sulphate+frusemide 40mg/20mg tablet; tenoret 50 tablet; tenoretic tablet; tolerzide tablet; viskaldix tablet; timolol maleate+bendrofluazide 10mg/2.5mg tablet; timolol maleate+bendrofluazide 20mg/5mg tablet; atenixco 50mg/12.5mg tablet; beta-adalat capsule; tenif capsule; co-betaloc tablet; inderetic capsule; inderex capsule; kalten capsule; lopresoretic tablet; moducren tablet; prestim tablet; atenolol+nifedipine 50mg/20mg m/r capsule; monocor 5mg tablet; emcor 10mg tablet; celectol 200mg tablet; adalat 5mg capsule; monozide 10 tablet; antipressan 25mg tablet; angilol 10mg tablet; cardinol 10mg tablet; acebutolol; atenolol; tenormin 25 tablet; vasaten 50mg tablet; apsolol 10mg tablet; propanix 10mg tablet; betadur cr 160mg m/r capsule; beta-prograne 160mg m/r capsule; berkolol 10mg tablet; half-betadur cr 80mg m/r capsule; half-inderal la 80mg m/r capsule; half beta-prograne 80mg m/r capsule; inderal 10mg tablet; concordin 5mg tablet; betaxolol; bisoprolol; celiprolol; metoprolol; labetalol; penbutolol; sotalol; timolol; adalate 10mg capsule; avlocardyl retard 160mg m/r capsule; carvedilol; totaretic 50mg/12.5mg tablet; sloprolol 80mg m/r capsule; probeta la 160mg m/r capsule; lopranol la 160mg m/r capsule; atenix 25mg tablet; co-tenidone; atenolol+chlorthalidone; atenolol+bendrofluazide; tenben capsule; half propanix la 80mg m/r capsule; half propatard la 80mg m/r capsule; nebilet 5mg tablet; eucardic 3.125 tablet; dorzolamide+timolol; cardicor 1.25mg tablet; syprol 5mg/5ml oral solution; soloc 5mg tablet; tensomex 100mg tablet; bipranix 5mg tablet; latanoprost+timolol; rapranol sr 80mg m/r capsule; vivacor 5mg tablet; calcicard 60mg tablet; lidoflazine; clinium 120mg tablet; vasad 5mg capsule; synadrin 60mg tablet; veractil 25mg tablet; nifedipine; calcilat 10mg capsule; angiopine 5mg capsule; nifensar xl 20mg m/r tablet; coracten sr 10mg m/r capsule; tildiem 60mg m/r tablet; britiazim 60mg m/r tablet; angiozem 60mg m/r tablet; adizem-60 m/r tablet; cardene 20mg capsule; isradipine; istin 5mg tablet; lacidipine; motens 2mg tablet; half securon sr 120mg m/r tablet; securon 40mg tablet; geangin 40mg tablet; berkatens 40mg tablet; cordilox 40mg tablet; parmid 10mg tablet; nimotop 30mg tablet; nimodipine; nicardipine; univer 120mg m/r capsule; verapamil; nifelease 20mg m/r tablet; slozem 120mg m/r capsule; calanif 5mg capsule; angitil sr 90 m/r capsule; adipine mr 10 m/r tablet; kentiazem 60mg m/r capsule; unipine xl 30mg m/r tablet; adizem-xl plus m/r capsule; cardilate mr 10mg m/r tablet; tensipine mr 10 m/r tablet; plendil 2.5mg m/r tablet; nisoldipine; syscor mr 10mg m/r tablet; fortipine la40 m/r tablet; slofedipine 20mg m/r tablet; nifedotard 20mr m/r tablet; verapress mr 240 m/r tablet; viazem xl 120mg m/r capsule; genalat retard 10mg m/r tablet; lercanidipine; zanidip 10mg tablet; mibefradil; calazem 60mg m/r tablet; optil 60mg m/r tablet; dilcardia sr 60mg m/r capsule; nifedipress mr 10 m/r tablet; nivaten retard 10mg m/r tablet; coroday mr 20mg m/r tablet; zemtard 120 xl m/r capsule; ethimil mr 240 m/r tablet; vertab sr 240 m/r tablet; nifopress retard 20mg m/r tablet; zildil sr 60mg m/r capsule; calchan mr 10mg m/r tablet; zemret 180 xl m/r capsule; bi-carzem sr 60mg m/r capsule; horizem sr 90mg m/r capsule; zolvera 40mg/5ml oral solution; disogram sr 60mg m/r capsule; ranvera mr 240mg m/r tablet; cabren 2.5mg m/r tablet; vera-til sr 120mg m/r tablet; kentipine mr 10mg m/r tablet; felotens xl 5mg m/r tablet; felogen xl 5mg m/r tablet; hypolar retard 10mg m/r tablet; valni 20 retard 20mg m/r tablet; cardioplen xl 5mg m/r tablet; amlostin 5mg tablet; neofel xl 5mg m/r tablet; parmid xl 5mg

m/r tablet.

1140851692; 1140860696; 1140860706; 1140860714; 1140860728; 1140860736; 1140860750; 1140860752; 1140860758; 1140860764; 1140860776; 1140860784; 1140860790; 1140860802; 1140860806; 1140860878; 1140860882; 1140860892; 1140860904; 1140860912; 1140860918; 1140864618; 1140864910; 1140864952; 1140866078; 1140879802; 1140881706; 1140888552; 1140888556; 1140888560; 1140888646; 1140916356; 1140916362; 1140923718; 1141145660; 1141145668; 1141150328; 1141150560; 1141151016; 1141151018; 1141152998; 1141153006; 1141153316; 1141153328; 1141156836; 1141156846; 1141164148; 1141164154; 1141165470; 1141165476; 1141166006; 1141167758; 1141167822; 1141170544; 1141170870; 1141171336; 1141172492; 1141172682; 1141172686; 1141179974; 1141180592; 1141180598; 1141187788; 1141188408; 1141190934; 1141193282; 1141193346; 1141199940; 1141200698; 1141200726; 1141201038; 1141201040; 1140851332; 1140851336; 1140851338; 1140851362; 1140851364; 1140851368; 1140851660; 1140860332; 1140860404; 1140860422; 1140860562; 1140860738; 1140864950; 1140866072; 1140866074; 140866084; 1140866086; 1140866092; 1140866096; 1140866108; 1140866110; 1140866128; 1140866132; 1140866136; 1140866138; 1140866140; 1140866146; 1140866156; 1140866158; 1140866162; 1140866164; 1140866168; 1140866422; 1140866440; 1140866446; 1140888918; 1140888922; 1140909706; 1140916870; 1140917068; 1140926778; 1141146378; 1141180772; 1141180778; 1141188636; 1141194794; 1141194800; 1141194804; 1141194808; 1141194810; 1140851360; 1140851418; 1140851420; 1140851428; 1140851430; 1140851436; 1140860292; 1140860322; 1140860336;1140864550; 1140864574; 1140866220; 1140866226; 1140866232; 1140866236; 1140866244; 1140866248; 1140866280; 1140866282; 1140866306; 1140866308; 1140866312; 1140866318; 1140866324; 1140866328; 1140866330; 1140866332; 1140866334; 1140866340; 1140866352; 1140866354; 1140866356; 1140866360; 1140866388; 1140866390; 1140866396; 1140866400; 1140866402; 1140866404; 1140866406; 1140866410; 1140866416; 1140866418; 1140866420; 1140866426; 1140866438; 1140866442; 1140866444; 1140866448; 1140881894; 1140888512; 1140909708; 1140909722; 1140922324; 1140923272; 1140923276; 1140923282; 1140923402; 1140927174; 1140928624; 1141146128; 1141150898; 1141167108; 1141181520; 1141195254; 1141195258; 1141201250; 1140851508; 1140851522; 1140851556; 1140860172; 1140860180; 1140860232; 1140860250; 1140860266; 1140860278; 1140860308; 1140860314; 1140860318; 1140860320; 1140860324; 1140860328; 1140860330; 1140860338; 1140860340; 1140860342; 1140860348; 1140860356; 1140860358; 1140860386; 1140860394; 1140860396; 1140860398; 1140860402; 1140860406; 1140860410; 1140860426; 1140860434; 1140860492; 1140860498; 1140861090; 1140864176; 1140864410; 1140866704; 1140866712; 1140866724; 1140866738; 1140866756; 1140866758; 1140866764; 1140866766; 1140866778; 1140866782; 1140866784; 1140866798; 1140866800; 1140866802; 1140866804; 1140867734; 1140879758;

1140879760; 1140879762; 1140879818; 1140879824; 1140879834; 1140879854; 1140879866; 1140881702; 1140881722; 1140909368; 1140916628; 1140916730; 1140916868; 1140917076; 1140922930; 1140923336; 1141146124; 1141146126; 1141146184; 1141152076; 1141156754; 1141164280; 1141168498; 1141169516; 1141171152; 1141172742; 1141182904; 1141182968; 1141184324; 1141184722; 1141187048; 1141187780; 1140851730; 1140851784; 1140851786; 1140851790; 1140851800; 1140855976; 1140861088; 1140861106; 1140861110; 1140861114; 1140861120; 1140861128; 1140861130; 1140861136; 1140861138; 1140861176; 1140861190; 1140861202; 1140861276; 1140861282; 1140866460; 1140866466; 1140866484; 1140866546; 1140866554; 1140868036; 1140872472; 1140872568; 1140879810; 1140881692; 1140888510; 1140911088; 1140911698; 1140916930; 1140917428; 1140923572; 1140923618; 1140926188; 1140926780; 1140927934; 1140927940; 1140928212; 1140928226; 1140928234; 1141145870; 1141150500; 1141150538; 1141150926; 1141151474; 1141152600; 1141153026; 1141153032; 1141153394; 1141153454; 1141156656; 1141157136; 1141157140; 1141162546; 1141166752; 1141167832; 1141169096; 1141169710; 1141169730; 1141171804; 1141173766; 1141174684; 1141175224; 1141180238; 1141184390; 1141185444; 1141187056; 1141187094; 1141187774; 1141187962; 1141188152; 1141188576; 1141188936; 1141190548; 1141199858; 1141200400; 1141200782; 1141201814	
3. Antidiabetic medication	20003; 6177; 6153
Glibornuride; daonil 5mg tablet; glutril 25mg tablet; semi-daonil 2.5mg tablet; glymidine; euglucon 2.5mg tablet; gondafon 500mg tablet ; malix 2.5mg tablet ; pramidex 500mg tablet; diabetamide 2.5mg tablet; glipizide; gliclazide; glibenese 5mg tablet; diamicron 80mg tablet; minodiab 2.5mg tablet; insulin product; tolazamide; metformin; tolanase 100mg tablet; glimepiride; tolbutamide; troglitazone; glyconon 500mg tablet; romozin 200mg tablet ; rastinon 500mg tablet ; amaryl 1mg tablet ; glucophage 500mg tablet; pioglitazone; orabet 500mg tablet; actos 15mg tablet; chlorpropamide; rosiglitazone; diabinese 100mg tablet; avandia 4mg tablet; glymese 250mg tablet; rosiglitazone 1mg / metformin 500mg tablet; glibenclamide; avandamet 1mg / 500mg tablet	
1140857494; 1140874724; 1140857496; 1140874726;1140857500;1140874728; 1140857502; 1140874732; 1140857506; 1140874736; 1140874646; 1140874744; 1140874650; 1140874746; 1140874652; 1140883066; 1140874664; 1140884600; 1140874666; 1141152590; 1140874674; 1141153254; 1140874678; 1141153262; 1140874680; 1141156984; 1140874686; 1141171646; 1140874690; 1141171652; 1140874706; 1141177600; 1140874712; 1141177606; 1140874716; 1141189090; 1140874718; 1141189094;	

eTable 4. ICD-10 Codes and UK Biobank Data-Field IDs Defining Clinical Outcomes and CKM Comorbidities

Outcome Ascertainment: First-onset cardiovascular disease (CVD), including coronary heart disease (CHD), stroke, atrial fibrillation (AF), heart failure (HF), and peripheral artery disease (PAD), was ascertained from the UK Biobank "first occurrence" dataset (Category 1712). This dataset rigorously integrates diagnoses recorded both before and after the baseline assessment visit, identified through deterministic linkage to primary care records, hospital inpatient data, death registries, and self-reported medical conditions.

For each participant, the earliest recorded diagnosis date across all available data sources was assigned as the incident date. During the baseline assessment, trained nurses also collected self-reported medical histories by asking participants whether they had ever received a physician-confirmed diagnosis of specific conditions. When both registry-derived ICD-10 codes and self-reported diagnoses were available for a specific condition, the earliest date between the two sources was prioritized. Further details on the derivation algorithms of the "first occurrence" data are available in the official UK Biobank documentation.

Disease	Data field ID [a]	ICD-10
Cardiovascular disease	Composite of the secondary outcomes below	Composite of the secondary outcomes below
Coronary heart disease	131296; 131298; 131300; 131302; 131304; 131306	I20.0;I20.1;I20.8;I20.9; I21.0; I21.1; I21.2; I21.3; I21.4; I21.9; I22.0; I22.1; I22.8; I22.9; I23; I23.0; I23.1; I23.2; I23.3; I23.5; I23.6; I23.8; I24.0; I24.1; I24.8; I24.9; I25.0; I25.1; I25.2; I25.3; I25.4; I25.5; I25.6; I25.8; I25.9;
Stroke	131360; 131362; 131364; 131366; 131368	I60.0; I60.1; I60.2; I60.3; I60.4; I60.5; I60.6; I60.7; I60.8; I60.9; I61.0; I61.1; I61.2; I61.3; I61.4; I61.5; I61.6; I61.8; I61.9; I62.1; I61.9; I63.0; I63.1; I63.2; I63.3; I63.4; I63.5; I63.6; I63.8; I63.9; I64;
Heart failure	131354	I50.0; I50.1; I50.9;

Atrial fibrillation	131350			I48.0; I48.1; I48.2; I48.3; I48.4; I48.9
PAD	131370;	131372;	131374;	I70.0; I70.00; I70.01; I70.1; I70.10; I70.11; I70.2; I70.20; I70.21; I70.8; I70.80; I70.81;
	131376;	131378;	131380;	I70.9; I70.90; I70.91; I71.0; I71.1; I71.2; I71.3; I71.4; I71.5; I71.6; I71.8; I71.9; I72.0;
	131382;	131384;	131386;	I72.1; I72.2; I72.3; I72.4; I72.5; I72.6; I72.8; I72.9; I73.0; I73.1; I73.8; I73.9; I74.0;
	131388;	131390;	131392;	I74.1; I74.2; I74.3; I74.4; I74.5; I74.8; I74.9; I77.1; I77.2; I77.3; I77.4; I77.5; I77.6;
	131394			I77.8; I77.9; I78.0; I78.1; I78.8; I78.9; I79.1; I79.2; I79.8
Comorbidities for CKM Staging [b]				
Type 2 diabetes	130708			E11.0; E11.1; E11.2; E11.3; E11.4; E11.5; E11.6; E11.7; E11.8; E11.9;
Hypertension	131286;	131288;	131290;	I10; I11.0; I11.9; I12.0; I12.9; I13.0; I13.1; I13.2 I13.9; I15.0; I15.1; I15.2; I15.8; I15.9
	131292; 131294;			
Dyslipidemia	130814			E78.0; E78.1; E78.2; E78.3; E78.4; E78.5; E78.6; E78.8; E78.9;

Abbreviations: CKM, cardiovascular-kidney-metabolic; ICD-10, International Classification of Diseases, Tenth Revision; UKB, UK Biobank.

Notes: a. Data-Field IDs refer to the specific fields within the UK Biobank Category 1712 (First occurrences) used to extract the date of the earliest known diagnosis for each respective condition. b. These conditions were utilized primarily to exclude participants with prevalent CVD at baseline and to classify participants into the progressive stages of the CKM syndrome framework (e.g., CKM Stage 2).

eTable 5. The Akaike information criterion and the Bayesian information criterion in model selection.

	Model 1	**Model 2**	**Model 3**
Cardiovascular Disease (CVD)			
AIC	965237.80	948380.27	947179.51
BIC	965254.96	949461.39	948286.37
Coronary Heart Disease (CHD)			
AIC	475587.62	466704.80	465924.54
BIC	475603.36	467696.57	466939.91
Stroke			
AIC	145180.00	142689.32	142593.91
BIC	145193.37	143531.11	143455.74
Atrial Fibrillation (AF)			
AIC	376105.83	366247.85	365499.32
BIC	376121.09	367209.48	366483.85
Heart Failure (HF)			
AIC	163910.42	159519.08	158886.44
BIC	163924.03	160376.53	159764.30
Peripheral Artery Disease (PAD)			
AIC	191034.16	188571.76	188322.76
BIC	191048.07	189447.92	189219.78

Note on Model Selection: Model 1 was unadjusted. Model 2 adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, alcohol consumption status, continuous polygenic risk score, genotyping batch, and the first 10 genetic principal components. Model 3 further adjusted for Model 2 covariates plus lipid-lowering, antihypertensive, and glucose-lowering medication use. In accordance with statistical parsimony, **Model 3** exhibited the lowest AIC and BIC values

across all cardiovascular outcomes. However, **Model 2** was predefined as the primary analytical model to avoid potential over-adjustment bias, as pharmacological interventions (antihypertensive, lipid-lowering, and glucose-lowering medications) are frequently situated on the causal pathway between cardiovascular health behaviors and clinical outcomes. The progressive decrease in AIC/BIC from Model 1 to Model 2 confirms the significant incremental explanatory power of the covariables included in our primary research framework. AIC, Akaike information criterion; BIC, Bayesian information criterion.

eTable 6. Baseline Characteristics of the Study Population Stratified by Cardiovascular-Kidney-Metabolic (CKM) Stages

	Total (N=242 951)	CKM stages			
		CKM Stage 0 (n=42 142)	CKM Stage 1 (n=47 415)	CKM Stage 2 (n=147 954)	CKM Stage 3 (n=5440)
Age, mean (SD), y	55.7 (8.1)	52.6 (7.9)	53.8 (8.0)	56.9 (7.8)	64.4 (4.5)
Sex, No. (%)					
Female	128 956 (53.1)	29 666 (70.4)	29 191 (61.6)	68 801 (46.5)	1298 (23.9)
Male	113 995 (46.9)	12 476 (29.6)	18 224 (38.4)	79 153 (53.5)	4142 (76.1)
Race and Ethnicity, No. (%)					
White (British)	231 029 (95.1)	40 900 (97.1)	44 823 (94.5)	140 185 (94.7)	5121 (94.1)
Other	11 922 (4.9)	1242 (2.9)	2592 (5.5)	7769 (5.3)	319 (5.9)
Townsend Deprivation Index, mean (SD)	-1.5 (2.9)	-1.7 (2.8)	-1.6 (2.9)	-1.5 (3.0)	-1.1 (3.1)
Education Level, No. (%)					
College or above	88 659 (36.5)	20 777 (49.3)	18 177 (38.3)	48 454 (32.7)	1251 (23.0)
High school or equivalent	126 974 (52.3)	21 365 (50.7)	24 587 (51.9)	78 425 (53.0)	2597 (47.7)
Less than high school	27 318 (11.2)	0	4651 (9.8)	21 075 (14.2)	1592 (29.3)
Smoking Status, No. (%)					
Never	135 631 (55.8)	26 696 (63.3)	28 059 (59.2)	78 951 (53.4)	1925 (35.4)
Current	23 314 (9.6)	3461 (8.2)	4001 (8.4)	14 462 (9.8)	1390 (25.6)
Former	84 006 (34.6)	11 985 (28.4)	15 355 (32.4)	54 541 (36.9)	2125 (39.1)
Alcohol Consumption, No. (%)					
Never	8723 (3.6)	1119 (2.7)	1500 (3.2)	5860 (4.0)	244 (4.5)
Current	226 824 (93.4)	39 967 (94.8)	44 753 (94.4)	137 164 (92.7)	4940 (90.8)
Former	7404 (3.0)	1056 (2.5)	1162 (2.5)	4930 (3.3)	256 (4.7)
Biomarkers and Physical Measures, mean (SD)					
C-reactive protein, mg/L	2.5 (4.1)	1.3 (3.2)	2.2 (4.0)	2.9 (4.3)	3.6 (5.4)

eGFR, mL/min/1.73 m²	95.9 (13.8)	102.4 (11.4)	98.6 (12.3)	93.8 (13.7)	80.9 (19.8)
Total cholesterol, mmol/L	5.7 (1.1)	5.5 (1.0)	5.6 (1.0)	5.9 (1.2)	5.3 (1.2)
LDL cholesterol, mmol/L	3.6 (0.8)	3.3 (0.7)	3.5 (0.7)	3.7 (0.9)	3.3 (0.9)
Glycated hemoglobin, mmol/mol	35.7 (6.2)	33.3 (3.0)	34.2 (3.7)	36.6 (6.6)	44.4 (12.1)
Medical History, No. (%)					
Hypertension	58 562 (24.1)	0	0	54 481 (36.8)	4081 (75.0)
Diabetes	14 308 (5.9)	0	0	12 757 (8.6)	1551 (28.5)
Dyslipidemia	53 700 (22.1)	0	0	50 751 (34.3)	2949 (54.2)
Medications and supplements, n (%)					
Lipid-lowering medication	28 480 (11.7)	90 (0.2)	173 (0.4)	25 817 (17.4)	2400 (44.1)
Antihypertensive medication	40 861 (16.8)	383 (0.9)	447 (0.9)	36 522 (24.7)	3509 (64.5)
Anti-diabetic medication	7227 (3.0)	8 (<0.1)	15 (<0.1)	5375 (3.6)	1829 (33.6)
Genetic Risk Assessment					
PRS, mean (SD)	-0.14 (0.97)	-0.23 (0.97)	-0.23 (0.97)	-0.09 (0.97)	-0.03 (0.97)
Low genetic risk, No. (%)	80 982 (33.3)	15 563 (36.9)	17 332 (36.6)	46 513 (31.4)	1574 (28.9)
Intermediate genetic risk, No. (%)	80 985 (33.3)	13 958 (33.1)	15 693 (33.1)	49 508 (33.5)	1826 (33.6)
High genetic risk, No. (%)	80 984 (33.3)	12 621 (29.9)	14 390 (30.3)	51 933 (35.1)	2040 (37.5)
CVH Metric Scores, mean (SD)					
Life's Essential 8 total score	70.4 (11.8)	81.3 (9.1)	73.5 (9.7)	66.8 (10.7)	57.7 (10.9)
Diet score	65.9 (27.6)	68.8 (26.8)	66.8 (27.2)	64.8 (27.8)	63.8 (28.2)
Physical activity score	85.3 (33.8)	89.5 (29.0)	87.4 (31.5)	83.5 (35.4)	80.7 (38.1)
Sleep health score	89.9 (18.0)	92.2 (15.7)	90.4 (17.3)	89.0 (18.7)	88.4 (19.7)
Nicotine exposure score	73.3 (34.9)	75.9 (34.6)	74.8 (34.4)	72.6 (34.7)	58.0 (40.5)
Blood pressure score	44.1 (30.9)	62.4 (31.4)	52.8 (30.8)	37.2 (27.7)	13.9 (19.9)
Blood lipids score	46.2 (30.3)	62.2 (28.2)	52.7 (28.9)	39.8 (29.1)	39.4 (33.2)
Body mass index score	67.0 (27.6)	99.7 (3.2)	67.1 (20.4)	58.3 (26.4)	50.7 (26.6)

Blood glucose score	91.8 (18.2)	99.8 (3.0)	95.9 (12.2)	89.2 (20.2)	66.6 (29.9)
CVH Categories, No. (%)					
Poor CVH (<50)	11 463 (4.7)	67 (0.2)	628 (1.3)	9563 (6.5)	1205 (22.2)
Intermediate CVH (50–79)	178 063 (73.3)	16 802 (39.9)	33 994 (71.7)	123 095 (83.2)	4172 (76.7)
Ideal CVH (≥80)	53 425 (22.0)	25 273 (60.0)	12 793 (27.0)	15 296 (10.3)	63 (1.2)

Abbreviations: CKM, cardiovascular-kidney-metabolic; CVH, cardiovascular health; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; LE8, Life's Essential 8; PRS, polygenic risk score.

eTable 7. Baseline Characteristics of the Study Population Stratified by Genetic Risk Categories

	Total (N=242 951)	Low Genetic Risk (n=80 982)	Intermediate Genetic Risk (n=80 985)	High Genetic Risk (n=80 984)
Age, mean (SD), y	55.7 (8.1)	55.9 (8.1)	55.8 (8.1)	55.5 (8.1)
Sex, No. (%)				
Female	128 956 (53.1)	42 464 (52.4)	42 818 (52.9)	43 674 (53.9)
Male	113 995 (46.9)	38 518 (47.6)	38 167 (47.1)	37 310 (46.1)
Race and Ethnicity, No. (%)				
White (British)	231 029 (95.1)	77 226 (95.4)	77 315 (95.5)	76 488 (94.4)
Other	11 922 (4.9)	3756 (4.6)	3670 (4.5)	4496 (5.6)
Townsend Deprivation Index, mean (SD)	-1.5 (2.9)	-1.6 (2.9)	-1.5 (2.9)	-1.5 (3.0)
Education Level, No. (%)				
College or above	88 659 (36.5)	30 780 (38.0)	29 490 (36.4)	28 389 (35.1)
High school or equivalent	126 974 (52.3)	41 601 (51.4)	42 324 (52.3)	43 049 (53.2)
Less than high school	27 318 (11.2)	8601 (10.6)	9171 (11.3)	9546 (11.8)
Smoking Status, No. (%)				
Never	135 631 (55.8)	45 621 (56.3)	45 052 (55.6)	44 958 (55.5)
Current	23 314 (9.6)	7494 (9.3)	7810 (9.6)	8010 (9.9)
Former	84 006 (34.6)	27 867 (34.4)	28 123 (34.7)	28 016 (34.6)
Alcohol Consumption, No. (%)				
Never	8723 (3.6)	2865 (3.5)	2864 (3.5)	2994 (3.7)
Current	226 824 (93.4)	75 732 (93.5)	75 629 (93.4)	75 463 (93.2)
Former	7404 (3.0)	2385 (2.9)	2492 (3.1)	2527 (3.1)
Biomarkers and Physical Measures, mean (SD)				
C-reactive protein, mg/L	2.5 (4.1)	2.4 (4.1)	2.5 (4.2)	2.5 (4.1)
eGFR, mL/min/1.73 m^2	95.9 (13.8)	95.9 (13.7)	95.9 (13.8)	95.9 (13.9)

Total cholesterol, mmol/L	5.7 (1.1)	5.7 (1.1)	5.7 (1.1)	5.8 (1.1)
LDL cholesterol, mmol/L	3.6 (0.8)	3.6 (0.8)	3.6 (0.8)	3.6 (0.9)
Glycated hemoglobin, mmol/mol	35.7 (6.2)	35.6 (5.9)	35.8 (6.3)	35.9 (6.2)
Medical History, No. (%)				
Hypertension	58 562 (24.1)	16 420 (20.3)	19 607 (24.2)	22 535 (27.8)
Diabetes	14 308 (5.9)	4162 (5.1)	4754 (5.9)	5392 (6.7)
Dyslipidemia	53 700 (22.1)	15 206 (18.8)	17 808 (22.0)	20 686 (25.5)
Medication Use, No. (%)				
Lipid-lowering medication	28 480 (11.7)	7898 (9.8)	9416 (11.6)	11 166 (13.8)
Antihypertensive medication	40 861 (16.8)	11 262 (13.9)	13 523 (16.7)	16 076 (19.9)
Anti-diabetic medication	7227 (3.0)	2072 (2.6)	2385 (2.9)	2770 (3.4)
Genetic Risk Assessment, mean (SD)				
PRS	-0.1 (1.0)	-1.2 (0.5)	-0.1 (0.2)	0.9 (0.5)
CKM Syndrome Stage, No. (%)				
Stage 0	42 142 (17.3)	15 563 (19.2)	13 958 (17.2)	12 621 (15.6)
Stage 1	47 415 (19.5)	17 332 (21.4)	15 693 (19.4)	14 390 (17.8)
Stage 2	147 954 (60.9)	46 513 (57.4)	49 508 (61.1)	51 933 (64.1)
Stage 3	5440 (2.2)	1574 (1.9)	1826 (2.3)	2040 (2.5)
CVH Metric Scores, mean (SD)				
Life's Essential 8 total score	70.4 (11.8)	71.3 (11.8)	70.4 (11.8)	69.6 (11.7)
Diet score	65.9 (27.6)	65.7 (27.6)	65.8 (27.6)	66.1 (27.5)
Physical activity score	85.3 (33.8)	85.6 (33.4)	85.3 (33.7)	84.9 (34.2)
Sleep health score	89.9 (18.0)	90.1 (17.8)	89.9 (18.0)	89.6 (18.3)
Nicotine exposure score	73.3 (34.9)	73.6 (34.8)	73.2 (34.9)	73.0 (35.0)
Blood pressure score	44.1 (30.9)	46.9 (31.4)	43.8 (30.8)	41.5 (30.2)
Blood lipids score	46.2 (30.3)	48.2 (30.4)	46.1 (30.4)	44.3 (30.1)

Body mass index score	67.0 (27.6)	68.2 (27.3)	66.9 (27.6)	66.1 (27.7)
Blood glucose score	91.8 (18.2)	92.3 (17.6)	91.8 (18.3)	91.3 (18.7)
CVH Categories, No. (%)				
Poor CVH (<50)	11 463 (4.7)	3433 (4.2)	3822 (4.7)	4208 (5.2)
Intermediate CVH (50–79)	178 063 (73.3)	57 604 (71.1)	59 503 (73.5)	60 956 (75.3)
Ideal CVH (≥80)	53 425 (22.0)	19 945 (24.6)	17 660 (21.8)	15 820 (19.5)

Abbreviations: CKM, cardiovascular-kidney-metabolic; CVH, cardiovascular health; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; LE8, Life's Essential 8; PRS, polygenic risk score.

eTable 8. Baseline Characteristics of Participants Included in the Final Analytical Cohort and Otherwise Eligible Participants Excluded Because of Incomplete Analysis Data.

Characteristic	Included (n=242,951)	Excluded (n=179,236)	SMD
Age, years	55.72 (8.10)	57.04 (8.00)	0.163
Townsend Deprivation Index	-1.53 (2.93)	-1.03 (3.24)	0.160
Body mass index, kg/m^2	27.59 (4.58)	28.23 (4.92)	0.134
Systolic blood pressure, mm Hg	139.42 (19.46)	141.41 (19.73)	0.101
Diastolic blood pressure, mm Hg	82.60 (10.62)	82.96 (10.62)	0.034
eGFR, mL/min/1.73 m^2	95.91 (13.83)	93.99 (14.73)	0.134
C-reactive protein, mg/L	2.49 (4.12)	2.87 (4.64)	0.086
Waist circumference, cm	90.73 (13.17)	91.62 (13.49)	0.067
Sex, No. (%)			0.104
Female	128,956 (53.1)	104,363 (58.2)	
Male	113,995 (46.9)	74,873 (41.8)	
Ethnicity, source-coded, No. (%)			0.184
Missing/not available	0 (0.0)	2,843 (1.6)	
Other	26,777 (11.0)	21,796 (12.2)	
White (British)	216,174 (89.0)	154,597 (86.3)	
Education, No. (%)			0.522
College/university degree	88,659 (36.5)	46,974 (26.2)	
Other qualification	126,974 (52.3)	82,678 (46.1)	
No formal qualification	27,318 (11.2)	33,887 (18.9)	
Missing/unknown	0 (0.0)	15,697 (8.8)	
Alcohol consumption, No. (%)			0.153
Never	8,723 (3.6)	9,901 (5.5)	
Previous	7,404 (3.0)	7,040 (3.9)	

Current	226,824 (93.4)	161,263 (90.0)	
Missing/unknown	0 (0.0)	1,032 (0.6)	
Smoking status, No. (%)			0.111
Never	135,631 (55.8)	97,196 (54.2)	
Previous	84,006 (34.6)	60,425 (33.7)	
Current	22,805 (9.4)	20,008 (11.2)	
Missing/unknown	509 (0.2)	1,607 (0.9)	
Hypertension, No. (%)			0.393
Yes	58,562 (24.1)	43,695 (24.4)	
No	184,389 (75.9)	122,832 (68.5)	
Missing	0 (0.0)	12,709 (7.1)	
Diabetes, No. (%)			0.104
No	228,643 (94.1)	168,072 (93.8)	
Yes	14,308 (5.9)	9,883 (5.5)	
Missing	0 (0.0)	1,281 (0.7)	
Chronic kidney disease, No. (%)			0.522
eGFR >=60	240,339 (98.9)	155,156 (86.6)	
eGFR <60	2,612 (1.1)	2,853 (1.6)	
Missing eGFR	0 (0.0)	21,227 (11.8)	
CKM stage, No. (%)			0.137
Stage 0	42,142 (17.3)	31,094 (17.3)	
Stage 1	47,415 (19.5)	46,031 (25.7)	
Stage 2	147,954 (60.9)	95,338 (53.2)	
Stage 3	5,440 (2.2)	6,773 (3.8)	

Note: Continuous variables are presented as mean (SD), and categorical variables as number (percentage). The comparison population comprised all 422,187 participants in CKM stages 0-3 who were free of baseline cardiovascular disease before exclusions for unavailable PRS, missing Life's Essential 8 or covariate data, or

incomplete survival tracking. Standardized mean differences (SMDs) were used as the primary measure of between-group imbalance; an absolute SMD of 0.10 or greater was considered potentially meaningful. P values were calculated in the analysis output but are not emphasized because the large sample size makes even small differences statistically significant.

Definitions: Hypertension was defined in the comparison file as systolic blood pressure at least 130 mm Hg, diastolic blood pressure at least 80 mm Hg, or use of antihypertensive medication. Chronic kidney disease was defined as eGFR below 60 mL/min/1.73 m^2. Some large SMDs, particularly for education, hypertension, and chronic kidney disease, partly reflect higher missingness among excluded participants.

Abbreviations: CKM, cardiovascular-kidney-metabolic; eGFR, estimated glomerular filtration rate; PRS, polygenic risk score; SMD, standardized mean difference.

eTable 9. Association of Polygenic Risk Categories With Incident Cardiovascular Outcomes Across Progressive Adjustment Models.

Outcome / Genetic Risk	No. of Events / Total Participants	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Cardiovascular Disease				
Low genetic risk	11 177 / 80 982	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate genetic risk	12 975 / 80 985	1.18 (1.15–1.21)	1.19 (1.16–1.22)	1.18 (1.15–1.21)
High genetic risk	15 203 / 80 984	1.40 (1.37–1.44)	1.46 (1.43–1.50)	1.44 (1.41–1.48)
Coronary Heart Disease				
Low genetic risk	4663 / 80 982	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate genetic risk	6314 / 80 985	1.37 (1.32–1.42)	1.38 (1.33–1.43)	1.37 (1.32–1.42)
High genetic risk	8386 / 80 984	1.85 (1.78–1.91)	1.93 (1.86–2.01)	1.91 (1.84–1.99)
Stroke				
Low genetic risk	1682 / 80 982	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate genetic risk	1913 / 80 985	1.14 (1.07–1.22)	1.14 (1.07–1.22)	1.13 (1.06–1.20)
High genetic risk	2295 / 80 984	1.37 (1.29–1.46)	1.41 (1.32–1.50)	1.39 (1.31–1.48)
Heart Failure				
Low genetic risk	1881 / 80 982	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate genetic risk	2252 / 80 985	1.18 (1.11–1.25)	1.20 (1.13–1.28)	1.19 (1.12–1.26)
High genetic risk	2535 / 80 984	1.34 (1.27–1.42)	1.40 (1.32–1.49)	1.37 (1.29–1.46)
Atrial Fibrillation				
Low genetic risk	4751 / 80 982	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate genetic risk	5071 / 80 985	1.12 (1.07–1.16)	1.12 (1.07–1.17)	1.12 (1.07–1.17)

High genetic risk	5423 / 80 984	1.30 (1.24–1.35)	1.34 (1.29–1.40)	1.33 (1.28–1.39)
Peripheral Artery Disease				
Low genetic risk	2312 / 80 982	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate genetic risk	2576 / 80 985	1.16 (1.10–1.23)	1.17 (1.10–1.24)	1.16 (1.10–1.23)
High genetic risk	2850 / 80 984	1.32 (1.25–1.40)	1.38 (1.30–1.46)	1.35 (1.28–1.44)

Abbreviations: CI, confidence interval; HR, hazard ratio.

Notes: Model 1 was unadjusted. Model 2 adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, genotyping batch, and the first 10 genetic principal components. Model 3 further adjusted for Model 2 covariates plus cardiovascular health categories (Life's Essential 8).

eTable 10. Association of Alternative Polygenic Risk Score Parameterizations With Incident Cardiovascular Disease Overall and Across CKM Stages

PRS parameterization	Overall HR (95% CI)	CKM stage 0 HR (95% CI)	CKM stage 1 HR (95% CI)	CKM stage 2 HR (95% CI)	CKM stage 3 HR (95% CI)	P for interaction
Per 1-SD increase	1.190 (1.178-1.202)	1.105 (1.066-1.145)	1.149 (1.115-1.185)	1.189 (1.175-1.203)	1.140 (1.093-1.189)	<0.001
Highest 10% vs remaining 90%	1.442 (1.400-1.485)	1.303 (1.157-1.469)	1.353 (1.226-1.495)	1.424 (1.377-1.472)	1.355 (1.205-1.524)	0.195

Note: The continuous PRS was standardized using the mean and SD of the full analytical cohort and was modeled per 1-SD increase. Extreme genetic risk was defined as a PRS at or above the 90th percentile of the analytical cohort (cutoff, 1.10527), with the remaining 90% serving as the reference group. Models were adjusted for cardiovascular health category, age, sex, race and ethnicity, education, alcohol consumption, Townsend Deprivation Index, genotyping batch, and the first 10 genetic principal components. The P values for interaction were obtained from likelihood ratio tests comparing models with and without the corresponding PRS x CKM stage interaction terms. All overall and CKM stage-specific associations shown in the table had $P < 0.001$. The numbers of participants/events were 242,951/39,355 overall; 42,142/3,094 in CKM stage 0; 47,415/4,291 in stage 1; 147,954/29,626 in stage 2; and 5,440/2,344 in stage 3.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; HR, hazard ratio; PRS, polygenic risk score; SD, standard deviation.

eTable 11. Detailed Hazard Ratios and Event Counts for the Joint Association of Cardiovascular Health, Polygenic Risk, and CKM Stage With Cardiovascular Outcomes

Outcome / CKM Stage / Genetic Risk	Ideal CVH (≥80)			Intermediate CVH (50–79)			Poor CVH (<50)		
	Events / N	HR (95% CI)	*P*	Events / N	HR (95% CI)	*P*	Events / N	HR (95% CI)	*P*
Coronary Heart Disease									
CKM Stage 0									
Low genetic risk	121 / 9767	1.00 [Reference]	—	142 / 5776	1.59 (1.25–2.02)	< .001	0 / 20	—	—
Intermediate genetic risk	139 / 8272	1.39 (1.09–1.78)	.01	151 / 5663	1.76 (1.38–2.23)	< .001	3 / 23	8.15 (2.59–25.65)	< .001
High genetic risk	167 / 7234	1.98 (1.57–2.50)	< .001	197 / 5363	2.58 (2.06–3.24)	< .001	0 / 24	—	—
CKM Stage 1									
Low genetic risk	76 / 5007	1.11 (0.84–1.48)	.46	304 / 12 119	1.50 (1.21–1.85)	< .001	12 / 206	3.36 (1.86–6.09)	< .001
Intermediate genetic risk	102 / 4266	1.83 (1.41–2.39)	< .001	409 / 11 217	2.24 (1.83–2.75)	< .001	15 / 210	4.03 (2.36–6.90)	< .001
High genetic risk	76 / 3520	1.72 (1.29–2.29)	< .001	473 / 10 658	2.85 (2.34–3.48)	< .001	16 / 212	4.80 (2.85–8.09)	< .001
CKM Stage 2									
Low genetic risk	333 / 5159	3.60 (2.93–4.44)	< .001	3011 / 38 501	3.85 (3.21–4.62)	< .001	345 / 2852	6.18 (5.02–7.61)	< .001
Intermediate genetic risk	406 / 5098	4.55 (3.71–5.57)	< .001	4218 / 41 224	5.22 (4.35–6.25)	< .001	465 / 3186	7.74 (6.33–9.46)	< .001
High genetic risk	509 / 5038	5.90 (4.83–7.19)	< .001	5711 / 43 369	7.15 (5.97–8.57)	< .001	657 / 3525	10.67 (8.79–12.97)	< .001
CKM Stage 3									
Low genetic risk	1 / 12	2.14 (0.30–15.32)	.45	215 / 1207	5.45 (4.36–6.83)	< .001	103 / 355	9.92 (7.62–12.92)	< .001
Intermediate genetic risk	6 / 24	6.83 (3.00–15.53)	< .001	304 / 1399	6.99 (5.65–8.64)	< .001	96 / 403	8.09 (6.18–10.59)	< .001
High genetic risk	10 / 27	11.54 (6.04–22.03)	< .001	426 / 1566	9.23 (7.53–11.31)	< .001	144 / 447	12.08 (9.47–15.41)	< .001
Stroke									
CKM Stage 0									
Low genetic risk	84 / 9767	1.00 [Reference]	—	87 / 5776	1.37 (1.02–1.85)	.04	0 / 20	—	—
Intermediate genetic risk	70 / 8272	1.01 (0.73–1.38)	.97	74 / 5663	1.21 (0.88–1.65)	.24	0 / 23	—	—
High genetic risk	69 / 7234	1.16 (0.85–1.60)	.35	85 / 5363	1.57 (1.16–2.12)	< .001	0 / 24	—	—

CKM Stage 1									
Low genetic risk	34 / 5007	0.72 (0.49–1.08)	.11	160 / 12 119	1.13 (0.87–1.47)	.37	4 / 206	1.58 (0.58–4.32)	.37
Intermediate genetic risk	50 / 4266	1.30 (0.92–1.85)	.14	165 / 11 217	1.29 (0.99–1.68)	.06	7 / 210	2.71 (1.25–5.86)	.01
High genetic risk	31 / 3520	1.02 (0.68–1.54)	.92	181 / 10 658	1.55 (1.20–2.01)	< .001	6 / 212	2.64 (1.15–6.05)	.02
CKM Stage 2									
Low genetic risk	106 / 5159	1.58 (1.19–2.11)	< .001	1002 / 38 501	1.80 (1.44–2.25)	< .001	93 / 2852	2.39 (1.78–3.22)	< .001
Intermediate genetic risk	122 / 5098	1.86 (1.41–2.46)	< .001	1160 / 41 224	1.97 (1.58–2.47)	< .001	132 / 3186	3.12 (2.37–4.12)	< .001
High genetic risk	128 / 5038	1.98 (1.50–2.61)	< .001	1465 / 43 369	2.48 (1.99–3.10)	< .001	136 / 3525	3.01 (2.29–3.96)	< .001
CKM Stage 3									
Low genetic risk	1 / 12	2.92 (0.40–20.99)	.29	84 / 1207	2.77 (2.04–3.77)	< .001	26 / 355	3.25 (2.09–5.07)	< .001
Intermediate genetic risk	2 / 24	2.99 (0.73–12.20)	.13	97 / 1399	2.76 (2.05–3.72)	< .001	34 / 403	3.67 (2.46–5.49)	< .001
High genetic risk	1 / 27	1.53 (0.21–11.02)	.67	145 / 1566	3.83 (2.92–5.04)	< .001	48 / 447	5.06 (3.54–7.25)	< .001
Heart Failure									
CKM Stage 0									
Low genetic risk	62 / 9767	1.00 [Reference]	—	58 / 5776	1.18 (0.82–1.69)	.37	0 / 20	—	—
Intermediate genetic risk	70 / 8272	1.38 (0.98–1.95)	.06	45 / 5663	0.95 (0.65–1.40)	.80	0 / 23	—	—
High genetic risk	48 / 7234	1.12 (0.77–1.64)	.55	69 / 5363	1.68 (1.19–2.37)	< .001	3 / 24	13.74 (4.30–43.88)	< .001
CKM Stage 1									
Low genetic risk	45 / 5007	1.25 (0.85–1.84)	.25	162 / 12 119	1.41 (1.05–1.89)	.02	3 / 206	1.39 (0.44–4.44)	.58
Intermediate genetic risk	36 / 4266	1.24 (0.82–1.86)	.31	175 / 11 217	1.71 (1.28–2.28)	< .001	4 / 210	1.78 (0.65–4.91)	.26
High genetic risk	29 / 3520	1.26 (0.81–1.97)	.30	158 / 10 658	1.70 (1.27–2.28)	< .001	3 / 212	1.56 (0.49–4.98)	.45
CKM Stage 2									
Low genetic risk	114 / 5159	2.06 (1.51–2.81)	< .001	1138 / 38 501	2.38 (1.84–3.07)	< .001	124 / 2852	3.62 (2.67–4.92)	< .001
Intermediate genetic risk	123 / 5098	2.28 (1.68–3.10)	< .001	1393 / 41 224	2.78 (2.15–3.59)	< .001	193 / 3186	5.25 (3.94–7.01)	< .001
High genetic risk	131 / 5038	2.45 (1.81–3.32)	< .001	1589 / 43 369	3.19 (2.47–4.11)	< .001	230 / 3525	6.01 (4.53–7.97)	< .001
CKM Stage 3									

Low genetic risk	0 / 12	—	—	119 / 1207	4.06 (2.98–5.54)	< .001	56 / 355	7.07 (4.91–10.18)	< .001
Intermediate genetic risk	2 / 24	2.99 (0.73–12.26)	.13	145 / 1399	4.36 (3.23–5.89)	< .001	66 / 403	7.75 (5.46–11.00)	< .001
High genetic risk	3 / 27	5.18 (1.62–16.54)	.01	207 / 1566	5.71 (4.28–7.61)	< .001	65 / 447	7.03 (4.95–9.99)	< .001
Atrial Fibrillation									
CKM Stage 0									
Low genetic risk	237 / 9767	1.00 [Reference]	—	198 / 5776	1.03 (0.86–1.25)	.72	0 / 20	—	—
Intermediate genetic risk	225 / 8272	1.17 (0.97–1.40)	.09	197 / 5663	1.07 (0.89–1.30)	.46	0 / 23	—	—
High genetic risk	188 / 7234	1.16 (0.96–1.40)	.13	187 / 5363	1.19 (0.98–1.44)	.08	1 / 24	1.05 (0.15–7.49)	.96
CKM Stage 1									
Low genetic risk	143 / 5007	1.07 (0.87–1.32)	.49	491 / 12 119	1.15 (0.98–1.34)	.08	7 / 206	0.92 (0.43–1.94)	.82
Intermediate genetic risk	145 / 4266	1.37 (1.12–1.69)	< .001	462 / 11 217	1.21 (1.04–1.42)	.02	15 / 210	1.95 (1.16–3.29)	.01
High genetic risk	107 / 3520	1.30 (1.04–1.64)	.02	453 / 10 658	1.32 (1.13–1.55)	< .001	13 / 212	1.92 (1.10–3.36)	.02
CKM Stage 2									
Low genetic risk	340 / 5159	1.67 (1.42–1.97)	< .001	2818 / 38 501	1.59 (1.39–1.82)	< .001	236 / 2852	1.99 (1.66–2.39)	< .001
Intermediate genetic risk	345 / 5098	1.75 (1.48–2.06)	< .001	3076 / 41 224	1.67 (1.46–1.91)	< .001	262 / 3186	2.04 (1.71–2.43)	< .001
High genetic risk	377 / 5038	1.98 (1.68–2.33)	< .001	3385 / 43 369	1.87 (1.64–2.14)	< .001	324 / 3525	2.43 (2.05–2.87)	< .001
CKM Stage 3									
Low genetic risk	1 / 12	0.76 (0.11–5.43)	.79	199 / 1207	1.86 (1.53–2.25)	< .001	81 / 355	2.98 (2.31–3.85)	< .001
Intermediate genetic risk	4 / 24	1.80 (0.67–4.84)	.25	259 / 1399	2.13 (1.78–2.54)	< .001	81 / 403	2.56 (1.99–3.30)	< .001
High genetic risk	5 / 27	2.50 (1.03–6.06)	.04	301 / 1566	2.31 (1.95–2.75)	< .001	82 / 447	2.50 (1.94–3.21)	< .001
Peripheral Artery Disease									
CKM Stage 0									
Low genetic risk	167 / 9767	1.00 [Reference]	—	136 / 5776	1.11 (0.89–1.40)	.35	0 / 20	—	—
Intermediate genetic risk	150 / 8272	1.08 (0.87–1.35)	.49	134 / 5663	1.14 (0.91–1.43)	.26	2 / 23	3.85 (0.95–15.53)	.06
High genetic risk	117 / 7234	0.99 (0.78–1.25)	.92	124 / 5363	1.17 (0.93–1.48)	.18	2 / 24	3.33 (0.82–13.43)	.09
CKM Stage 1									

Low genetic risk	90 / 5007	0.96 (0.74–1.24)	.75	219 / 12 119	0.79 (0.65–0.97)	.02	2 / 206	0.39 (0.10–1.58)	.19
Intermediate genetic risk	63 / 4266	0.82 (0.61–1.09)	.17	234 / 11 217	0.94 (0.77–1.14)	.51	5 / 210	0.95 (0.39–2.33)	.92
High genetic risk	68 / 3520	1.11 (0.84–1.47)	.47	219 / 10 658	0.95 (0.78–1.16)	.61	7 / 212	1.50 (0.70–3.19)	.29
CKM Stage 2									
Low genetic risk	154 / 5159	1.22 (0.98–1.52)	.07	1238 / 38 501	1.16 (0.98–1.36)	.08	151 / 2852	1.95 (1.56–2.43)	< .001
Intermediate genetic risk	171 / 5098	1.39 (1.12–1.72)	< .001	1461 / 41 224	1.30 (1.10–1.53)	< .001	165 / 3186	1.92 (1.55–2.39)	< .001
High genetic risk	177 / 5038	1.45 (1.18–1.80)	< .001	1694 / 43 369	1.49 (1.27–1.75)	< .001	201 / 3525	2.19 (1.78–2.69)	< .001
CKM Stage 3									
Low genetic risk	1 / 12	1.56 (0.22–11.15)	.66	102 / 1207	1.90 (1.48–2.44)	< .001	51 / 355	3.47 (2.53–4.77)	< .001
Intermediate genetic risk	1 / 24	0.85 (0.12–6.09)	.87	126 / 1399	2.05 (1.62–2.59)	< .001	64 / 403	3.95 (2.95–5.29)	< .001
High genetic risk	2 / 27	1.75 (0.43–7.06)	.43	178 / 1566	2.65 (2.13–3.29)	< .001	60 / 447	3.36 (2.49–4.53)	< .001

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVH, cardiovascular health; HR, hazard ratio; PRS, polygenic risk score.

Notes: Cardiovascular health (CVH) categories were defined according to the American Heart Association Life's Essential 8 scoring system: poor (<50), intermediate (50–79), and ideal (≥80).

Hazard ratios (HRs) and 95% CIs were estimated using multivariable Cox proportional hazards models adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, alcohol consumption status, genotyping batch, and the first 10 genetic principal components (Model 2).

Global Reference Group Strategy: To provide a consistent benchmark for risk assessment across multiple clinical endpoints and the entire cardiometabolic-genetic continuum, participants in **CKM Stage 0 with low genetic risk and ideal CVH** served as the universal reference group (HR = 1.00) for all calculations within each specific outcome (e.g., CHD, Stroke, Heart Failure).

Data Interpretation for Sparse Cells: Dashes (—) signify that HRs and *P* values could not be reliably estimated due to zero incident events in those specific sub-strata. In CKM Stage 0 and Stage 1, the sample sizes for the "Poor CVH" categories are inherently small (N = 20 to 24 at Stage 0). These wide confidence intervals and instances of zero events reflect the biological reality that metabolic health is strongly correlated with overall cardiovascular health behaviors; individuals clinically classified as having Stage 0 CKM syndrome (absence of metabolic risk factors) rarely exhibit extremely poor CVH metrics.

Multiple Testing Correction: To account for the evaluation of multiple secondary endpoints, the Benjamini-Hochberg procedure was applied to control the false discovery rate (FDR) across the 36 cross-categories for each outcome. The *P* values presented are nominal; however, associations that survived FDR correction are highlighted in the main text Results and Discussion.

eTable 12. Ten-Year Cumulative Incidence of Incident Cardiovascular Disease by Polygenic Risk Category Within CKM Stages, Accounting for Competing All-Cause Mortality.

CKM stage	Low PRS 10-year risk (95% CI)	Intermediate PRS 10-year risk (95% CI)	High PRS 10-year risk (95% CI)	High-Low absolute risk difference (95% CI), percentage points	Gray test P value
0	4.37% (4.05%–4.69%)	4.68% (4.33%–5.03%)	4.98% (4.60%–5.36%)	0.61 (0.12–1.11)	<.001
1	5.14% (4.81%–5.46%)	5.93% (5.56%–6.30%)	6.30% (5.91%–6.70%)	1.17 (0.65–1.68)	<.001
2	11.57% (11.28%–11.86%)	13.17% (12.87%–13.47%)	15.41% (15.10%–15.72%)	3.83 (3.41–4.26)	<.001
3	27.32% (25.12%–29.52%)	30.07% (27.96%–32.17%)	33.24% (31.19%–35.28%)	5.92 (2.91–8.92)	<.001

Note: Values are unadjusted cumulative incidence estimates at 10 years. Incident CVD was the event of interest, and all-cause death before incident CVD was treated as the competing event. Low, intermediate, and high genetic risk were defined by tertiles of the CVD-specific PRS in the analytical cohort. The high–low absolute risk difference was calculated as the cumulative incidence in the high-PRS group minus that in the low-PRS group within each CKM stage and is reported in percentage points. Pointwise 95% CIs were derived from the estimated variance of the cumulative incidence function. Gray's test assessed the overall equality of the three PRS-specific cumulative incidence functions within each CKM stage.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; PRS, polygenic risk score.

eTable 13. Association Between the Behavioral Cardiovascular Health Score and Incident Cardiovascular Disease Overall and Across CKM Stages.

Population	N	CVD events	HR per 10-point increase (95% CI)	P value	P for interaction
Overall	242,951	39,355	0.923 (0.917-0.929)	<0.001	0.241
CKM stage 0	42,142	3,094	0.944 (0.921-0.967)	<0.001	
CKM stage 1	47,415	4,291	0.946 (0.927-0.966)	<0.001	
CKM stage 2	147,954	29,626	0.935 (0.929-0.942)	<0.001	
CKM stage 3	5,440	2,344	0.929 (0.907-0.951)	<0.001	

Note: The behavioral cardiovascular health score was calculated as the unweighted mean of the diet quality, physical activity, nicotine exposure, and sleep health component scores and was modeled per 10-point increase. Models were adjusted for age, sex, race and ethnicity, education, alcohol consumption, Townsend Deprivation Index, continuous polygenic risk score, genotyping batch, and the first 10 genetic principal components. The P value for interaction was obtained from a likelihood ratio test comparing models with and without the behavioral cardiovascular health score x CKM stage interaction terms.

Abbreviations: CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; HR, hazard ratio; PRS, polygenic risk score.

eTable 14. Association of Cardiovascular Health Categories With Incident Cardiovascular Outcomes (Model 4).

Outcome (Model 4)	Poor CVH (<50)	Intermediate CVH (50–79)	Ideal CVH (≥80)
	HR (Reference)	HR (95% CI)	HR (95% CI)
Cardiovascular Disease	1.00	0.72 (0.69-0.74)	0.66 (0.63-0.69)
Coronary Heart Disease	1.00	0.69 (0.66-0.73)	0.58 (0.54-0.62)
Stroke	1.00	0.76 (0.69-0.84)	0.64 (0.57-0.73)
Heart Failure	1.00	0.62 (0.57-0.67)	0.52 (0.47-0.59)
Atrial Fibrillation	1.00	0.81 (0.76-0.87)	0.85 (0.78-0.91)
Peripheral Artery Disease	1.00	0.68 (0.63-0.74)	0.69 (0.62-0.76)

Abbreviations: CI, confidence interval; CVH, cardiovascular health; HR, hazard ratio.

Notes: Model 4 adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, alcohol consumption, continuous polygenic risk score, genotyping batch, 10 genetic principal components, medication use (lipid-lowering, antihypertensive, and glucose-lowering), **C-reactive protein, and cardiovascular-kidney-metabolic (CKM) stages**.

eTable 15. Sensitivity Analyses of the Association Between Cardiovascular Health and Incident Cardiovascular Outcomes Excluding Events Within the First 1 and 3 Years of Follow-up.

Outcome / CVH Categories	Full Cohort	Excluding First 1 Year	Excluding First 3 Years
Cardiovascular Disease			
No. of Events / Total Participants	39 355/242 951	37 490/241 086	33 102/236 698
Poor CVH	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate CVH	0.62 (0.60 - 0.64)	0.62 (0.60 - 0.65)	0.64 (0.61 - 0.67)
Ideal CVH	0.47 (0.45 - 0.49)	0.47 (0.45 - 0.49)	0.48 (0.46 - 0.50)
Coronary Heart Disease			
No. of Events / Total Participants	19 363/242 951	18 457/242 045	16 207/239 795
Poor CVH	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate CVH	0.58 (0.55 - 0.61)	0.58 (0.55 - 0.61)	0.60 (0.57 - 0.63)
Ideal CVH	0.35 (0.33 - 0.37)	0.35 (0.33 - 0.38)	0.37 (0.34 - 0.39)
Stroke			
No. of Events / Total Participants	5890/242 951	5696/242 757	5233/242 294
Poor CVH	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate CVH	0.66 (0.60 - 0.73)	0.66 (0.60 - 0.73)	0.68 (0.61 - 0.75)
Ideal CVH	0.47 (0.42 - 0.53)	0.48 (0.42 - 0.54)	0.48 (0.42 - 0.54)
Heart Failure			
No. of Events / Total Participants	6668/242 951	6563/242 846	6214/242 497
Poor CVH	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate CVH	0.50 (0.46 - 0.54)	0.50 (0.46 - 0.54)	0.51 (0.47 - 0.56)
Ideal CVH	0.33 (0.30 - 0.37)	0.33 (0.30 - 0.37)	0.35 (0.31 - 0.39)
Atrial Fibrillation			
No. of Events / Total Participants	15 245/242 951	14 721/242 427	13 407/241 113

Poor CVH	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate CVH	0.73 (0.69 - 0.78)	0.74 (0.69 - 0.79)	0.75 (0.70 - 0.80)
Ideal CVH	0.66 (0.61 - 0.71)	0.66 (0.61 - 0.71)	0.66 (0.61 - 0.72)
Peripheral Artery Disease			
No. of Events / Total Participants	7738/242 951	7403/242 616	6644/241 857
Poor CVH	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate CVH	0.58 (0.53 - 0.63)	0.58 (0.54 - 0.63)	0.58 (0.53 - 0.63)
Ideal CVH	0.53 (0.49 - 0.59)	0.53 (0.48 - 0.59)	0.51 (0.46 - 0.57)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; CVH, cardiovascular health; HR, hazard ratio.

Notes: Hazard ratios (HRs) and 95% CIs were estimated using multivariable Cox proportional hazards models. All models were adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, alcohol consumption status, continuous polygenic risk score, genotyping batch, and the first 10 genetic principal components (Model 2).

Sensitivity analyses were performed by excluding participants who experienced an incident cardiovascular event within the first 1 year and the first 3 years of follow-up, respectively, to minimize the potential impact of reverse causation bias (i.e., the possibility that subclinical or undiagnosed disease at baseline influenced the participants' cardiovascular health metrics). All *P* values for the associations in the full and restricted cohorts remained < .001.

eTable 16. Independent and Stratified Subdistribution Hazard Ratios (sdHRs) for Incident Cardiovascular Outcomes.

Variables	Cardiovascular Disease	Coronary Heart Disease	Heart Failure	Stroke	Atrial Fibrillation	Peripheral Artery Disease
Cardiovascular Health (CVH)						
Categorical						
Poor CVH (<50)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Intermediate CVH (50-79)	0.62 (0.60-0.65)***	0.58 (0.55-0.61)***	0.50 (0.46-0.54)***	0.66 (0.60-0.73)***	0.74 (0.69-0.78)***	0.58 (0.54-0.63)***
Ideal CVH (≥80)	0.47 (0.45-0.49)***	0.35 (0.33-0.37)***	0.33 (0.30-0.37)***	0.47 (0.42-0.53)***	0.66 (0.61-0.71)***	0.54 (0.49-0.59)***
Continuous (per 1-SD increase)						
Overall Cohort	0.80 (0.79-0.81)***	0.74 (0.73-0.75)***	0.71 (0.69-0.73)***	0.81 (0.78-0.83)***	0.88 (0.87-0.90)***	0.82 (0.80-0.84)***
Stratified by CKM Stages						
CKM Stage 0	0.91 (0.87-0.96)***	0.80 (0.73-0.87)***	0.92 (0.79-1.07)	0.79 (0.70-0.89)***	1.09 (1.00-1.18)*	0.88 (0.80-0.96)**
CKM Stage 1	0.89 (0.85-0.92)***	0.82 (0.77-0.87)***	0.88 (0.79-0.97)*	0.85 (0.77-0.94)**	0.96 (0.90-1.02)	0.94 (0.87-1.03)
CKM Stage 2	0.86 (0.85-0.88)***	0.83 (0.82-0.85)***	0.76 (0.74-0.78)***	0.88 (0.85-0.91)***	0.93 (0.91-0.95)***	0.85 (0.83-0.88)***
CKM Stage 3	0.84 (0.80-0.88)***	0.86 (0.81-0.91)***	0.80 (0.74-0.88)***	0.86 (0.77-0.96)**	0.94 (0.87-1.01)	0.78 (0.71-0.86)***
Polygenic Risk Score (PRS)						
Categorical						
Low Genetic Risk	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Intermediate Genetic Risk	1.18 (1.15-1.21)***	1.36 (1.31-1.41)***	1.19 (1.12-1.27)***	1.13 (1.06-1.21)***	1.07 (1.03-1.12)***	1.11 (1.05-1.18)***
High Genetic Risk	1.44 (1.41-1.48)***	1.88 (1.81-1.95)***	1.38 (1.30-1.46)***	1.39 (1.30-1.48)***	1.20 (1.16-1.25)***	1.25 (1.19-1.33)***
Continuous (per 1-SD increase)						
Overall Cohort	1.19 (1.18-1.20)***	1.34 (1.32-1.36)***	1.16 (1.13-1.19)***	1.17 (1.14-1.20)***	1.09 (1.07-1.11)***	1.12 (1.09-1.15)***

Notes: For each outcome, the specified incident cardiovascular outcome was the event of interest, and all-cause death before that outcome was treated as the competing event. CVH models adjusted for continuous PRS, age, sex, race and ethnicity, education, alcohol consumption, Townsend Deprivation Index, genotyping batch, and the first 10 genetic principal components. PRS models adjusted for CVH category and the same covariates. Subdistribution hazard ratios and robust 95% CIs were estimated from Fine–Gray expanded data using weighted Cox models with participant-level clustered robust standard errors. Participants with an incident outcome but

missing outcome time were excluded only from the corresponding outcome-specific analysis. *P<.05; **P<.01; ***P<.001.

Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; HF, heart failure; PAD, peripheral artery disease; PRS, polygenic risk score; SD, standard deviation; sdHR, subdistribution hazard ratio.

eTable 17. Distribution and Diagnostics of the Normalized Stabilized IPSW.

Diagnostic	Normalized raw IPSW	Normalized IPSW truncated at 1st-99th percentiles
Mean	1.000	1.000
SD	0.183	0.175
Minimum	0.701	0.757
1st percentile	0.755	0.757
Median	0.958	0.960
95th percentile	1.352	1.355
99th percentile	1.636	1.639
Maximum	3.609	1.639
Weight >5, No.	0	0
Weight >10, No.	0	0
Effective sample size	235,049	235,750

Note: The inclusion model converged without evidence of structural separation or practical positivity violations. Predicted inclusion probabilities ranged from 0.127 to 0.823; none were below $1x10^{-6}$ or above $1-1x10^{-6}$. Stabilized weights were normalized to have a mean of 1. The marginal probability of inclusion was 0.575. For the truncation analysis, 2,430 weights below the 1st percentile and 2,430 weights above the 99th percentile were winsorized.

Abbreviation: IPSW, inverse-probability-of-selection weight.

eTable 18. Associations of Cardiovascular Health With Incident Cardiovascular Disease and Global Interaction Tests Before and After IPSW.

Analysis	Intermediate vs poor CVH, HR (95% CI)	Ideal vs poor CVH, HR (95% CI)	P for CKM x CVH	P for CKM x PRS
Unweighted complete-case model	0.623 (0.600-0.646)	0.472 (0.451-0.494)	.4877	.0033
Normalized raw stabilized IPSW	0.616 (0.593-0.640)	0.461 (0.440-0.483)	.5650	.0201
Normalized IPSW truncated at 1st-99th percentiles	0.618 (0.595-0.642)	0.462 (0.442-0.484)	.5320	.0212

Note: The CVH main-effect model adjusted for age, sex, race and ethnicity, education, Townsend Deprivation Index, alcohol consumption, continuous PRS, genotyping batch, and the first 10 genetic principal components. The CKM x CVH model included CVH category, CKM stage, their product terms, and the same covariates. The CKM x PRS model included PRS tertile, CKM stage, their product terms, CVH category, and the remaining Model 2 covariates; continuous PRS was not entered in that model. Global interaction P values were obtained from joint robust Wald tests of all 6 interaction coefficients. Survey-weighted Cox models used design-based robust variance estimation. All CVH main-effect P values were less than .001.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; HR, hazard ratio; IPSW, inverse-probability-of-selection weighting; PRS, polygenic risk score.

eTable 19. Incremental Predictive Performance of the Polygenic Risk Score for 10-Year Incident Cardiovascular Disease.

Panel A. Discrimination			
Model	**10-year time-dependent AUC (95% CI)**	**Change in AUC vs base model (95% CI)**	**P value**
Base model	0.7212 (0.7187-0.7238)	Reference	-
Extended model	0.7257 (0.7231-0.7282)	0.0045 (0.0039-0.0052)	<0.001
Panel B. Calibration			
Model	**Calibration slope (95% CI)**	**Mean predicted 10-year risk**	**Observed 10-year risk (95% CI)**
Base model	0.991 (0.977-1.006)	10.81%	10.81% (10.68%-10.93%)
Extended model	0.992 (0.978-1.006)	10.81%	10.81% (10.68%-10.93%)

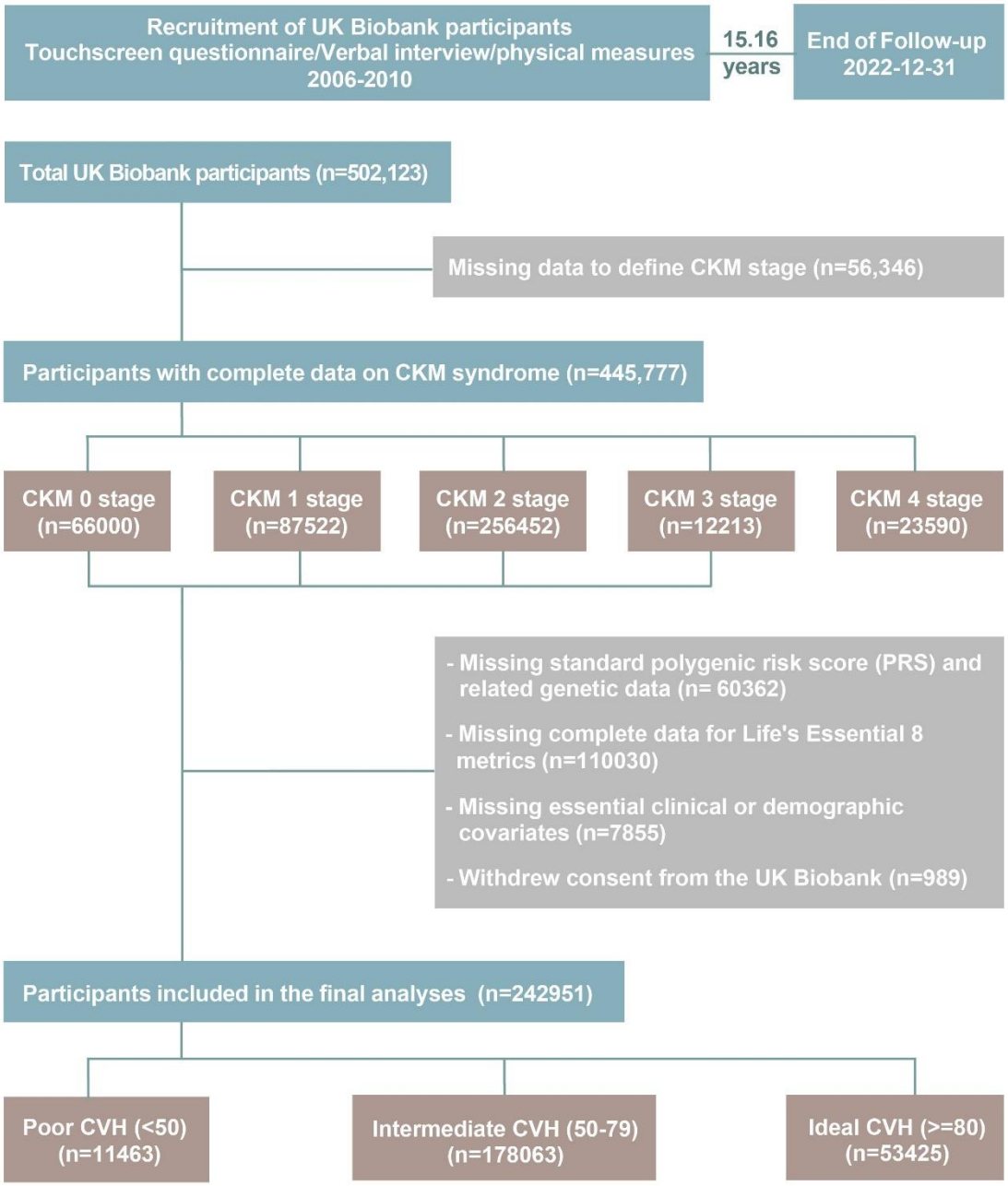
Note: The base model included CKM stage, continuous cardiovascular health score, age, sex, race and ethnicity, education, alcohol consumption, Townsend Deprivation Index, genotyping batch, and the first 10 genetic principal components. The extended model additionally included the standardized continuous polygenic risk score.

Internal validation: Predictions were generated using stratified 10-fold cross-validation, with folds stratified by CVD event status and CKM stage. Time-dependent AUCs at 10 years were estimated with inverse probability of censoring weighting. The 95% CIs for the AUCs and their difference were obtained from 500 nonparametric bootstrap samples of the out-of-fold predictions.

Calibration: Calibration slopes were estimated from out-of-fold linear predictors; a slope of 1 indicates ideal calibration. The observed 10-year CVD risk was estimated using the Kaplan-Meier method. The change in AUC was calculated as the extended-model AUC minus the base-model AUC.

Abbreviations: AUC, area under the time-dependent receiver operating characteristic curve; CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; PRS, polygenic risk score.

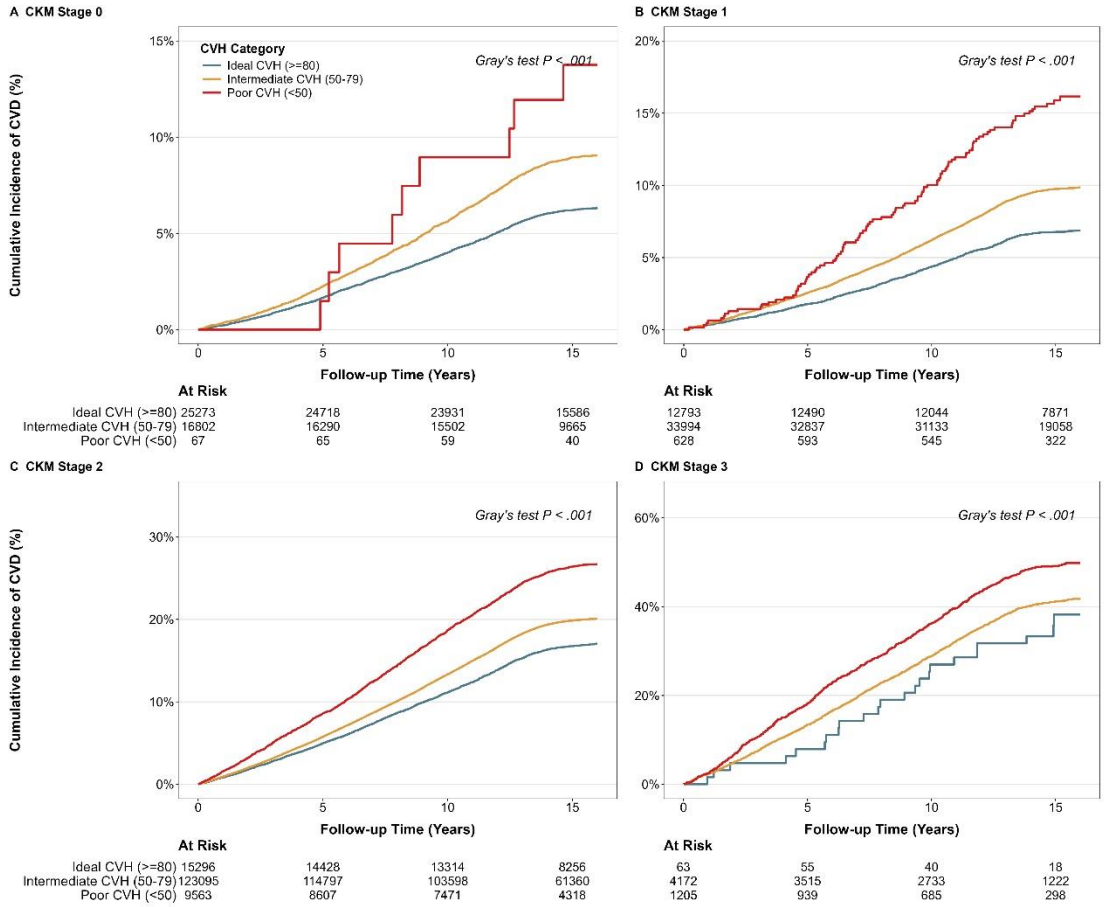
eFigure 1. Flow Diagram of Participant Selection



Abbreviations: CKM, cardiovascular-kidney-metabolic; CVH, cardiovascular health; LE8, Life's Essential 8; PRS, polygenic risk score.

Notes: Baseline recruitment for the UK Biobank was conducted between 2006 and 2010. The median follow-up duration was 15.16 years, ending on December 31, 2022. Of the initial 502,123 participants, individuals with insufficient data to define CKM stages were excluded. Notably, participants classified as having CKM Stage 4 (n = 23,590) were excluded from the downstream prospective analyses, as this stage indicates established cardiovascular disease at baseline, to ensure the investigation of strictly *incident* cardiovascular outcomes. Further exclusions were applied for missing standard polygenic risk scores, incomplete Life's Essential 8 metrics, missing essential clinical/demographic covariates, or withdrawal of consent. A total of 242,951 participants were included in the final analyses, stratified by their overall cardiovascular health status (poor, intermediate, or ideal) according to LE8 scores.

eFigure 2. Cumulative Incidence of Incident Cardiovascular Disease Stratified by Cardiovascular Health Category Across CKM Stages.

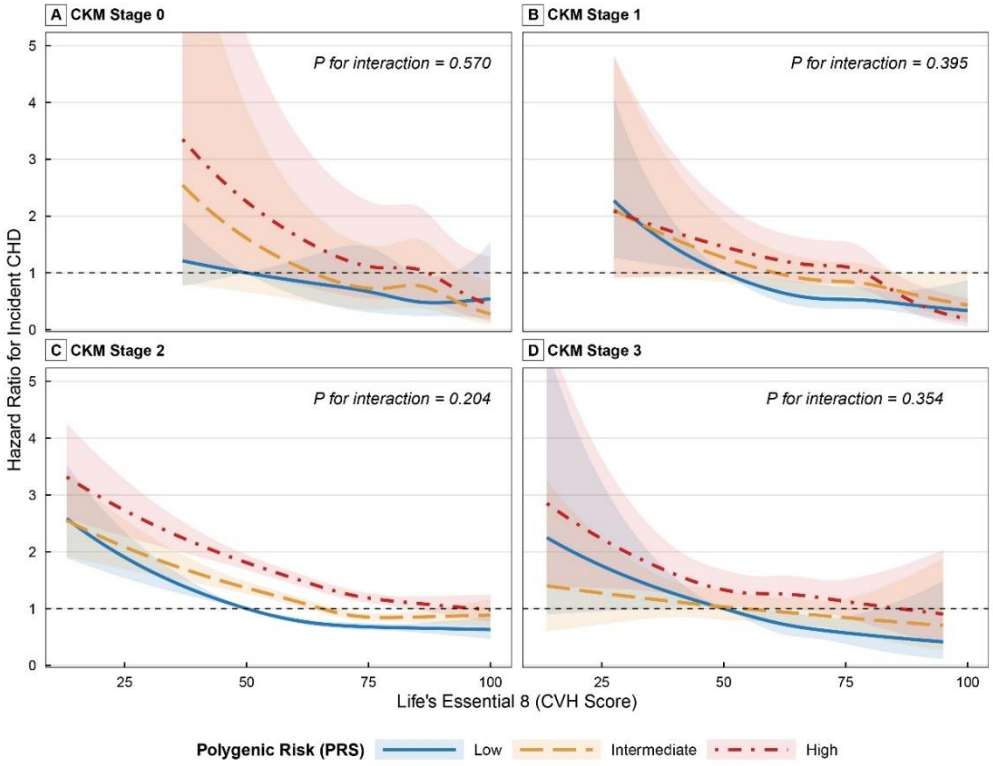


Abbreviations: CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health.

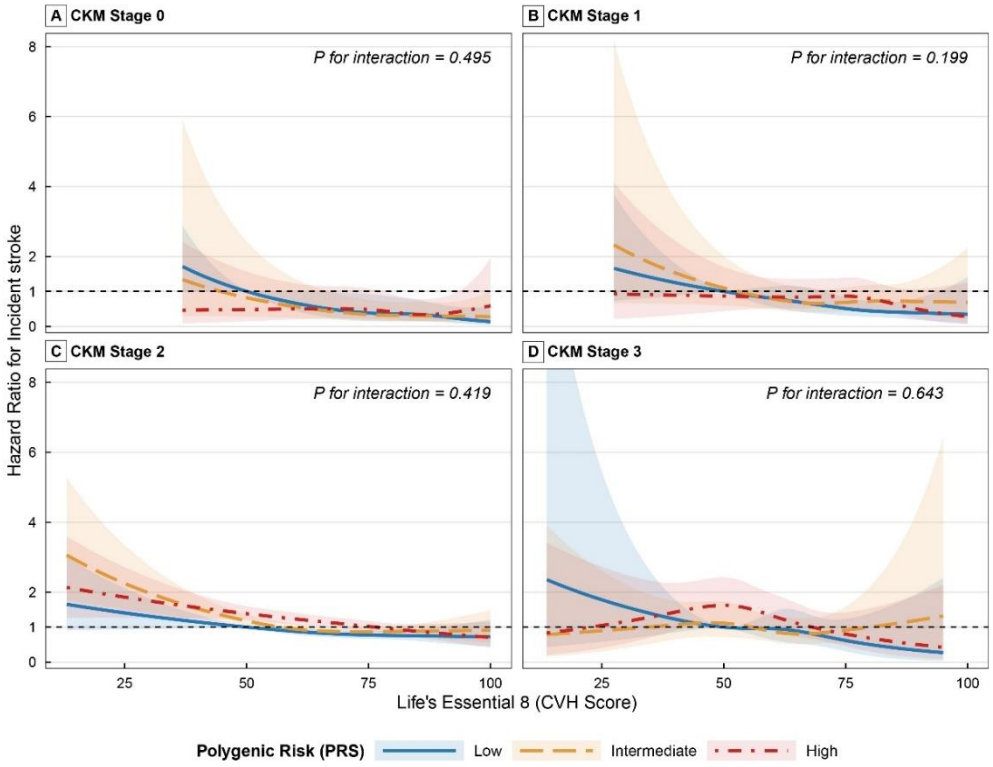
Notes: Cumulative incidence of incident CVD is presented over 15 years within CKM stages 0 through 3: (A) stage 0; (B) stage 1; (C) stage 2; and (D) stage 3. Within each panel, participants were stratified by CVH category according to Life's Essential 8 scores: poor (<50, red lines), intermediate (50–79, orange lines), and ideal (≥80, blue lines). All-cause death before incident CVD was treated as the competing event, and differences between CVH categories were evaluated using Gray's test. The tables below the x-axes show the numbers of participants remaining at risk at 5-year intervals. Because some extreme CVH strata contained few participants, their cumulative incidence estimates should be interpreted cautiously. The y-axis scales differ across panels to reflect differences in baseline risk across CKM stages.

eFigure 3. Dose-Response Associations of Cardiovascular Health with Specific Cardiovascular Outcomes, Stratified by CKM Stage and Polygenic Risk.

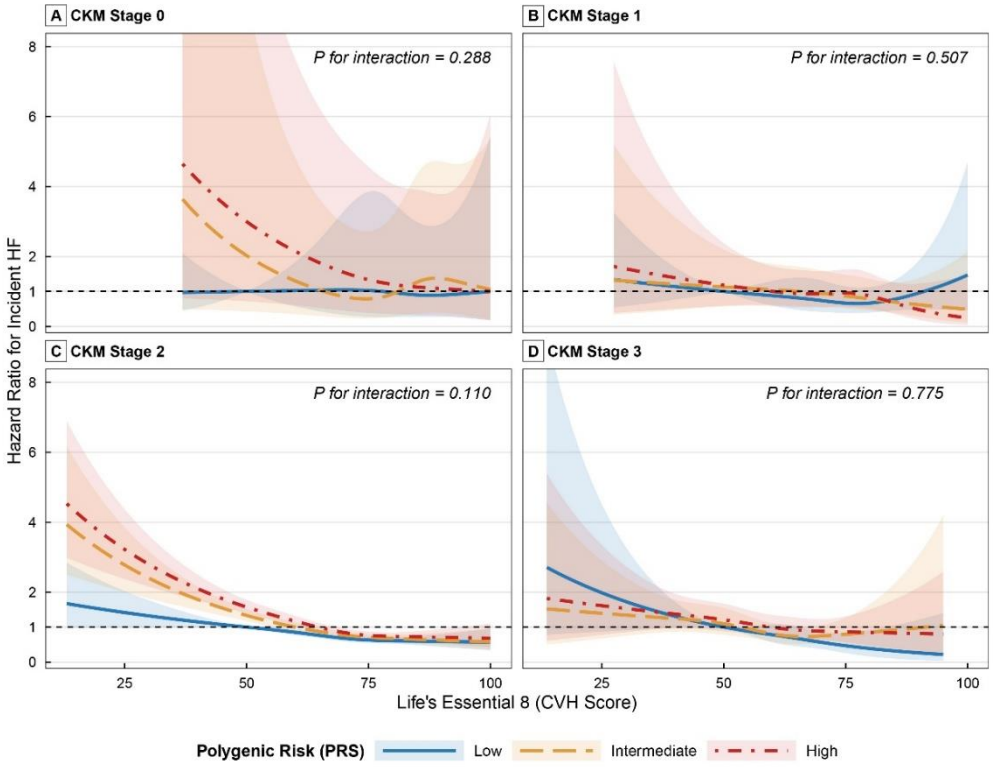
Coronary Heart Disease



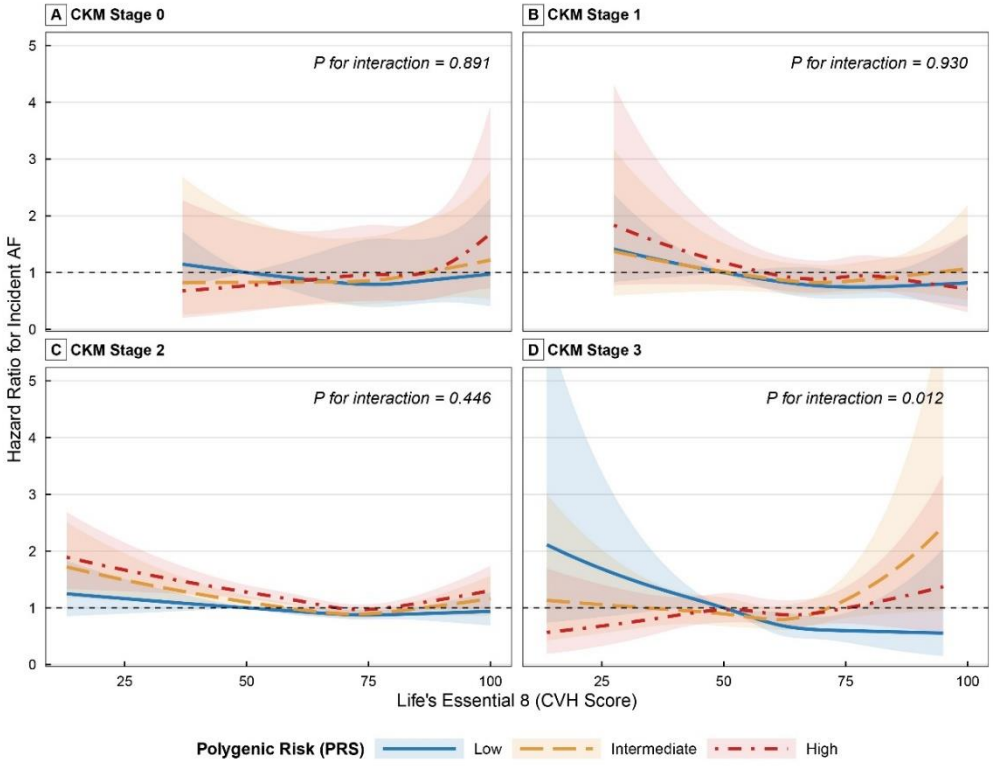
Stroke



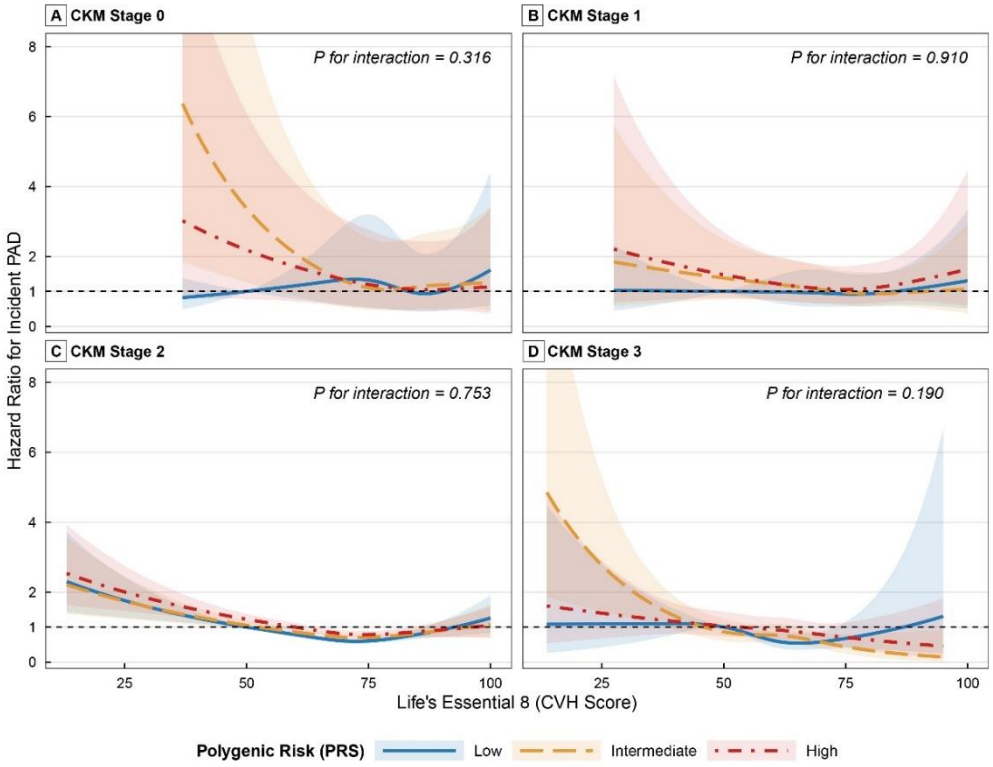
Heart Failure



Atrial Fibrillation



Peripheral Artery Disease



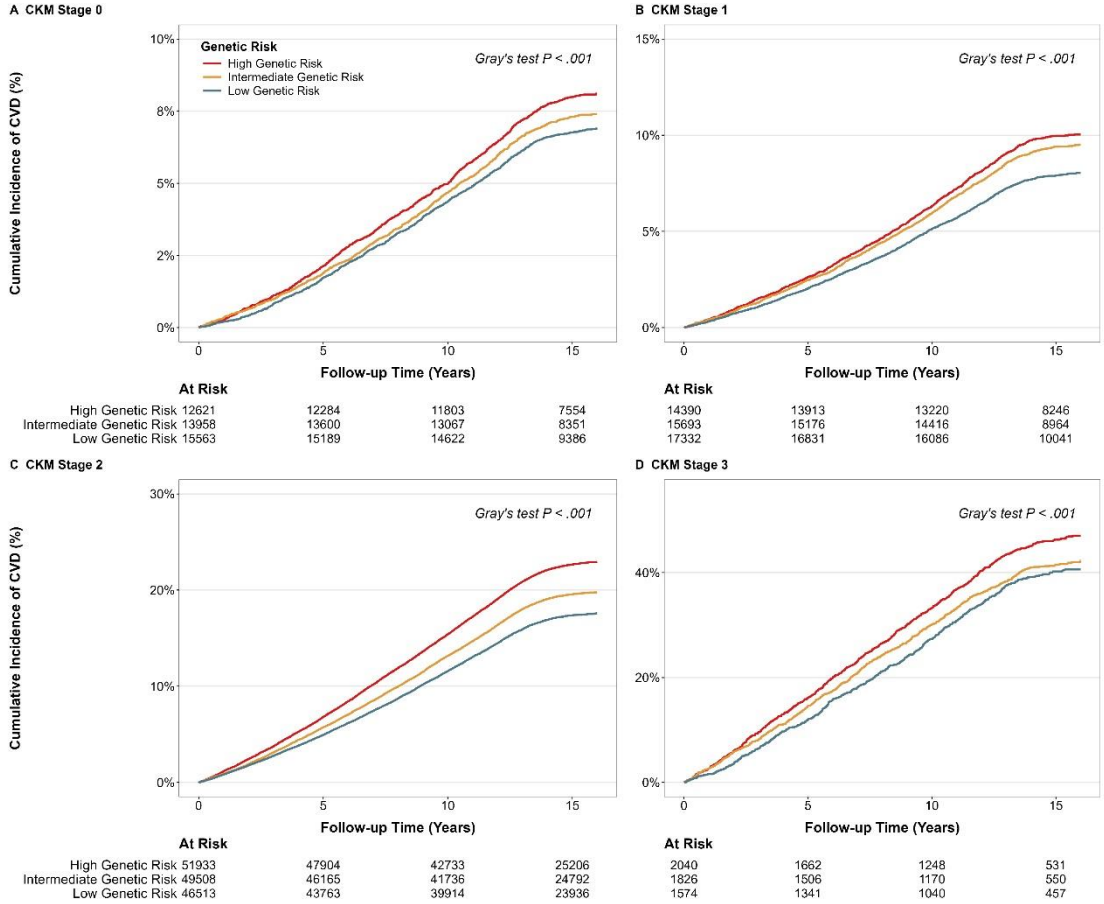
Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVH, cardiovascular health; HF, heart failure; HR, hazard ratio; LE8, Life's Essential 8; PAD, peripheral artery disease; PRS, polygenic risk score.

Notes: Restricted cubic splines (RCS) illustrate the continuous dose-response relationships between the **CVH score** (measured by the Life's Essential 8 [LE8] metrics, ranging from 0 to 100) and the hazard ratios (HRs) for incident coronary heart disease (CHD), stroke, heart failure (HF), atrial fibrillation (AF), and peripheral artery disease (PAD).

For each clinical outcome, the four internal panels represent the respective Cardiovascular-Kidney-Metabolic (CKM) stages: **(A)** Stage 0; **(B)** Stage 1; **(C)** Stage 2; and **(D)** Stage 3. The distinct lines represent the estimated hazard ratios, and the shaded areas indicate the 95% confidence intervals. Within each panel, the curves are further stratified by polygenic risk score (PRS) tertiles: low risk (solid blue line), intermediate risk (dashed orange line), and high risk (dash-dotted red line).

To ensure comparability across the diverse cardiometabolic and genetic strata, the **universal reference group (HR = 1.0)**, indicated by the horizontal dashed line, was defined as participants with a **CVH score of 50 and low polygenic risk (solid blue line)**. Hazard ratios were estimated using multivariable Cox proportional hazards models adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, alcohol consumption status, genotyping batch, and the first 10 genetic principal components (**Model 2**). The *P* for interaction presented in the upper right of each panel evaluates the multiplicative interaction between the continuous CVH score and the PRS categories within that specific CKM stage.

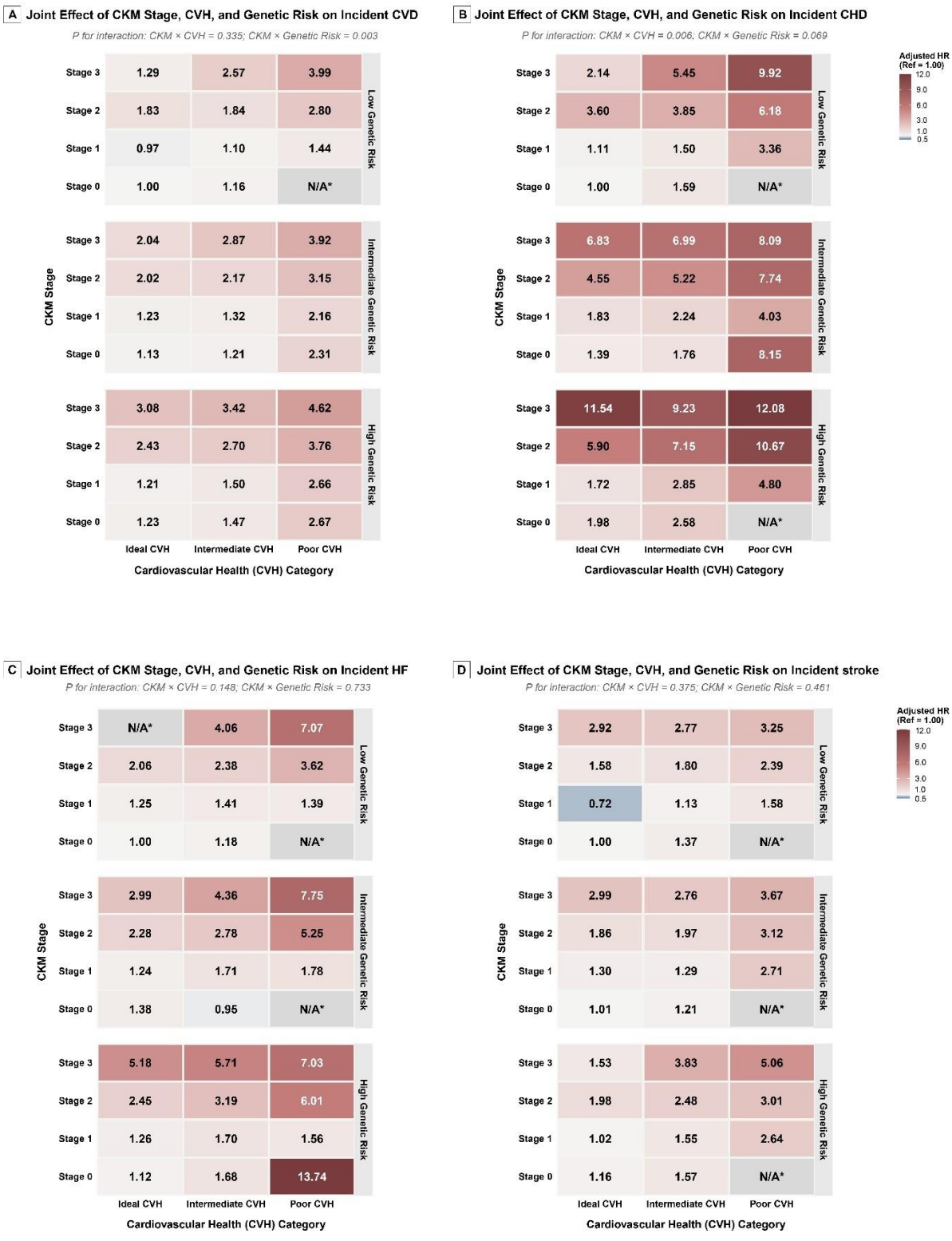
eFigure 4. Cumulative Incidence of Incident Cardiovascular Disease Stratified by Genetic Risk Category Across CKM Stages.

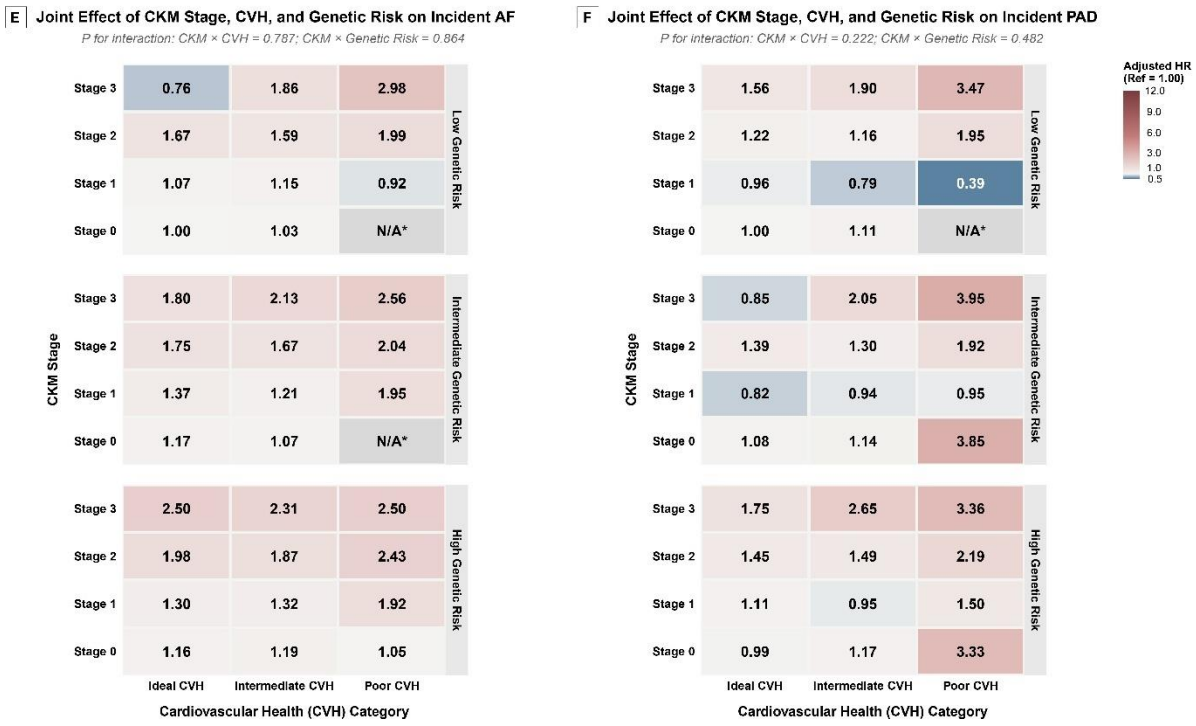


Abbreviations: CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; PRS, polygenic risk score.

Notes: Cumulative incidence of incident CVD is presented over 15 years within CKM stages 0 through 3: (A) stage 0; (B) stage 1; (C) stage 2; and (D) stage 3. Within each panel, participants were stratified into low, intermediate, and high genetic risk groups according to tertiles of the CVD-specific PRS, shown by blue, orange, and red lines, respectively. All-cause death before incident CVD was treated as the competing event, and differences between genetic risk categories were evaluated using Gray's test. The tables below the x-axes show the numbers of participants remaining at risk at 5-year intervals. The y-axis scales differ across panels to reflect differences in baseline risk across CKM stages.

eFigure 5. Joint Associations of CKM Stage, Cardiovascular Health, and Polygenic Risk With Incident Cardiovascular Outcomes.


A Joint Effect of CKM Stage, CVH, and Genetic Risk on Incident CVD
P for interaction: CKM × CVH = 0.335; CKM × Genetic Risk = 0.003
B Joint Effect of CKM Stage, CVH, and Genetic Risk on Incident CHD
P for interaction: CKM × CVH = 0.006; CKM × Genetic Risk = 0.069
C Joint Effect of CKM Stage, CVH, and Genetic Risk on Incident HF
P for interaction: CKM × CVH = 0.148; CKM × Genetic Risk = 0.733
D Joint Effect of CKM Stage, CVH, and Genetic Risk on Incident stroke
P for interaction: CKM × CVH = 0.375; CKM × Genetic Risk = 0.461
Adjusted HR (Ref = 1.00)
12.0
9.0
6.0
3.0
1.0
0.5
CKM Stage
Stage 3
Stage 2
Stage 1
Stage 0
Low Genetic Risk
Intermediate Genetic Risk
High Genetic Risk
Ideal CVH
Intermediate CVH
Poor CVH
Cardiovascular Health (CVH) Category
1.29 2.57 3.99
1.83 1.84 2.80
0.97 1.10 1.44
1.00 1.16 N/A*
2.04 2.87 3.92
2.02 2.17 3.15
1.23 1.32 2.16
1.13 1.21 2.31
3.08 3.42 4.62
2.43 2.70 3.76
1.21 1.50 2.66
1.23 1.47 2.67
2.14 5.45 9.92
3.60 3.85 6.18
1.11 1.50 3.36
1.00 1.59 N/A*
6.83 6.99 8.09
4.55 5.22 7.74
1.83 2.24 4.03
1.39 1.76 8.15
11.54 9.23 12.08
5.90 7.15 10.67
1.72 2.85 4.80
1.98 2.58 N/A*
N/A* 4.06 7.07
2.06 2.38 3.62
1.25 1.41 1.39
1.00 1.18 N/A*
2.99 4.36 7.75
2.28 2.78 5.25
1.24 1.71 1.78
1.38 0.95 N/A*
5.18 5.71 7.03
2.45 3.19 6.01
1.26 1.70 1.56
1.12 1.68 13.74
2.92 2.77 3.25
1.58 1.80 2.39
0.72 1.13 1.58
1.00 1.37 N/A*
2.99 2.76 3.67
1.86 1.97 3.12
1.30 1.29 2.71
1.01 1.21 N/A*
1.53 3.83 5.06
1.98 2.48 3.01
1.02 1.55 2.64
1.16 1.57 N/A*



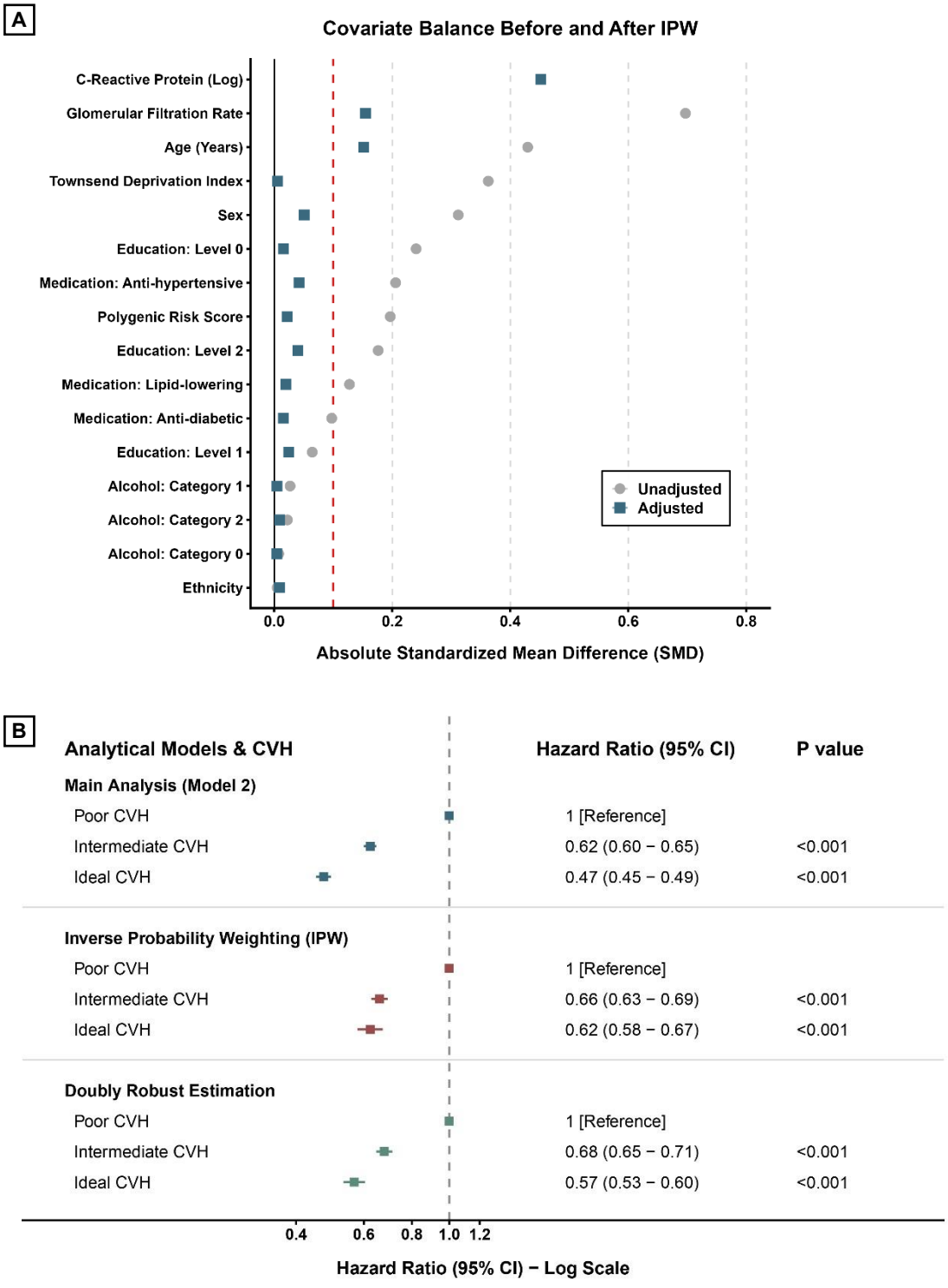
Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; HF, heart failure; HR, hazard ratio; PAD, peripheral artery disease.

Notes: Heatmaps display the adjusted hazard ratios (HRs) for the three-way joint associations of Cardiovascular-Kidney-Metabolic (CKM) stage, Cardiovascular Health (CVH) category, and polygenic risk strata with incident cardiovascular outcomes: **(A)** cardiovascular disease (CVD); **(B)** coronary heart disease (CHD); **(C)** heart failure (HF); **(D)** stroke; **(E)** atrial fibrillation (AF); and **(F)** peripheral artery disease (PAD).

The color gradient represents the magnitude of the HR, ranging from blue (HR < 1.00) to dark red (indicating the highest risk). To maintain comparability across the 36 risk strata within each panel, the universal reference group (**HR = 1.00**) was defined as participants in **CKM Stage 0 with Ideal CVH and Low Genetic Risk**. Cells denoted with "**N/A***" indicate specific strata with an insufficient number of incident events to yield statistically reliable HR estimates.

Hazard ratios were estimated using multivariable Cox proportional hazards models adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, alcohol consumption status, genotyping batch, and the first 10 genetic principal components (**Model 2**). The *P* values for interaction presented at the top of each panel evaluate the overall multiplicative interactions between CKM stage and CVH category, and between CKM stage and genetic risk. The detailed numerical HR estimates and corresponding 95% confidence intervals for Panel A are provided in **Table 3** of the main manuscript, while data for Panels B through F are presented in **eTable 11**.

eFigure 6. Robustness Assessment of Statistical Models: Covariate Balance and Sensitivity Analyses.



Abbreviations: CI, confidence interval; CRP, C-reactive protein; CVH, cardiovascular health; GFR, glomerular filtration rate; HR, hazard ratio; IPW, inverse probability weighting; SMD, standardized mean difference.

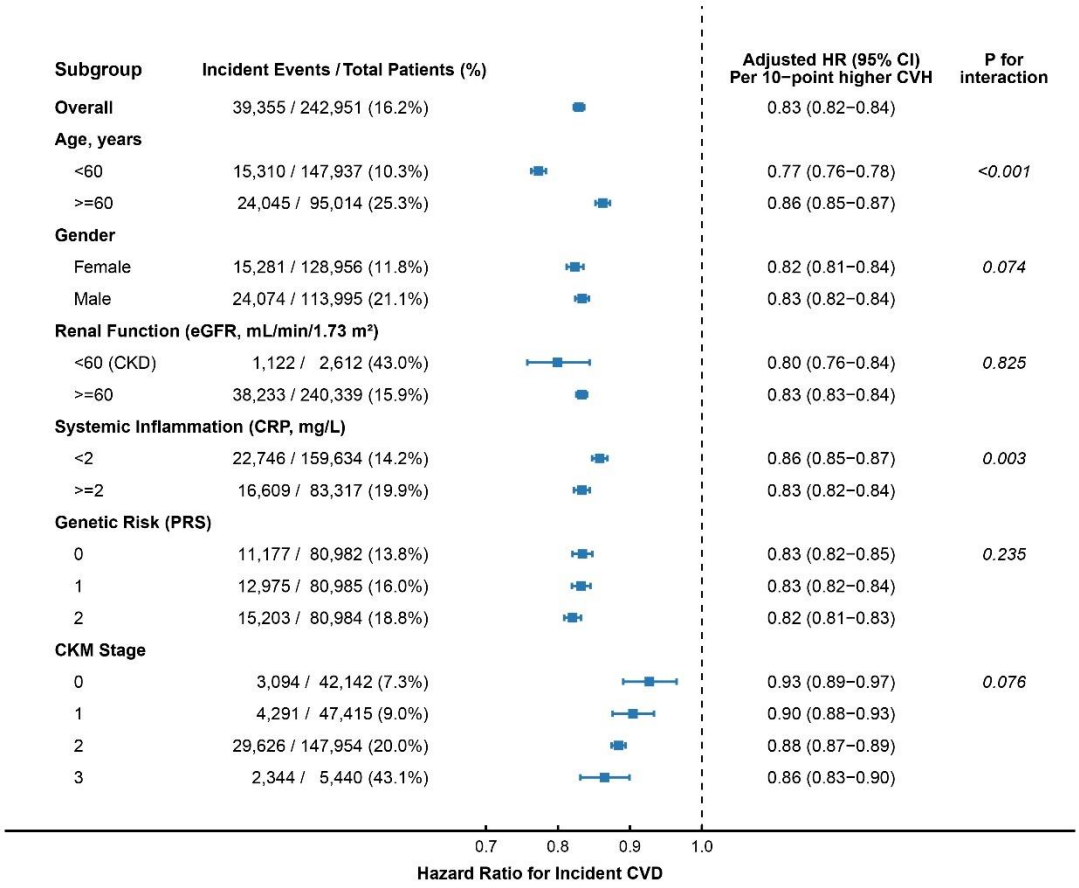
Panel A. Love Plot of Covariate Balance Before and After Inverse Probability Weighting. The Love plot illustrates the absolute standardized mean differences (SMDs) for potential confounders

before (gray circles) and after (blue squares) applying inverse probability weighting (IPW). **Balance Threshold:** The vertical red dashed line indicates the threshold of **0.1**[8]. An SMD below this value is widely accepted as indicating excellent balance between groups. **Weighting Performance:** Following IPW, balance significantly improved for most covariates. However, absolute SMDs for age, log-CRP, and glomerular filtration rate (GFR) remained slightly above the 0.1 threshold. To address this residual confounding, these three variables were specifically included for additional adjustment within the outcome regression component of the doubly robust estimation.

Panel B. Sensitivity Analyses of the Association Between CVH Categories and Incident CVD

Forest plots compare hazard ratios (HRs) and 95% confidence intervals (CIs) estimated across three distinct statistical frameworks to evaluate the stability of the primary findings: i) **Main Analysis (Model 2):** Standard multivariable Cox proportional hazards model. ii) **Inverse Probability Weighting (IPW):** Propensity score-based weighting using the weights generated in Panel A to improve covariate balance across CVH categories and reduce measured confounding. iii) **Doubly Robust Estimation**[9]**:** An advanced causal inference approach combining the outcome regression and the propensity score model. Notably, this model performed a **double adjustment** for age, log-CRP, and GFR to eliminate the residual imbalances identified in Panel A. This method provides unbiased estimates even if one of the underlying models is misspecified.

eFigure 7. Subgroup Analyses of the Association Between Cardiovascular Health Score and Incident Cardiovascular Disease.



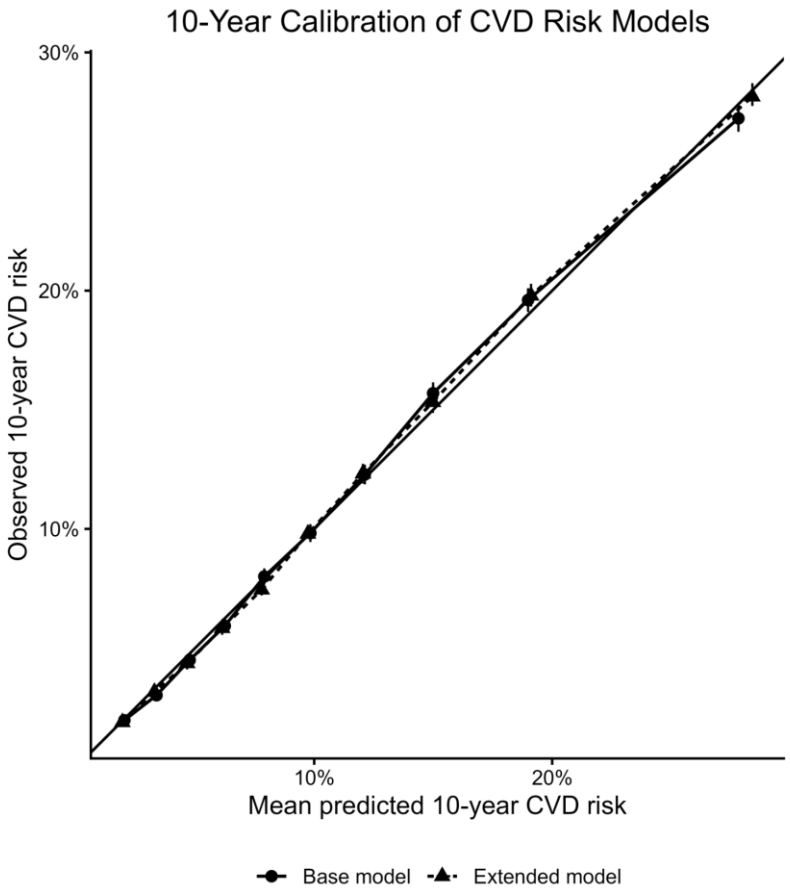
Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CRP, C-reactive protein; CVD, cardiovascular disease; CVH, cardiovascular health; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PRS, polygenic risk score.

Notes: The forest plot displays the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CVD associated with **each 10-point higher Cardiovascular Health (CVH) score** (measured by Life's Essential 8 metrics).

Analyses are stratified by key demographic and clinical factors, including age (<60 vs. ≥60 years), gender, renal function (eGFR <60 vs. ≥60 mL/min/1.73 m²), systemic inflammation (CRP <2 vs. ≥2 mg/L), genetic risk (standardized PRS tertiles), and CKM stage (0, 1, 2, and 3). Hazard ratios were estimated using multivariable Cox proportional hazards models adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, alcohol consumption status, genotyping batch, and the first 10 genetic principal components (**Model 2**), excluding the variable used for stratification in each respective subgroup analysis.

P values for interaction were calculated to assess the heterogeneity of the association across subgroups. While significant interactions were observed for age ($P < .001$) and CRP level ($P = .003$), the protective association of a higher CVH score remained consistent across all analyzed strata, with all HRs significantly below 1.0.

eFigure 8. Calibration of the Base and Extended Models for 10-Year Incident Cardiovascular Disease.



Note: Points represent deciles of predicted 10-year CVD risk. The x-axis shows the mean predicted risk and the y-axis shows the Kaplan-Meier observed risk within each decile. Vertical bars indicate 95% CIs for the observed risks. The diagonal line represents perfect agreement between predicted and observed risk. The base model included CKM stage, continuous CVH score, and the prespecified covariates; the extended model additionally included standardized continuous PRS.

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