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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HAO ZHANG**
MINGYANG LI**
SIZHUANG HUANG
YANWEN FANG
HAIHUA ZHANG
WEIXIAN YANG
MENGYUE YU

*Author affiliations can be found in the back matter of this article

**These authors contributed equally to this work

ABSTRACT

Background: Prior studies of cardiovascular health (CVH) and genetic susceptibility have not accounted for heterogeneity in underlying cardiometabolic-renal states. Whether ideal CVH protects against cardiovascular disease (CVD) across the cardiovascular-kidney-metabolic (CKM) syndrome continuum, and whether this benefit is modified by CKM stage or genetic susceptibility, remains unknown.

Methods: This prospective study included 242,951 UK Biobank participants (aged 37–73) in CKM Stages 0–3, free of CVD at baseline (2006–2010), followed through 2022. CVH was quantified using Life's Essential 8 (LE8) (poor, <50; intermediate, 50–79; ideal, ≥80). A cardiovascular-specific polygenic risk score (PRS) was categorized into tertiles. The primary outcome was incident composite CVD. Multivariable Cox models estimated hazard ratios (HRs); cumulative incidence functions accounting for competing mortality were compared by Gray's test.

Results: Among 242,951 participants (mean age, 55.7 years; 53.1% women), 39,355 incident CVD events occurred over a median follow-up of 15.2 years. Ideal CVH was associated with 53% lower CVD risk versus poor CVH (HR, 0.47; 95% CI, 0.45–0.49), with the largest reductions for heart failure (HF) (HR, 0.33) and coronary heart disease (CHD) (HR, 0.35). Higher CVH was associated with lower CVD risk across genetic risk strata. No CKM × CVH interaction was detected (P = .335), indicating preserved protection across the disease continuum; a significant CKM × PRS interaction (P = .003) indicated amplified polygenic risk impact in advanced stages. Both CVH- and PRS-based stratification significantly separated cumulative CVD incidence across all CKM stages (all Gray's test P < .001). Results were robust to inverse probability weighting (IPW), competing risk models, and landmark analyses.

Conclusion: Favorable CVH was associated with substantially lower CVD risk across the full CKM continuum without attenuation in advanced disease, whereas polygenic risk consequences were amplified in later CKM stages. These findings support integrating CVH assessment as a complementary axis within CKM risk stratification.

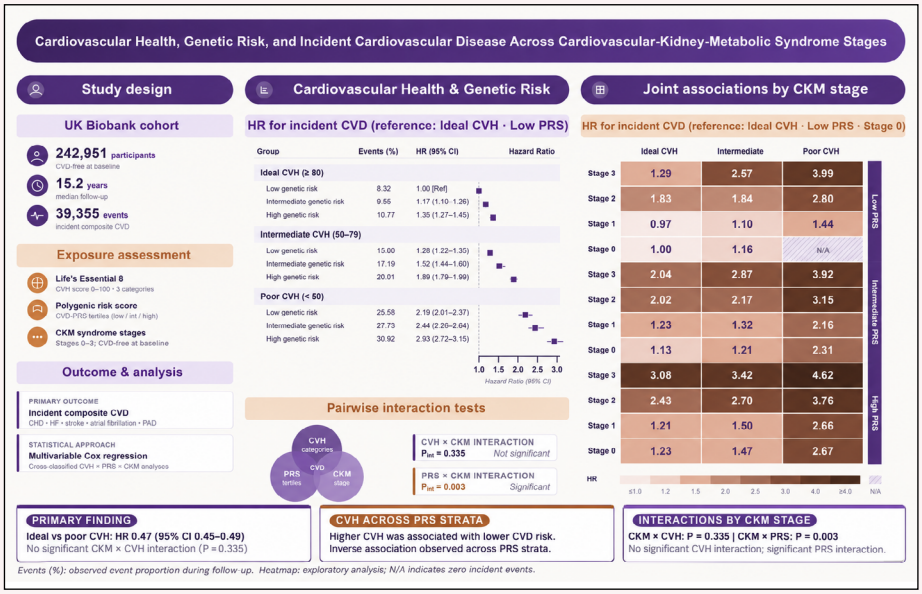
CORRESPONDING AUTHORS:
Mengyue Yu
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China
yumengyue@fuwaihospital.org

Weixian Yang
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China
fwywx66@fuwai.com

KEYWORDS:
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GRAPHICAL ABSTRACT



INTRODUCTION

Cardiovascular, kidney, and metabolic disorders constitute an interconnected pathophysiological network and a leading cause of global morbidity and mortality (1). Recognizing this synergistic burden, the American Heart Association (AHA) defined the cardiovascular-kidney-metabolic (CKM) syndrome, a framework that classifies individuals along a progressive continuum from metabolic risk factor accumulation through subclinical organ damage to overt clinical disease, underscoring the need for stage-specific risk stratification (2–4).

The pathogenesis of cardiovascular disease (CVD) reflects the interplay between genetic susceptibility and modifiable lifestyle factors (5, 6). Previous studies demonstrate that favorable cardiovascular health (CVH), operationalized by the AHA's Life's Essential 8 (LE8) metrics, is associated with substantially lower CVD risk even among individuals with high polygenic susceptibility (7, 8). However, studies jointly examining CVH and genetic susceptibility have not accounted for heterogeneity in baseline cardiometabolic-renal states (9). It remains uncertain whether the protective association of ideal CVH persists in advanced CKM stages characterized by systemic inflammation, vascular aging, and subclinical target organ damage—or whether this benefit attenuates as the disease continuum progresses (10). Clarifying whether favorable CVH remains associated with lower CVD risk across CKM stages may inform the complementary use of LE8 and CKM staging for risk assessment and prevention.

To address this gap, we examined the independent and joint associations of CVH and genetic susceptibility (quantified by a polygenic risk score [PRS]) with incident CVD across CKM Stages 0 through 3, and tested whether the CVH-associated risk reduction was modified by CKM stage or genetic risk stratum.

METHODS

STUDY DESIGN AND POPULATION

This study used data from the UK Biobank, a population-based prospective cohort of 502,123 adults aged 37–73 years, recruited across 22 assessment centers in the UK between 2006 and 2010. The UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (11/NW/0382), and all participants provided written informed consent. This secondary analysis was conducted under application number 532333. From 445,777 participants with ascertainable baseline CKM stages, we sequentially excluded those with prevalent CVD (CKM Stage 4; n = 23,590), unavailable PRS (n = 60,362), missing LE8 or covariate data (n = 117,885), and incomplete survival tracking (n = 989), yielding an analytical cohort of 242,951 participants in CKM Stages 0 through 3 (eFigure 1).

ASSESSMENT OF CARDIOVASCULAR HEALTH

CVH was quantified using the AHA's LE8 metrics, comprising four health behaviors (diet quality, physical activity, nicotine exposure, sleep health) and four health factors (body mass index, non-high-density lipoprotein cholesterol, blood glucose, blood pressure). Each metric was scored 0–100 per standardized AHA algorithms, and the overall CVH score was calculated as the unweighted mean (eTable 2). Participants were categorized as having poor (<50), intermediate (50–79), or ideal (≥80) CVH (7). For sensitivity analysis, a behavioral CVH score was calculated as the unweighted mean of the diet quality, physical activity, nicotine exposure, and sleep health component scores and modeled continuously per 10-point increase.

CKM STAGE CLASSIFICATION

Baseline CKM stages were classified per the 2023 AHA Presidential Advisory (3, 11): Stage 0, absence of metabolic risk factors and chronic kidney disease (CKD); Stage 1, excess adiposity or adipose tissue dysfunction; Stage 2, metabolic derangements (hypertension, hypertriglyceridemia, diabetes, metabolic syndrome) or moderate-to-high-risk CKD (12); Stage 3, very high-risk CKD or 10-year Predicting Risk of cardiovascular disease EVENTs (PREVENT) cardiovascular risk of 20% or higher (13). Participants with prevalent CVD (Stage 4) were excluded. PREVENT was retained to preserve the original AHA CKM staging definition. Detailed definitions of CKM classification are provided in eMethods.

GENETIC RISK ASSESSMENT

The CVD-specific PRS was extracted from the standard PRS release via the UK Biobank Research Access Platform (14, 15). These pre-computed scores were derived from trait-specific meta-analyses of multi-ancestry genome-wide association studies to mitigate cohort-specific overfitting. The individual-level PRS was calculated using a Bayesian framework as the genome-wide sum of variant-specific posterior effect sizes multiplied by corresponding allele dosages. The continuous CVD-PRS was divided into tertiles based on the distribution within the analytical cohort. In sensitivity analyses, the PRS was additionally standardized and modeled per 1-SD increase, and extreme genetic risk was defined as the highest 10% of the PRS distribution versus the remaining 90%.

OUTCOME ASCERTAINMENT

The primary incident outcome was a composite of CVD, encompassing coronary heart disease (CHD), stroke, heart failure (HF), atrial fibrillation (AF), and peripheral artery disease (PAD), which clinically represents the transition to CKM Stage 4. Each component of the composite outcome was prespecified and evaluated as a secondary end point. Incident clinical end points were ascertained via deterministic linkage to national administrative databases, including hospital inpatient records (Hospital Episode Statistics for England, Scottish Morbidity Record, and Patient Episode Database for Wales) and underlying cause-of-death registries. Diagnoses were cataloged using ICD-10 codes, harmonized with definitions validated by the UK Biobank Outcome Adjudication Group (eTable 4). Follow-up ended at the first outcome, death, loss to follow-up, or administrative censoring; death was censored in Cox models and treated as a competing event in cumulative incidence and Fine-Gray analyses.

STATISTICAL ANALYSIS

Baseline characteristics were summarized as means (SDs) for continuous variables and frequencies (percentages) for categorical variables. Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs for associations between CVH categories and incident outcomes. To avoid over-adjustment given the overlap between LE8 components and standard cardiovascular risk factors, sequential models were specified: Model 1 was unadjusted; Model 2 adjusted for age, sex, ethnicity, education, Townsend Deprivation Index, alcohol consumption, continuous PRS, genotyping batch, and the first 10 genetic principal components; Model 3 additionally adjusted for lipid-lowering, antihypertensive, and glucose-lowering medication use. Although Model 3 yielded the lowest Akaike and Bayesian information criterion values

across all outcomes (eTable 5), Model 2 was prespecified as the primary analytical model to avoid potential over-adjustment bias, as pharmacological interventions are frequently situated on the causal pathway between CVH behaviors and clinical outcomes. The proportional hazards assumption was verified using Schoenfeld residuals. Restricted cubic splines with four knots (5th, 35th, 65th, and 95th percentiles) were fitted to continuous CVH scores to assess nonlinear dose-response relationships (16). The knot locations followed established methodological recommendations and were based on the CVH score distribution rather than clinical thresholds.

JOINT AND INTERACTION ANALYSES

To evaluate the joint associations of CVH, genetic risk, and CKM stage with incident CVD, fully adjusted HRs were estimated across the cross-stratification of CVH (three categories), PRS (three tertiles), and CKM stage (four stages), using CKM Stage 0/ideal CVH/low genetic risk as the common reference group. Cumulative incidence functions accounting for competing risk of all-cause mortality were constructed within each CKM stage, stratified separately by CVH category and genetic risk tertile, and compared using Gray's test. For the PRS analyses, 10-year cumulative incidence estimates and pointwise 95% CIs were extracted, and absolute risk differences were calculated as the cumulative incidence in the high-PRS group minus that in the low-PRS group within each CKM stage. To test for effect modification, multiplicative interaction terms (CVH × PRS; CVH × CKM stage; CKM stage × PRS) were introduced into the primary Cox models. The alternative PRS parameterizations were evaluated in the overall cohort and separately within CKM stages, with interaction tested by comparing models with and without the corresponding PRS × CKM stage terms using likelihood ratio tests. The 36-group analysis was considered exploratory because some strata were sparse.

INCREMENTAL PREDICTIVE VALUE OF PRS

To assess the incremental predictive value of PRS, we compared a base Cox model including CKM stage, continuous CVH score, and the prespecified non-PRS covariates with an extended model additionally including standardized continuous PRS. Internal validation was performed using stratified 10-fold cross-validation. Model discrimination was assessed using the 10-year time-dependent area under the receiver operating characteristic curve (AUC), with 95% CIs for the AUCs and their difference estimated from 500 nonparametric bootstrap samples. Calibration was evaluated using calibration slopes, the agreement between the mean predicted and Kaplan–Meier-observed 10-year risks, and calibration plots across deciles of predicted risk.

SENSITIVITY AND SUBGROUP ANALYSES

Robustness was assessed through five approaches: (i) an extended model (Model 4) additionally adjusting for C-reactive protein (CRP) and CKM stage beyond Model 3, with estimated glomerular filtration rate (eGFR) omitted because it contributes to CKM staging; (ii) stabilized inverse probability weighting (IPW) with doubly robust estimation to address residual covariate imbalances (standardized mean difference [SMD] >0.10 for age, CRP, and eGFR after initial weighting); (iii) Fine-Gray subdistribution hazard models to account for competing risk of all-cause mortality; (iv) two separate landmark analyses excluding events within the first year and within the first three years of follow-up; and (v) prespecified subgroup analyses across age, sex, CRP, eGFR, genetic risk, and CKM stage, with *P* for interaction to assess effect modification. A behavioral CVH score based on the four behavioral LE8 components was modeled per 10-point increase overall and by CKM stage, with interaction assessed using likelihood ratio tests. Selection bias from complete-case inclusion was assessed by comparing included and otherwise eligible excluded participants using SMDs, and stabilized inverse-probability-of-selection weighting (IPSW) was used to re-estimate CVH associations and CKM-stage interactions, with weights truncated at the 1st and 99th percentiles in a sensitivity analysis. All analyses were performed using R (R Foundation for Statistical Computing). A two-sided $P < .05$ indicated significance; Bonferroni correction for five secondary end points (adjusted significance threshold, $P < .01$) was applied, and the Benjamini-Hochberg procedure was used for cross-stratified analyses.

RESULTS

BASELINE CHARACTERISTICS

Of 242,951 participants (mean [SD] age, 55.7 [8.1] years; 53.1% women), 4.7% were categorized as having poor CVH, 73.3% intermediate, and 22.0% ideal (Table 1). Compared to those with poor CVH, individuals with ideal CVH were younger, more frequently women, and had a more favorable cardiometabolic profile, including a substantially lower prevalence of hypertension (10.0% vs. 40.9%) and diabetes (1.1% vs. 21.4%). Among participants with ideal CVH, 47.3% were in CKM Stage 0, whereas 93.9% of those with poor CVH were in CKM Stage 2 or 3 (eTable 6). Across genetic risk strata, higher polygenic risk was associated with a stepwise decrease in overall CVH scores and a greater burden of clinical comorbidities (eTable 7). Excluded participants were modestly older, more deprived, and had a less favorable cardiometabolic profile (eTable 8).

CHARACTERISTIC	TOTAL (N = 242,951)	POOR CVH (N = 11,463)	INTERMEDIATE CVH (N = 178,063)	IDEAL CVH (N = 53,425)
Age, mean (SD), y	55.7 (8.1)	56.3 (7.6)	56.5 (7.9)	53.1 (8.2)
Sex, No. (%)				
Female	128,956 (53.1)	4427 (38.6)	87,240 (49.0)	37,289 (69.8)
Male	113,995 (46.9)	7036 (61.4)	90,823 (51.0)	16,136 (30.2)
Race and Ethnicity, No. (%)				
White (British)	231,029 (95.1)	10,870 (94.8)	169,550 (95.2)	50,609 (94.7)
Other	11,922 (4.9)	593 (5.2)	8513 (4.8)	2816 (5.3)
Townsend Deprivation Index, mean (SD)	−1.53 (2.93)	−0.62 (3.28)	−1.53 (2.93)	−1.71 (2.82)
Education Level, No. (%)				
College or above	88,659 (36.5)	2655 (23.2)	60,786 (34.1)	25,218 (47.2)
High school or equivalent	126,974 (52.3)	6322 (55.2)	94,624 (53.1)	26,028 (48.7)
Less than high school	27,318 (11.2)	2486 (21.7)	22,653 (12.7)	2179 (4.1)
Smoking Status, No. (%)				
Never	135,631 (55.8)	2194 (19.1)	91,024 (51.1)	42,413 (79.4)
Current	23,314 (9.6)	4417 (38.5)	18,174 (10.2)	723 (1.4)
Former	84,006 (34.6)	4852 (42.3)	68,865 (38.7)	10,289 (19.3)
Alcohol Consumption, No. (%)				
Never	8723 (3.6)	382 (3.3)	6164 (3.5)	2177 (4.1)
Current	226,824 (93.4)	10,466 (91.3)	166,544 (93.5)	49,814 (93.2)
Former	7404 (3.0)	615 (5.4)	5355 (3.0)	1434 (2.7)
Biomarkers and Physical Measures, mean (SD)				
C-reactive protein, mg/L	2.49 (4.12)	4.45 (5.45)	2.62 (4.12)	1.64 (3.56)
eGFR, mL/min/1.73 m^2	95.91 (13.83)	91.10 (14.93)	94.78 (13.76)	100.71 (12.61)
Total cholesterol, mmol/L	5.74 (1.10)	6.15 (1.22)	5.86 (1.10)	5.25 (0.91)
LDL cholesterol, mmol/L	3.60 (0.84)	3.97 (0.92)	3.71 (0.83)	3.15 (0.67)
Glycated hemoglobin, mmol/mol	35.74 (6.16)	41.36 (11.30)	36.00 (6.04)	33.67 (3.47)
Medical History, No. (%)				
Hypertension	58,562 (24.1)	4690 (40.9)	48,535 (27.3)	5337 (10.0)
Diabetes	14,308 (5.9)	2458 (21.4)	11,266 (6.3)	584 (1.1)

(Contd.)

Table 1 Baseline characteristics of the study population stratified by cardiovascular health (CVH) categories.

Notes: Data are presented as mean (SD) for continuous variables and No. (%) for categorical variables. CVH categories were defined according to the AHA's LE8 scoring system: poor (<50), intermediate (50–79), and ideal (≥80). CKM syndrome stages were classified in accordance with the 2023 AHA Presidential Advisory; participants with CKM Stage 4 (prevalent CVD) at baseline were excluded from this incident analysis cohort. PRS categories represent tertiles of the standardized CVD-specific PRS.

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

CHARACTERISTIC	TOTAL (N = 242,951)	POOR CVH (N = 11,463)	INTERMEDIATE CVH (N = 178,063)	IDEAL CVH (N = 53,425)
Medication Use, No. (%)				
Lipid-lowering medication	28,480 (11.7)	2220 (19.4)	22,723 (12.8)	3537 (6.6)
Antihypertensive medication	40,861 (16.8)	3232 (28.2)	33,554 (18.8)	4075 (7.6)
Antidiabetic medication	7227 (3.0)	1178 (10.3)	5761 (3.2)	288 (0.5)
Genetic Risk Assessment				
PRS, mean (SD)	−0.14 (0.97)	−0.05 (0.97)	−0.12 (0.97)	−0.24 (0.98)
Low genetic risk, No. (%)	80,982 (33.3)	3433 (29.9)	57,604 (32.4)	19,945 (37.3)
Intermediate genetic risk, No. (%)	80,985 (33.3)	3822 (33.3)	59,503 (33.4)	17,660 (33.1)
High genetic risk, No. (%)	80,984 (33.3)	4208 (36.7)	60,956 (34.2)	15,820 (29.6)
CKM Syndrome Stage, No. (%)				
Stage 0	42,142 (17.3)	67 (0.6)	16,802 (9.4)	25,273 (47.3)
Stage 1	47,415 (19.5)	628 (5.5)	33,994 (19.1)	12,793 (23.9)
Stage 2	147,954 (60.9)	9563 (83.4)	123,095 (69.1)	15,296 (28.6)
Stage 3	5440 (2.2)	1205 (10.5)	4172 (2.3)	63 (0.1)
CVH Metric Scores, mean (SD)				
Life's Essential 8 total score	70.42 (11.79)	43.88 (5.11)	67.54 (7.59)	85.72 (4.69)
Diet score	65.88 (27.58)	42.78 (27.35)	63.34 (27.43)	79.32 (21.77)
Physical activity score	85.25 (33.75)	30.17 (44.17)	84.95 (33.83)	98.04 (11.47)
Sleep health score	89.85 (18.01)	75.75 (25.76)	89.16 (18.32)	95.17 (11.90)
Nicotine exposure score	73.26 (34.89)	38.10 (38.90)	70.53 (35.48)	89.88 (21.18)
Blood pressure score	44.08 (30.87)	25.25 (22.25)	37.81 (27.76)	68.99 (28.84)
Blood lipids score	46.19 (30.32)	26.93 (26.00)	40.76 (27.91)	68.44 (27.67)

PRIMARY AND SECONDARY CARDIOVASCULAR OUTCOMES

Over a median 15.2-year follow-up, 39,355 incident CVD events occurred. Cumulative CVD incidence demonstrated a graded inverse association with CVH status across all genetic risk strata (Figure 1) and across all CKM stages (eFigure 2). In multivariable analyses, compared with poor CVH, incident CVD risk was significantly lower for intermediate (HR, 0.62; 95% CI, 0.60–0.65) and ideal CVH (HR, 0.47; 95% CI, 0.45–0.49) (Table 2). Compared with poor CVH, ideal CVH was associated with lower risks across all secondary end points (Table 2): HF (HR, 0.33; 95% CI, 0.30–0.37), CHD (HR, 0.35; 95% CI, 0.33–0.37), stroke (HR, 0.47; 95% CI, 0.42–0.53), PAD (HR, 0.54; 95% CI, 0.49–0.59), and AF (HR, 0.66; 95% CI, 0.61–0.71). These associations remained robust after adjustment for medication use and Bonferroni correction. Restricted cubic spline analyses revealed a nonlinear dose-response: Risk decreased sharply until CVH scores reached 50, plateauing at ≥80 points. This pattern was consistent across all CKM and genetic strata, without significant multiplicative interactions (Figure 2, eFigure 3).

GENETIC RISK STRATIFICATION AND JOINT EFFECTS

High polygenic risk independently increased CVD risk (HR, 1.46; 95% CI, 1.43–1.50) compared to low polygenic risk, with the strongest association with CHD (HR, 1.93; 95% CI, 1.86–2.01). These associations were minimally attenuated after adjustment for CVH category, indicating that genetic and behavioral factors contribute independently to CVD risk (eTable 9). The association remained evident when PRS was modeled continuously (per 1-SD increase: HR, 1.19; 95% CI, 1.18–1.20) or as the highest decile versus the remaining 90% (HR, 1.44; 95% CI, 1.40–1.49), although only continuous PRS showed significant interaction with CKM stage (*P* for interaction < .001 vs. .195; eTable 10). Cross-classification revealed a graded increase in CVD risk driven by

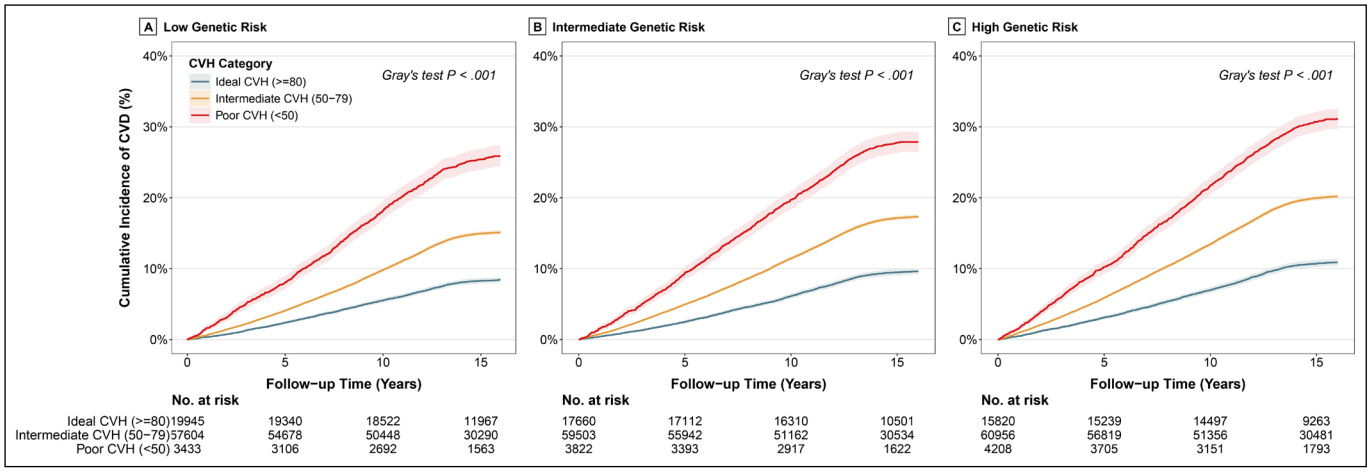


Figure 1 Cumulative incidence of CVD stratified by CVH status across genetic risk strata.

Notes: The panels display the cumulative incidence of composite CVD over a 15-year follow-up period among participants with **(A)** low, **(B)** intermediate, and **(C)** high genetic risk. Within each polygenic risk stratum, participants are categorized by CVH status according to the AHA's LE8 scoring system: poor (<50, red lines), intermediate (50–79, orange lines), and ideal (≥80, blue lines). *P* values were calculated using Gray's test to evaluate differences in cumulative incidence functions across CVH categories, accounting for the competing risk of all-cause mortality. The tables below the x-axes denote the number of participants at risk at five-year intervals.

Abbreviations: CVD, cardiovascular disease; CVH, cardiovascular health.

OUTCOME/CVH CATEGORIES	NO. OF EVENTS/ PARTICIPANTS	MODEL 1	MODEL 2	MODEL 3
Cardiovascular Disease				
Poor CVH	3239/11,463	1 [Reference]	1 [Reference]	1 [Reference]
Intermediate CVH	31,065/178,063	0.57 (0.55–0.59)	0.62 (0.60–0.65)	0.66 (0.63–0.68)
Ideal CVH	5051/53,425	0.30 (0.28–0.31)	0.47 (0.45–0.49)	0.52 (0.49–0.54)
Coronary Heart Disease				
Poor CVH	1856/11,463	1 [Reference]	1 [Reference]	1 [Reference]
Intermediate CVH	15,561/178,063	0.52 (0.49–0.54)	0.58 (0.55–0.61)	0.62 (0.59–0.65)
Ideal CVH	1946/53,425	0.21 (0.20–0.22)	0.35 (0.33–0.37)	0.39 (0.36–0.42)
Stroke				
Poor CVH	486/11,463	1 [Reference]	1 [Reference]	1 [Reference]
Intermediate CVH	4706/178,063	0.62 (0.56–0.68)	0.66 (0.60–0.73)	0.69 (0.63–0.76)
Ideal CVH	698/53,425	0.30 (0.27–0.34)	0.47 (0.42–0.53)	0.51 (0.45–0.57)
Heart Failure				
Poor CVH	747/11,463	1 [Reference]	1 [Reference]	1 [Reference]
Intermediate CVH	5258/178,063	0.44 (0.41–0.48)	0.50 (0.46–0.54)	0.56 (0.52–0.60)
Ideal CVH	663/53,425	0.18 (0.17–0.20)	0.33 (0.30–0.37)	0.40 (0.35–0.44)
Atrial Fibrillation				
Poor CVH	1102/11,463	1 [Reference]	1 [Reference]	1 [Reference]
Intermediate CVH	12,026/178,063	0.69 (0.65–0.73)	0.74 (0.69–0.78)	0.77 (0.73–0.82)
Ideal CVH	2117/53,425	0.40 (0.37–0.43)	0.66 (0.61–0.71)	0.73 (0.68–0.78)
Peripheral Artery Disease				
Poor CVH	710/11,463	1 [Reference]	1 [Reference]	1 [Reference]
Intermediate CVH	5866/178,063	0.52 (0.48–0.57)	0.58 (0.54–0.63)	0.62 (0.57–0.67)
Ideal CVH	1162/53,425	0.34 (0.31–0.38)	0.54 (0.49–0.59)	0.59 (0.54–0.66)

Table 2 Association of CVH categories with primary and secondary cardiovascular outcomes.

Notes: Data are presented as HRs and 95% CIs estimated using Cox proportional hazards models. CVH categories were defined according to the AHA's LE8 scoring system: poor (<50), intermediate (50–79), and ideal (≥80). Poor CVH served as the reference group. Model 1 was unadjusted. Model 2 (the primary analytical model) was adjusted for age, sex, race and ethnicity, education level, Townsend Deprivation Index, alcohol consumption status, continuous PRS, genotyping batch, and the first 10 genetic principal components. Model 3 additionally adjusted for baseline lipid-lowering, antihypertensive, and glucose-lowering medication use. Model 2 was prespecified as the primary model to avoid potential over-adjustment bias, as pharmacological interventions are frequently situated on the causal pathway between cardiovascular health behaviors and clinical outcomes. All hazard ratios presented for Model 2 and Model 3 were statistically significant ($P < .001$), surviving the Bonferroni-corrected threshold ($P < .01$) for the five secondary end points.

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

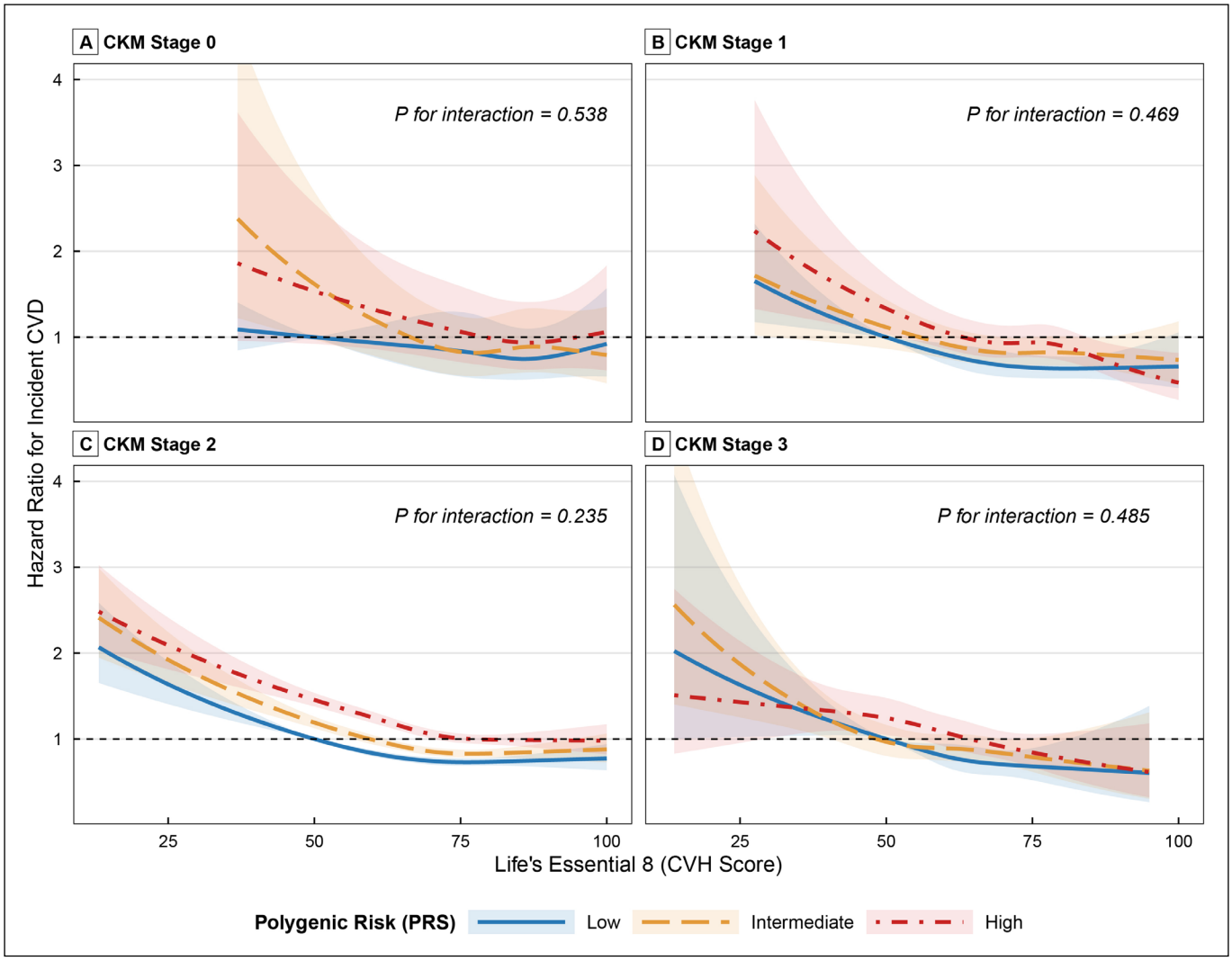


Figure 2 Dose-response association between continuous CVH score and incident CVD, stratified by polygenic risk and CKM stage.

Notes: Restricted cubic splines (RCS) illustrate the continuous dose-response relationship between the **CVH score** (measured by the LE8 metrics, ranging from 0 to 100) and the HRs for incident CVD.

Results are stratified by CKM stages: **(A)** Stage 0; **(B)** Stage 1; **(C)** Stage 2; and **(D)** Stage 3. Within each panel, participants are further categorized by PRS tertiles: low risk (solid blue line), intermediate risk (dashed orange line), and high risk (dash-dotted red line). The lines represent estimated HRs, and the corresponding shaded areas indicate the 95% CIs.

To maintain comparability across the cardiometabolic-genetic continuum, 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). HRs 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.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; HR, hazard ratio; LE8, Life's Essential 8; PRS, polygenic risk score.

both worsening CVH and higher genetic risk across all nine strata. Compared to the ideal CVH/low genetic risk reference (absolute risk, 8.32%), HRs ranged from 1.17 (95% CI, 1.10–1.26) for ideal CVH/intermediate genetic risk to 2.93 (95% CI, 2.72–3.15) for poor CVH/high genetic risk (Figure 3). Both CVH- and PRS-based stratification significantly separated cumulative CVD incidence across all CKM stages (all $P < .001$ by Gray's test; eFigures 2 and 4). The high-versus-low PRS 10-year absolute risk difference increased from 0.61 percentage points in CKM Stage 0 to 1.17, 3.83, and 5.92 percentage points in Stages 1, 2, and 3, respectively (eTable 12).

In the three-way joint analysis (CKM stage × CVH × genetic risk; reference: CKM Stage 0/ideal CVH/low genetic risk), the adjusted HR for CVD reached 4.62 (95% CI, 3.96–5.39) at CKM Stage 3/poor CVH/high genetic risk, with a significant CKM × genetic risk interaction ($P = .003$) but no CKM × CVH interaction ($P = .335$) (Table 3, eFigure 5). This pattern was most pronounced for CHD, for which the maximum HR reached 12.08 (95% CI, 9.47–15.41), and a significant CKM × CVH interaction was observed ($P = .006$) (eFigure 5; eTable 11). Sparse strata, particularly poor-CVH groups in CKM Stage 0, were interpreted cautiously.

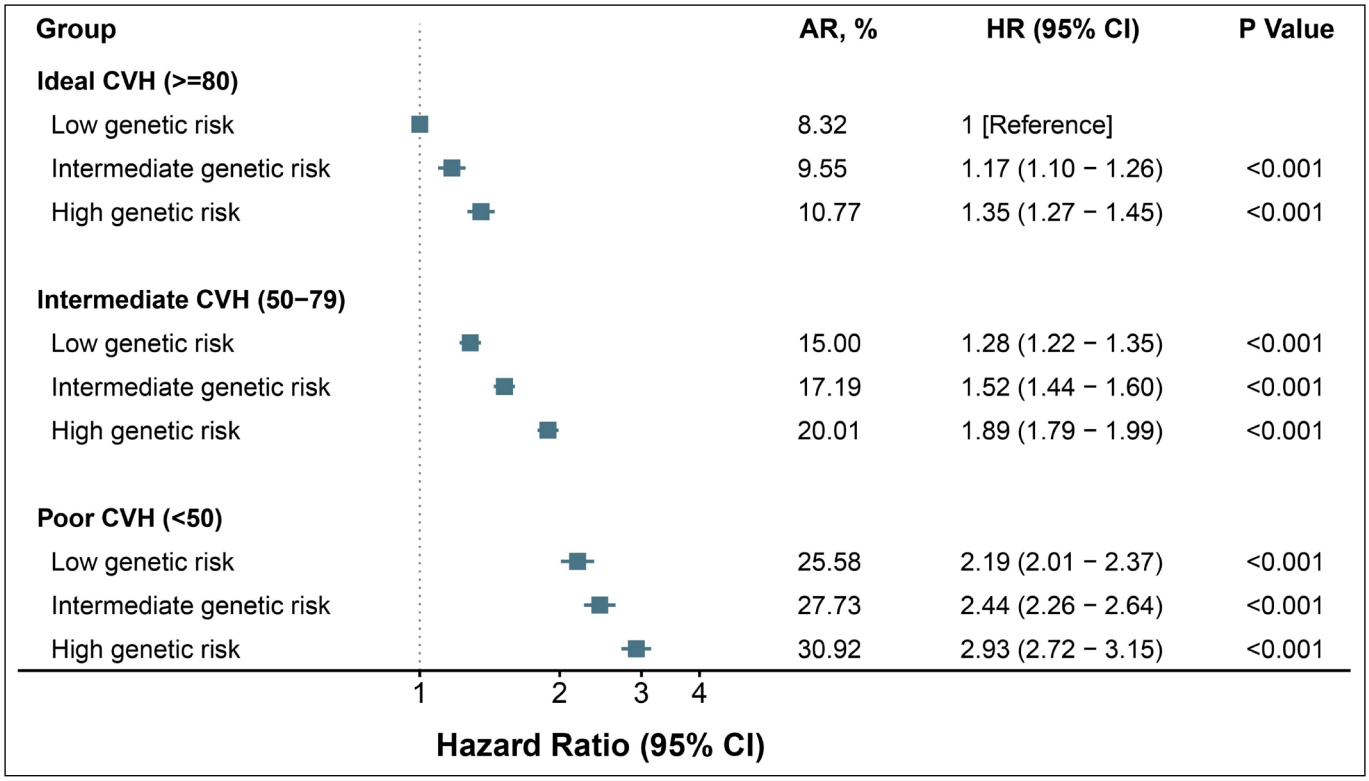


Figure 3 Joint association of CVH and polygenic risk with incident CVD.

Notes: The forest plot displays the absolute risk (AR, %) and adjusted HRs with 95% confidence intervals (CIs) for incident cardiovascular disease across nine cross-classified groups based on cardiovascular health (CVH) categories and polygenic risk tertiles. CVH categories were defined according to Life's Essential 8 scores: poor (<50), intermediate (50–79), and ideal (≥80). Participants with ideal CVH and low genetic risk served as the reference group (HR = 1 [Reference]). HRs 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. Of note, the HRs presented in this figure were estimated from the full analytical cohort pooled across all CKM stages, representing the overall joint association of CVH and genetic risk with incident CVD. These estimates differ from the CKM stage-stratified HRs reported in Table 3, which further partition the analysis by individual CKM stage.

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

CKM STAGE/ GENETIC RISK	IDEAL CVH (≥80)			INTERMEDIATE CVH (50–79)			POOR CVH (<50)		
	EVENTS/N	HR (95% CI)	*P*-VALUE	EVENTS/N	HR (95% CI)	*P*-VALUE	EVENTS/N	HR (95% CI)	*P*-VALUE
CKM Stage 0									
Low genetic risk	568/9767	1.00 [Reference]	—	492/5776	1.16 (1.03–1.31)	.01	0/20	—	—
Intermediate genetic risk	528/8272	1.13 (1.00–1.27)	.04	490/5663	1.21 (1.07–1.36)	< .001	4/23	2.31 (0.86–6.18)	.09
High genetic risk	484/7234	1.23 (1.09–1.38)	< .001	523/5363	1.47 (1.31–1.66)	< .001	5/24	2.67 (1.11–6.45)	.03
CKM Stage 1									
Low genetic risk	309/5007	0.97 (0.85–1.12)	.69	1047/12,119	1.10 (0.99–1.22)	.07	24/206	1.44 (0.96–2.17)	.08
Intermediate genetic risk	316/4266	1.23 (1.07–1.42)	< .001	1124/11,217	1.32 (1.20–1.47)	< .001	36/210	2.16 (1.54–3.03)	< .001
High genetic risk	246/3520	1.21 (1.04–1.41)	.01	1149/10,658	1.50 (1.35–1.66)	< .001	40/212	2.66 (1.93–3.67)	< .001
CKM Stage 2									
Low genetic risk	780/5159	1.83 (1.64–2.04)	< .001	6644/38,501	1.84 (1.69–2.01)	< .001	680/2852	2.80 (2.50–3.13)	< .001
Intermediate genetic risk	835/5098	2.02 (1.81–2.25)	< .001	8053/41,224	2.17 (1.99–2.37)	< .001	827/3186	3.15 (2.83–3.51)	< .001
High genetic risk	962/5038	2.43 (2.19–2.70)	< .001	9818/43,369	2.70 (2.48–2.94)	< .001	1027/3525	3.76 (3.40–4.17)	< .001

(Contd.)

CKM STAGE/ GENETIC RISK	IDEAL CVH (≥80)			INTERMEDIATE CVH (50–79)			POOR CVH (<50)		
	EVENTS/N	HR (95% CI)	*P*-VALUE	EVENTS/N	HR (95% CI)	*P*-VALUE	EVENTS/N	HR (95% CI)	*P*-VALUE
CKM Stage 3									
Low genetic risk	3/12	1.29 (0.41–4.01)	.66	456/1207	2.57 (2.27–2.92)	< .001	174/355	3.99 (3.37–4.74)	< .001
Intermediate genetic risk	8/24	2.04 (1.01–4.09)	.05	561/1399	2.87 (2.55–3.23)	< .001	193/403	3.92 (3.33–4.62)	< .001
High genetic risk	12/27	3.08 (1.74–5.46)	< .001	708/1566	3.42 (3.06–3.82)	< .001	229/447	4.62 (3.96–5.39)	< .001

Table 3 Joint associations of CKM stage, CVH, and genetic risk with incident CVD.

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

Notes: CVH categories were defined according to the AHA's LE8 scoring system: poor (<50), intermediate (50–79), and ideal (≥80).

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.

Global Reference Group: To allow for absolute and relative risk comparisons across the entire disease and genetic continuum, all HRs within this 36-strata joint analysis were calculated utilizing a single global reference group: participants in CKM Stage 0 with low genetic risk and ideal CVH.

Data Interpretation and Sparse Cells: Dashes (—) indicate that HRs and P-values could not be estimated due to zero incident events in that specific subgroup (e.g., CKM Stage 0/low genetic risk/poor CVH). Furthermore, estimates for the 'Poor CVH' subgroups within CKM Stage 0 should be interpreted with caution due to the very small sample sizes (N = 20–24) and correspondingly wide confidence intervals. This sparsity reflects the biological reality that poor CVH is exceedingly rare among individuals clinically classified as having Stage 0 CKM syndrome (i.e., absence of metabolic risk factors).

SENSITIVITY AND SUBGROUP ANALYSES

The protective association of ideal CVH was robust across all sensitivity analyses, including additional adjustment for CRP and CKM stage in the revised Model 4 (HR, 0.66; 95% CI, 0.63–0.69), IPW (HR, 0.62; 95% CI, 0.58–0.67), doubly robust estimation (HR, 0.57; 95% CI, 0.53–0.60), and exclusion of events within the first year (HR, 0.47; 95% CI, 0.45–0.49) and the first three years of follow-up (HR, 0.48; 95% CI, 0.46–0.50) (eTables 14–15, eFigure 6). In a sensitivity analysis restricted to the four behavioral LE8 components, each 10-point higher behavioral CVH score was associated with a lower hazard of incident CVD (HR, 0.923; 95% CI, 0.917–0.929), with no interaction by CKM stage (P = .241; eTable 13). Results were similar after IPSW for complete-case selection (ideal vs. poor CVH: HR, 0.46; 95% CI, 0.44–0.48), with a nonsignificant CKM stage × CVH interaction and a significant CKM stage × PRS interaction (P = .565 and .020, respectively; eTables 17–18). Competing risk models accounting for all-cause mortality yielded similar results (ideal vs. poor CVH: subdistribution hazard ratio (sdHR), 0.47; 95% CI, 0.45–0.49), with inverse associations of continuous CVH maintained across all CKM stages (eTable 16). In subgroup analyses, risk reductions per 10-point CVH increase were consistent across sex, renal function, genetic risk, and CKM stage (all P for interaction > .05). Significant effect modification was limited to age and baseline CRP, with greater relative reductions in participants <60 years (HR, 0.77 vs. 0.86) and those with CRP ≥2 mg/L (HR, 0.83 vs. 0.86) (eFigure 7).

INCREMENTAL PREDICTIVE VALUE OF PRS

In the internally validated prediction analysis, adding standardized continuous PRS to the base model increased the 10-year time-dependent AUC from 0.7212 (95% CI, 0.7187–0.7238) to 0.7257 (95% CI, 0.7231–0.7282), an absolute increase of 0.0045 (95% CI, 0.0039–0.0052; P < .001). Calibration was similar between models (slopes, 0.991 vs. 0.992), with a mean predicted 10-year risk of 10.81% in both models, matching the observed risk of 10.81% (eTable 19, eFigure 8).

DISCUSSION

In this large prospective cohort study, we systematically evaluated the joint associations of CVH, quantified by the LE8 metrics (7), and genetic susceptibility with incident CVD across the continuum of CKM stages (3). Our analysis yielded several principal findings: First, higher CVH was inversely associated with incident CVD and all secondary end points, irrespective of polygenic risk stratum; second, higher CVH was consistently associated with lower CVD risk across genetic risk strata; third, this protective association was consistent across the entire CKM

disease continuum, with no significant effect modification by CKM stage; and fourth, both CVH- and genetic risk-based stratification significantly separated cumulative CVD incidence across all CKM stages, with greater absolute PRS-related risk separation at more advanced CKM stages.

The independent roles of genetic predisposition and modifiable lifestyle factors in CVD pathogenesis have been widely established (17–19). Our findings extend the current literature by integrating the recently proposed CKM framework (3, 4), demonstrating that the protective association of ideal CVH persists across the CKM disease continuum. Across genetic risk strata, higher CVH was associated with lower incident CVD risk. However, direct comparisons between participants with high PRS and ideal CVH and those with low PRS and poor CVH were not performed; these findings should therefore not be interpreted as demonstrating that ideal CVH eliminates or fully offsets genetic susceptibility. Nevertheless, the consistent inverse association of CVH across PRS strata supports the relevance of favorable CVH regardless of genetic susceptibility (20–22).

A notable finding was that both CVH and genetic risk significantly stratified cumulative CVD incidence across all CKM stages, including Stage 0 (all Gray's test $P < .001$). However, the high- versus-low PRS 10-year absolute risk difference increased from 0.61 percentage points in Stage 0 to 5.92 percentage points in Stage 3. Thus, genetic susceptibility was detectable even in CKM Stage 0, but its absolute impact increased with advancing CKM burden. These findings support the joint consideration of genetic susceptibility and cardiometabolic burden when interpreting absolute CVD risk (8, 23–25).

A further important finding was the lack of significant interaction between CVH and CKM stage (P for interaction = .335), indicating that the protective association of higher CVH was preserved across the full disease spectrum. Although LE8 and CKM staging partially overlap in their metabolic and clinical components, the inverse association remained evident when CVH was restricted to the four behavioral components. The CKM staging system reflects progressive pathophysiology, and Stage 3 is characterized by overt target organ damage and elevated clinical risk (3). It might be expected that once substantial structural damage is established, the capacity for behavioral optimization to modify disease trajectory would be limited (26, 27). However, the relative risk reduction associated with a 10-point higher CVH score was not only preserved but numerically larger in Stage 3 (HR, 0.86; 95% CI, 0.83–0.90) compared with Stage 0 (HR, 0.93; 95% CI, 0.89–0.97). Given the higher baseline risk in advanced CKM stages, a similar relative association may correspond to a larger absolute risk difference, although this was not directly quantified. The inverse association remained evident in sensitivity analyses using IPW (HR, 0.62; 95% CI, 0.58–0.67) and doubly robust estimation addressing residual covariate imbalances in age, CRP, and eGFR (HR, 0.57; 95% CI, 0.53–0.60). Similar results were obtained with the revised Model 4 and IPSW accounting for measured determinants of complete-case inclusion.

Conversely, the significant CKM × genetic risk interaction ($P = .003$), together with the widening absolute risk difference across CKM stages, suggests that advancing CKM burden amplifies the cardiovascular consequences of polygenic susceptibility. This pattern is consistent with a gene-environment framework in which metabolic and inflammatory pathways may magnify the phenotypic expression of cardiovascular risk alleles (28). Although PRS provided statistically significant incremental prognostic information beyond CKM stage and CVH, the modest improvement in discrimination and largely unchanged calibration suggest limited incremental clinical value.

The interaction patterns also differed across individual clinical end points. While no significant CKM × CVH interaction was observed for composite CVD, a significant interaction was detected for CHD ($P = .006$), suggesting that the relative benefit of higher CVH may vary by CKM stage for atherosclerosis-specific outcomes. Specifically, the HR gradient across CVH categories widened progressively from CKM Stage 0 to Stage 3 for CHD, reaching 12.08 at Stage 3/poor CVH/high genetic risk—substantially higher than the corresponding composite CVD estimate of 4.62. This divergence likely reflects the direct mechanistic alignment between LE8 components and atherosclerotic pathways: The health factors embedded in LE8 target the metabolic and hemodynamic drivers of coronary atherosclerosis (29), and their impact may be amplified in the context of advanced CKM disease, where these drivers are most active. By contrast, the composite CVD outcome dilutes this signal by including end points with partially distinct pathophysiology, such as AF, for which the CKM × CVH interaction was nonsignificant. Consistent

with this mechanistic divergence, the overall magnitude of protection varied across secondary end points, with the strongest associations observed for HF (HR, 0.33; 95% CI, 0.30–0.37) and CHD (HR, 0.35; 95% CI, 0.33–0.37), and the most modest for AF (HR, 0.66; 95% CI, 0.61–0.71) (30–32).

These observations carry two main clinical implications. First, the robust risk reduction observed across all CKM stages suggests that lifestyle optimization yields substantial benefits even in advanced disease, although the observational design precludes definitive conclusions about whether this association reflects a direct causal effect of CVH improvement or residual confounding by overall health status (33). Second, our subgroup analysis revealed a significant interaction with age (P for interaction < .001), with the protective association being more pronounced among participants younger than 60 years (HR, 0.77 vs. 0.86). This suggests that primordial and primary prevention earlier in the life course may yield the largest relative risk reductions (a statistically significant but clinically marginal interaction was also noted for baseline CRP [P = .003]) (34). CVH assessment may complement CKM staging by identifying health domains requiring preventive attention, although longitudinal and interventional validation is needed before clinical or public health implementation.

This study has several limitations. First, despite rigorous propensity score weighting, the observational design precludes definitive causal inference due to potential residual confounding from unmeasured factors, such as environmental exposures or psychosocial stress. Second, CVH, medication use, and CKM stage were assessed only at baseline, precluding the assessment of subsequent changes and leaving potential for time-varying confounding from medical interventions during follow-up. Self-reported dietary data may also have been subject to recall and reporting bias. Third, PRS were derived from genome-wide association studies conducted primarily in European populations, and their transferability to other ancestries remains uncertain (18). Because PREVENT was developed mainly in US populations, calibration differences may have affected CKM Stage 3 classification in the UK Biobank; replacing it with QRISK3 would constitute a modified staging definition. Although IPSW yielded similar estimates, residual selection bias related to unmeasured determinants of complete-case inclusion cannot be excluded. Finally, participants in the UK Biobank are predominantly of European descent and subject to a well-documented healthy volunteer selection bias, limiting generalizability—particularly of the polygenic risk interactions—to more diverse populations (35).

CONCLUSIONS

Ideal CVH was associated with lower incident CVD risk across all CKM stages, irrespective of genetic susceptibility. Both CVH and polygenic risk stratified cumulative CVD incidence throughout the CKM continuum, while the absolute impact of genetic susceptibility increased with advancing CKM burden. These findings support incorporating LE8-based CVH assessment as a complementary axis within CKM staging and underscore the relevance of favorable CVH across the cardiometabolic continuum.

DATA ACCESSIBILITY STATEMENT

All data relevant to the study were acquired from the UK Biobank Resource under application number 532333. Data can be accessed through applications on the UK Biobank website (https://www.ukbiobank.ac.uk/).

ADDITIONAL FILE

The additional file for this article can be found as follows:

- **Supplementary Files.** Supplementary methods, tables, and figures supporting the study analyses. DOI: https://doi.org/10.5334/gh.1603.s1

ETHICS AND CONSENT

The UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (11/NW/0382), and all participants provided written informed consent. This secondary analysis was conducted under application number 532333.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

Hao Zhang: Writing – original draft, conceptualization.

Mingyang Li: Project administration, methodology, data curation.

Sizhuang Huang: Project administration, conceptualization.

Yanwen Fang: Project administration, methodology.

Haihua Zhang: Literature search and analyses.

Weixian Yang: Review and editing, supervision.

Mengyue Yu: Writing – review and editing, supervision, formal analysis, data curation.

Hao Zhang and Mingyang Li contributed equally to this work.

The authors take responsibility for all aspects of the integrity of the data and the accuracy of the data analysis.

AUTHOR AFFILIATIONS

Hao Zhang orcid.org/0000-0003-4118-5577
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China

Mingyang Li
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China

Sizhuang Huang
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China

Yanwen Fang
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China

Haihua Zhang
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China

Weixian Yang
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China

Mengyue Yu orcid.org/0000-0002-8704-6110
Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Science and Peking Union Medical College, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China

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