

Joint Associations of the Atherogenic Index of Plasma and Estimated Glucose Disposal Rate with Incident Cardio-Renal- Metabolic Multimorbidity: A Prospective Cohort Study in UK Biobank and CHARLS

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Abstract

Background

Atherogenic dyslipidemia and insulin resistance are implicated in cardio-renal-metabolic disease. The atherogenic index of plasma (AIP) and estimated glucose disposal rate (eGDR) capture complementary aspects of these metabolic disturbances. We examined the individual and joint associations of AIP and eGDR with incident cardio-renal-metabolic multimorbidity (CRMM).

Methods

We analyzed 394,483 UK Biobank participants and 8,671 participants from the China Health and Retirement Longitudinal Study (CHARLS). AIP was calculated as $\log_{10}[\text{triglycerides}/\text{high-density lipoprotein cholesterol}]$, and eGDR was derived from waist circumference, hypertension status, and glycated hemoglobin. Cox proportional hazards models were used to estimate associations with incident CRMM. Exploratory incremental performance was assessed using Harrell's C-index, time-dependent area under the receiver operating characteristic curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

Results

During follow-up, 23,289 UK Biobank participants (5.9%) and 1,185 CHARLS participants (13.7%) developed CRMM. In UK Biobank, high AIP and low eGDR were each associated with higher CRMM risk (fully adjusted HRs, 2.31 and 2.54, respectively). Compared with the low-AIP/high-eGDR phenotype, the high-AIP/low-eGDR phenotype had the highest risk (HR, 5.24; 95% CI, 4.97–5.52). In exploratory performance analyses, the C-index increased from 0.8033 for the basic model to 0.8459 after addition of both markers; the corresponding NRI and IDI were 0.6588 and 0.0354.

Conclusions

Higher AIP and lower eGDR were independently and jointly associated with incident CRMM in two prospective cohorts. The high-AIP/low-eGDR phenotype identified a group with substantially higher relative risk. The exploratory prediction analyses suggest potential incremental risk-stratification value, but further calibration and validation are required before clinical implementation.

Background

Cardio-renal-metabolic multimorbidity (CRMM), defined in this study as the presence of at least two among cardiovascular disease (CVD), type 2 diabetes (T2D), and chronic kidney disease (CKD), is an important public health concern [1]. Population-based studies have shown that cardiometabolic

multimorbidity is associated with greater mortality, disability, and functional decline than single-disease states [2, 3]. Given the interconnected and progressive nature of these conditions, identifying metabolic profiles associated with transition to multimorbidity may inform preventive research.

Atherogenic dyslipidemia may contribute to CRMM through lipid-mediated vascular injury and metabolic dysfunction. The atherogenic index of plasma (AIP), calculated as $\log_{10}$ of the molar triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio, is a composite marker derived from routine lipid measurements and is related to lipoprotein particle characteristics [4, 5]. Higher AIP has been associated with hypertension, diabetes, coronary artery disease, and adverse cardiovascular outcomes in diverse populations [6–10]. Its reliance on routinely measured lipid parameters makes AIP a practical marker for epidemiologic risk stratification.

Insulin resistance is another central mechanism linking CVD, T2D, and CKD. The estimated glucose disposal rate (eGDR) is a validated surrogate of insulin resistance based on routinely collected clinical measurements [11, 12]. Lower eGDR has been associated with incident atherosclerotic cardiovascular disease, CKD, stroke, and mortality in diabetic and general-population cohorts [13–17]. Accordingly, eGDR may complement lipid-based markers when characterizing cardio-renal-metabolic risk.

Although AIP and eGDR reflect related metabolic dysfunction, they capture partly distinct domains: AIP primarily summarizes an atherogenic lipid pattern, whereas eGDR reflects insulin resistance, central adiposity, hypertension, and glycemic status. Previous studies have examined combinations of eGDR with inflammatory indices [18], remnant cholesterol with body mass index [19], and AIP with eGDR for new-onset CVD [20]. However, the joint association of AIP and eGDR with the development and progression of CRMM has not been well characterized across independent prospective cohorts.

We therefore investigated the individual and joint associations of AIP and eGDR with incident CRMM in UK Biobank and examined the reproducibility of these associations in CHARLS. We also evaluated nonlinear exposure-response patterns, additive interaction, transition-specific associations in a multistate framework, and exploratory incremental prediction performance.

Methods

Study design and participants

The participant-selection process is shown in Supplementary Figure S1. UK Biobank recruited approximately 500,000 adults aged 37–73 years from England, Scotland, and Wales during 2006–2010 [21, 22]. Of 501,936 participants available for the present workflow, 6,172 with baseline CRMM, 94,696 with missing AIP or eGDR, and 6,585 with incomplete covariate data were excluded, leaving 394,483 participants for the primary UK Biobank analysis. Participants with none or only one of the three CRMM component diseases at baseline remained eligible.

CHARLS is a nationally representative prospective study of community-dwelling Chinese adults [23]. For the present analysis, the 2011 wave served as baseline and follow-up continued through 2020. Among 17,708 Wave 1 participants, 777 aged < 45 years were excluded. A further 1,863 participants were excluded because of prevalent CRMM at baseline (n = 848) or missing Wave 1 records/loss to follow-up (n = 1,015), and 6,397 with missing baseline AIP or eGDR were excluded, yielding 8,671 participants. CHARLS was treated as an independent replication cohort rather than a transported external validation of a single fitted prediction model.

The primary analyses were therefore based on participants with the required exposure and covariate information after the exclusions shown in Supplementary Figure S1. Because a substantial number of participants were excluded for missing exposure data, potential selection bias from complete-case restriction was considered when interpreting the findings.

Calculation of AIP, eGDR, and joint phenotypes

AIP and eGDR were calculated using established formulas [4, 11, 12]:

$$\text{AIP} = \log_{10}[\text{TG (mmol/L)} / \text{HDL-C (mmol/L)}]$$

$$\text{eGDR (mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}) = 21.158 - 0.09 \times \text{waist circumference (cm)} - 3.407 \times \text{hypertension (yes = 1, no = 0)} - 0.551 \times \text{HbA1c (\%)}$$

AIP and eGDR were dichotomized using cohort-specific medians. These medians were data-derived thresholds rather than clinical cut points. Participants were cross-classified into four joint phenotypes: G1, low AIP/high eGDR (reference); G2, high AIP/high eGDR; G3, low AIP/low eGDR; and G4, high AIP/low eGDR. Higher AIP and lower eGDR were considered the metabolically less favorable directions.

Ascertainment of incident CRMM

The primary endpoint was incident CRMM, defined as the first occurrence during follow-up at which a participant had at least two of CVD, T2D, and CKD, consistent with the cardiovascular-kidney-metabolic framework [1]. In UK Biobank, CVD comprised coronary heart disease (ICD-10 I20-I25), atrial fibrillation (I48), heart failure (I50), and stroke (I60-I64), ascertained from linked hospital records, national death registry data, and available self-reported information [21, 22, 24]. T2D was identified from hospital records (ICD-10 E11), death registry data, self-reported physician diagnosis, or HbA1c $\geq 6.5\%$ [25]. CKD was identified from hospital records (ICD-10 N18), death registry data, self-reported diagnosis, or eGFR < 60 mL/min/1.73 m² [26]. Because an isolated eGFR value does not establish persistence for at least 3 months, the eGFR-based component should be interpreted as an operational study definition rather than a complete clinical CKD diagnosis.

In CHARLS, baseline disease status was assessed in 2011 and incident component conditions were ascertained during subsequent waves through 2020; detailed definitions are provided in Supplementary Table S1. The two cohorts used the same conceptual CRMM endpoint but different ascertainment sources, with UK Biobank relying predominantly on linked electronic health records and registries and CHARLS relying more heavily on self-reported diagnoses supplemented by biomarker criteria. Follow-up time was calculated from baseline to incident CRMM, death, loss to follow-up, or administrative censoring, whichever occurred first.

Covariates

Potential confounders were prespecified on the basis of clinical relevance and prior literature. In UK Biobank, Model 2 included age, sex, race, Townsend deprivation index, educational attainment, smoking status, alcohol intake, sleep duration, lipid-lowering medication use, C-reactive protein (CRP), and low-density lipoprotein cholesterol (LDL-C). Smoking and alcohol status were categorized as never, former, or current [27, 28]. The Townsend deprivation index was used as an area-based measure of socioeconomic disadvantage [29]. Family history of cardiometabolic disease, used in a sensitivity analysis, was defined from self-reported first-degree family history of heart disease, stroke, hypertension, or diabetes [30]. Hypertension was defined by self-reported diagnosis, antihypertensive medication use, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg [31, 32]. In CHARLS, Model 2 included age, sex, education, marital status, hukou, alcohol intake, smoking status, sleep duration, lipid-lowering medication use, LDL-C, and high-sensitivity CRP (hs-CRP). Waist circumference, hypertension, and HbA1c were not entered separately in the primary fully adjusted models because they are components of eGDR.

Statistical analysis

Baseline characteristics were summarized across the four joint AIP-eGDR phenotypes. Continuous variables were reported as mean (standard deviation) or median (interquartile range), as appropriate, and categorical variables as n (%). Group comparisons used the statistical tests specified in the corresponding table notes.

Associations with incident CRMM were estimated using Cox proportional hazards regression and are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Three sequential models were fitted: a crude model without covariate adjustment; Model 1 adjusted for age and sex; and Model 2 adjusted for the full cohort-specific covariate set described above. AIP and eGDR were first examined separately and were then evaluated as the four joint phenotypes, with G1 (low AIP/high eGDR) as the reference. The same analytic framework was applied in CHARLS to evaluate cross-cohort consistency of the associations.

Continuous associations were explored using restricted cubic spline (RCS) models [33], and threshold/piecewise regression was used to summarize segments when nonlinear patterns were

evaluated. P values for nonlinearity and likelihood-ratio tests are reported in Supplementary Table S5.

Additive interaction between high AIP and low eGDR was quantified using the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI) [34, 35].

Exploratory incremental performance analyses compared a basic covariate model with models additionally including AIP, eGDR, or both markers. Harrell's C-index was evaluated over overall follow-up [36], and time-dependent AUCs were estimated at 5, 10, and 15 years in UK Biobank and at 3, 6, and 9 years in CHARLS [37]. IDI and category-free NRI were also calculated [38, 39]. These analyses were considered exploratory because calibration, overall prediction error, and resampling-based internal validation were not reported in the available analysis outputs.

Multistate Markov model

In UK Biobank, cause-specific Cox models within a multistate Markov framework were used to examine coarse and detailed CRMM transitions [40]. The coarse structure comprised three non-death states: no CRMM, dual comorbidity (any two of CVD, T2D, and CKD), and triple comorbidity (all three conditions); death was an absorbing state. The no-CRMM state intentionally included participants with either zero or one component disease and was therefore clinically heterogeneous. Allowed transitions were no CRMM to dual comorbidity, dual to triple comorbidity, and each non-death state to death.

The detailed structure separated dual comorbidity into CVD+T2D, CVD + CKD, and T2D + CKD. Transitions from no CRMM to each dual-comorbidity subtype, from each subtype to triple comorbidity, and from each relevant state to death were evaluated. Transition-specific HRs were estimated for high versus low AIP and for low versus high eGDR using the covariate set reported in Supplementary Tables S9 and S10.

Subgroup stratification and sensitivity analyses

Prespecified subgroup analyses were conducted in UK Biobank by age, sex, race/ethnicity, education, smoking, and alcohol intake, and in CHARLS by age, sex, education, hukou, smoking, and alcohol intake. Sensitivity analyses in UK Biobank additionally adjusted for family history of cardiometabolic disease, further adjusted for glucose-lowering and antihypertensive medications, and used Fine-Gray models treating death before CRMM as a competing event. Two-sided $P < 0.05$ was used as the nominal significance threshold. Because multiple subgroup interaction tests were performed without a reported multiplicity adjustment, these interaction findings were regarded as exploratory. Analyses were conducted in R version 4.4.1.

Results

Baseline characteristics

The analytic sample comprised 394,483 UK Biobank participants (mean age, 56.48 years; 54.0% female) and 8,671 CHARLS participants (mean age, 58.94 years; 53.4% female). In UK Biobank, the four phenotypes were G1 (n = 118,811; 30.1%), G2 (n = 78,431; 19.9%), G3 (n = 78,430; 19.9%), and G4 (n = 118,811; 30.1%). G4 had a less favorable measured profile, including greater waist circumference, higher HbA1c and CRP, and a higher prevalence of hypertension. During a median follow-up of 12.6 years (IQR, 11.9–13.3), 23,289 participants (5.9%) developed CRMM. In CHARLS, 1,185 participants (13.7%) developed CRMM during a median follow-up of 7.0 years (IQR, 4.0–8.0). Baseline characteristics are shown in Supplementary Tables S2 and S3.

Relationships between AIP, eGDR and incident CRMM risk

In UK Biobank, both AIP and eGDR were independently associated with incident CRMM. After full adjustment, high AIP was associated with higher CRMM risk (HR, 2.31; 95% CI, 2.24–2.38), and low eGDR showed a similarly elevated relative risk (HR, 2.54; 95% CI, 2.46–2.63). Associations in CHARLS were directionally consistent but attenuated (Fig. 1 and Supplementary Table S4).

Joint analyses showed a graded pattern across the four AIP-eGDR phenotypes. In UK Biobank, compared with G1 (low AIP/high eGDR), the fully adjusted HRs were 2.33 (95% CI, 2.19–2.47) for G2 (high AIP/high eGDR), 2.51 (95% CI, 2.38–2.66) for G3 (low AIP/low eGDR), and 5.24 (95% CI, 4.97–5.52) for G4 (high AIP/low eGDR). In CHARLS, the corresponding HRs were 1.34 (95% CI, 1.10–1.64), 1.99 (95% CI, 1.65–2.40), and 2.58 (95% CI, 2.18–3.05). In both cohorts, G4 had the highest relative risk (Supplementary Table S4; Supplementary Figure S2).

Restricted cubic spline analyses

RCS analyses suggested nonlinear associations of both AIP and eGDR with incident CRMM in UK Biobank (both P for nonlinearity < 0.001). Piecewise regression identified an AIP threshold of 0.348 and an eGDR threshold of 10.270. For AIP, the HRs per one-unit increase were 6.79 (95% CI, 6.33–7.27) below the threshold and 3.16 (95% CI, 2.79–3.59) above it. For eGDR, the corresponding HRs per one-unit increase were 0.76 (95% CI, 0.76–0.77) below the threshold and 0.52 (95% CI, 0.49–0.56) above it (Fig. 2; Supplementary Table S5).

In CHARLS, there was no evidence of nonlinearity for AIP (P for nonlinearity = 0.570), whereas eGDR showed a nonlinear pattern (P for nonlinearity = 0.001). Piecewise analysis identified an eGDR threshold of 11.146; the full segment-specific estimates are provided in Supplementary Table S5.

Prediction performance and additive interaction

In the exploratory performance analysis, the UK Biobank basic model had a C-index of 0.8033, compared with 0.8261 after adding AIP, 0.8351 after adding eGDR, and 0.8459 after adding both markers (Table 1). Relative to the basic model, the model containing both markers had an IDI of 0.0354 and a category-free NRI of 0.6588. These results indicate numerically higher discrimination and reclassification metrics after addition of the markers, but they should not be interpreted as establishing a clinically validated prediction tool.

Table 1
Exploratory C-index, IDI, and NRI for incident CRMM in UK Biobank

Model	Harrell's C-index (95% CI)	IDI	<i>P</i> value	NRI	<i>P</i> value
Basic model	0.8033 (0.7990–0.8076)	-	-	-	-
Basic model + AIP	0.8261 (0.8221–0.8301)	0.0191 (0.0029–0.0269)	< 0.001	0.4484 (0.2658–0.6676)	< 0.001
Basic model + eGDR	0.8351 (0.8313–0.8389)	0.0262 (0.0058–0.0486)	< 0.001	0.4607 (0.2937–0.5825)	< 0.001
Basic model + AIP + eGDR	0.8459 (0.8423–0.8495)	0.0354 (0.0083–0.0516)	< 0.001	0.6588 (0.5596–0.8758)	< 0.001
Note: AIP, atherogenic index of plasma; CI, confidence interval; CRMM, cardio-renal-metabolic multimorbidity; eGDR, estimated glucose disposal rate; IDI, integrated discrimination improvement; NRI, category-free net reclassification improvement. Harrell's C-index was estimated over overall follow-up. The basic model included age, sex, race, Townsend deprivation index, education, smoking status, alcohol intake, sleep duration, lipid-lowering medication use, LDL-C, and CRP. These incremental performance analyses were exploratory and were not intended to establish a clinically validated prediction model.					

Additive interaction analyses assessed whether the joint association of high AIP and low eGDR exceeded that expected from their individual associations on the scale used for the analysis. In UK Biobank, RERI was 1.400 (95% CI, 1.063–1.741), AP was 0.266 (95% CI, 0.211–0.319), and SI was 1.494 (95% CI, 1.357–1.641), with $P < 0.001$ for each measure. In CHARLS, the corresponding estimates were RERI 0.240 (95% CI, -0.396 to 0.875), AP 0.086 (95% CI, -0.171 to 0.303), and SI 1.217 (95% CI, 0.768–1.875), with $P = 0.457$. Thus, evidence of additive interaction was present in UK Biobank but not in CHARLS (Supplementary Tables S7 and S8).

Time-dependent AUCs were estimated at 5, 10, and 15 years in UK Biobank and at 3, 6, and 9 years in CHARLS. In UK Biobank, the 10-year AUC was 0.822 for the basic model and 0.843, 0.854, and 0.863 after adding AIP, eGDR, and both markers, respectively. Similar numerical patterns were observed at 5 and 15 years. In CHARLS, gains were smaller and less consistent, and the combined model showed only modest numerical improvement over the single-marker models at several time points (Supplementary Table S6; Fig. 3).

Subgroup analyses

Subgroup analyses evaluated the joint phenotypes across prespecified strata (Supplementary Figures S3 and S4). In UK Biobank, G4 was associated with higher CRMM risk in each reported stratum, with adjusted HRs versus G1 ranging from approximately 3.5 to 7.8. Nominal interaction P values were < 0.001 for age, sex, and education, with larger relative associations in younger participants, women, and participants with higher educational attainment. Given the number of subgroup comparisons and the

absence of a reported multiplicity correction, these potential effect modifications should be interpreted as exploratory. CHARLS subgroup estimates were directionally consistent across the reported strata.

Multistate Markov transition analysis

In UK Biobank, the multistate analyses included coarse and detailed transition structures. In the coarse model, high AIP was associated with transition from no CRMM to dual comorbidity (HR, 2.24; 95% CI, 2.18–2.31) and from dual to triple comorbidity (HR, 1.40; 95% CI, 1.29–1.53). In the detailed model, high AIP was associated with transitions from no CRMM to CVD+T2D (HR, 2.87; 95% CI, 2.74–3.00), CVD + CKD (HR, 1.42; 95% CI, 1.36–1.49), and T2D + CKD (HR, 3.76; 95% CI, 3.41–4.14). Among dual-comorbidity states, the largest HR for progression to triple comorbidity was observed for CVD + CKD (HR, 1.71; 95% CI, 1.41–2.06), followed by CVD+T2D (HR, 1.23; 95% CI, 1.10–1.37). Low eGDR showed broadly similar associations across many transitions (Supplementary Tables S9-S12; Fig. 4).

Sensitivity analyses

Sensitivity analyses in UK Biobank were directionally consistent after additional adjustment for family history of cardiometabolic disease, further adjustment for glucose-lowering and antihypertensive medications, and Fine-Gray competing-risk modeling with death before CRMM treated as a competing event (Supplementary Tables S13-S15).

Discussion

Across two prospective cohorts, higher AIP and lower eGDR were separately and jointly associated with incident CRMM. The high-AIP/low-eGDR phenotype had the highest relative risk, with an approximately fivefold HR in UK Biobank and an approximately 2.6-fold HR in CHARLS compared with the reference phenotype. Continuous analyses suggested nonlinear patterns for both markers in UK Biobank and for eGDR in CHARLS. Exploratory performance analyses showed higher discrimination and reclassification metrics after adding AIP and eGDR to the basic model, although these analyses were not designed to establish a clinically deployable prediction model.

The magnitude of the associations differed between UK Biobank and CHARLS despite broadly consistent directions. Several factors may contribute, including differences in age distribution, ethnicity, baseline disease burden, follow-up duration, healthcare access, and outcome ascertainment. UK Biobank relied predominantly on linked electronic health records and registry data, whereas CHARLS relied more heavily on self-reported diagnoses supplemented by biomarker criteria. Accordingly, CHARLS is best interpreted as an independent replication of the epidemiologic association rather than a strict external transport validation of a prediction model.

The multistate analyses provided additional information on CRMM progression routes. High AIP was associated with transitions from the clinically heterogeneous no-CRMM state to dual comorbidity and from dual to triple comorbidity. In the detailed model, the largest HR from no CRMM was observed for

transition to T2D + CKD, whereas the largest HR for progression from dual to triple comorbidity was observed for CVD + CKD. These transition-specific findings are descriptive associations and should not be interpreted as evidence that AIP causally drives a particular disease sequence.

The present findings are consistent with prior studies of the individual markers. Higher AIP has been associated with coronary artery disease, T2D, reduced kidney function, and adverse cardiovascular outcomes [6–10, 41, 42]. Lower eGDR has likewise been associated with incident CVD, CKD, stroke, and mortality across different populations [13–17].

Several recent studies have evaluated combined metabolic-marker profiles in relation to cardiometabolic outcomes. Yuan et al. [18] reported an association of low eGDR combined with greater systemic inflammation with mortality. Li et al. [19] examined remnant cholesterol together with body mass index in relation to cardiometabolic multimorbidity in CHARLS. Fan et al. [20] reported gradients of new-onset CVD risk across joint AIP-eGDR groups. Zhao et al. [43] provided Mendelian-randomization evidence relating remnant cholesterol and triglycerides to cardiometabolic multimorbidity. The present study extends this literature by examining AIP and eGDR jointly in relation to CRMM incidence and transition patterns across two prospective cohorts.

Biologically, the high-AIP/low-eGDR phenotype may represent the convergence of atherogenic dyslipidemia and insulin resistance. Elevated AIP reflects a triglyceride-rich, low-HDL lipid pattern and is related to small dense LDL particles, processes linked to endothelial dysfunction, oxidative stress, and foam-cell formation [4, 5, 44, 45]. Low eGDR reflects insulin resistance together with central adiposity, hypertension, and glycemic dysregulation, which may promote hepatic overproduction of atherogenic lipoproteins and chronic low-grade inflammation [46–48]. Co-occurrence of these pathways could plausibly contribute to shared cardiovascular, renal, and metabolic risk, although the present observational analyses cannot establish causal synergy [49, 50].

From a translational perspective, AIP and eGDR can be derived from routinely collected measurements and may therefore be useful for epidemiologic or clinical risk characterization. However, the present data do not establish that joint AIP-eGDR assessment should be implemented as a stand-alone clinical prediction tool. Before such use, the incremental performance findings require evaluation in component-inclusive comparator models, formal calibration and prediction-error assessment, resampling-based internal validation, and independent external validation of a prespecified model.

This study has several strengths, including the large UK Biobank sample, prospective follow-up, independent replication in CHARLS, evaluation of continuous and joint exposure patterns, competing-risk sensitivity analysis, and multistate characterization of disease progression.

Several limitations should also be considered. First, the observational design precludes causal inference, and residual or unmeasured confounding remains possible. Exposures and several covariates were assessed at baseline, so changes over time were not captured and regression-dilution bias is possible. Second, the analysis relied on participants with the required exposure and covariate data; the large

number excluded for missing AIP or eGDR may introduce selection bias. Third, median-based categories are data-driven and may not correspond to clinically meaningful thresholds, although continuous analyses partly mitigate the information loss from dichotomization.

Fourth, the no-CRMM starting state in the multistate analysis combined participants with zero and one component disease, creating clinical heterogeneity; analyses separating baseline disease-free participants from CVD-only, T2D-only, and CKD-only states would provide a more granular assessment. Fifth, outcome ascertainment differed between cohorts, and the CHARLS reliance on self-report may increase misclassification. The eGFR-based CKD definition did not by itself establish persistence for at least 3 months, which may also contribute to misclassification. Sixth, the prediction analyses were exploratory: calibration, Brier score or other prediction-error measures, and resampling-based internal validation were not reported, and the basic comparator model did not include all raw components of AIP and eGDR. Finally, multiple subgroup tests were performed and generalizability beyond predominantly European UK Biobank participants and middle-aged/older Chinese adults requires further study.

Conclusions

In conclusion, higher AIP and lower eGDR were independently and jointly associated with incident CRMM in UK Biobank, with directionally consistent associations in CHARLS. The high-AIP/low-eGDR phenotype identified participants with the highest relative risk. Joint assessment of these markers may provide additional risk-stratification information, but the prediction findings should be considered exploratory until calibration, internal validation, and external validation of a prespecified model are demonstrated.

Abbreviations

AIP, atherogenic index of plasma

AP, attributable proportion due to interaction

CHARLS, China Health and Retirement Longitudinal Study

CI, confidence interval

CKD, chronic kidney disease

CRMM, cardio-renal-metabolic multimorbidity

CVD, cardiovascular disease

eGDR, estimated glucose disposal rate

HbA1c, glycated hemoglobin

HR, hazard ratio

IDI, integrated discrimination improvement

NRI, net reclassification improvement

RERI, relative excess risk due to interaction

ROC, receiver operating characteristic

SI, synergy index

UKB, UK Biobank

AUC, area under the receiver operating characteristic curve; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCS, restricted cubic spline; T2D, type 2 diabetes

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and all methods were performed in accordance with relevant guidelines and regulations. UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/0382), and all participants provided written informed consent at recruitment. The present analyses were conducted using the UK Biobank Resource under Application Number 747364. CHARLS was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and the biomarker collection protocol received separate approval (IRB00001052-11014). All CHARLS participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The UK Biobank data used in this study are available to qualified researchers through application to the UK Biobank resource (<https://www.ukbiobank.ac.uk/>) under Application Number 747364. CHARLS data are available through the official study portal (<https://charls.charlsdata.com/>) following registration and approval.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MC, HK, QY, and JZ conceived and designed the study. MC, TY, RH, YS, QC, and ZZ performed data curation and formal analysis. MC, JZ, and QY developed the methodology. QT and HK contributed to data interpretation and provided clinical expertise. MC drafted the manuscript. QT critically revised and polished the manuscript. ZL, QY, JZ, and HK provided additional critical revisions for important intellectual content. All authors read and approved the final manuscript.

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Authors' information

Not applicable.

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Figures

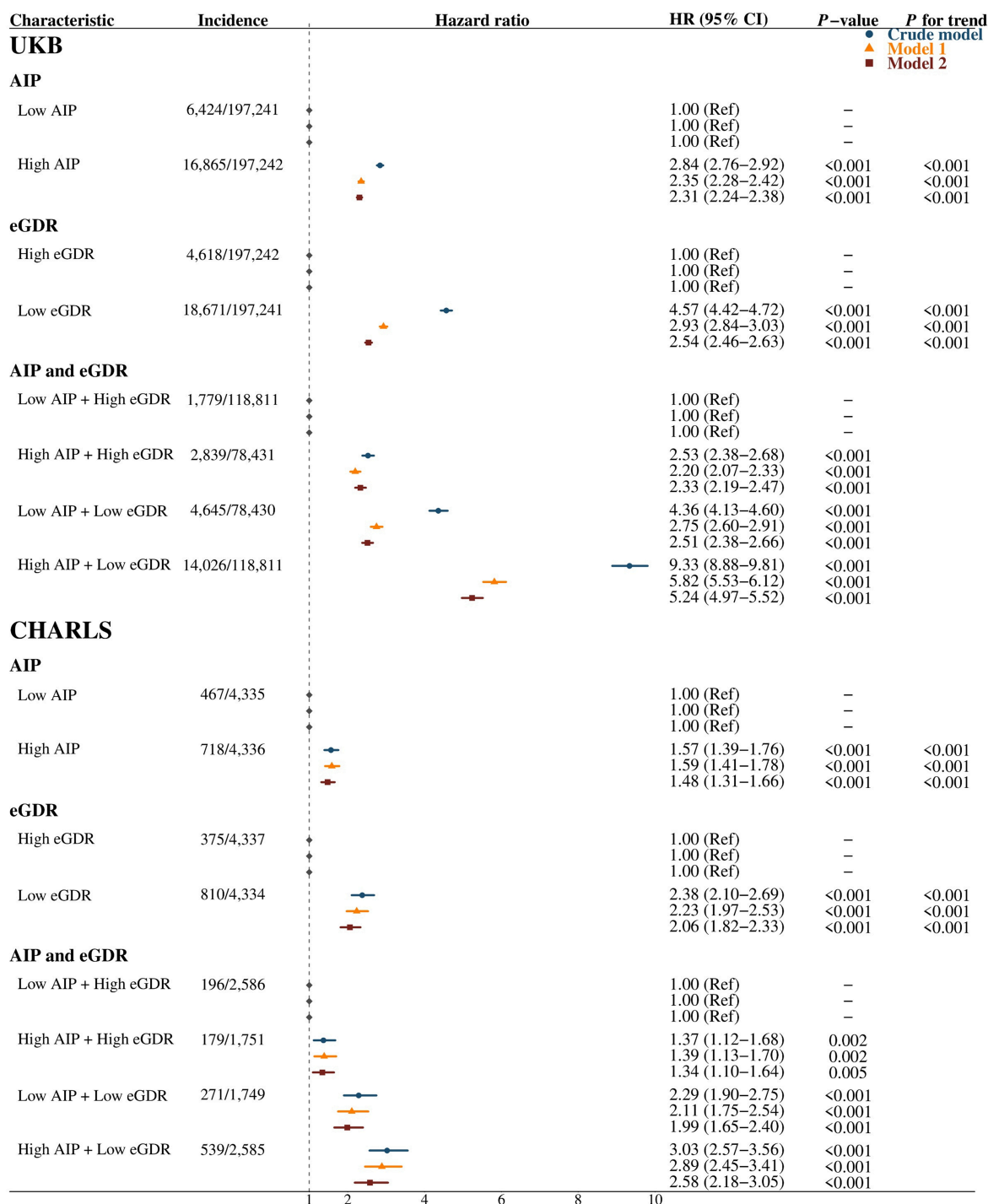
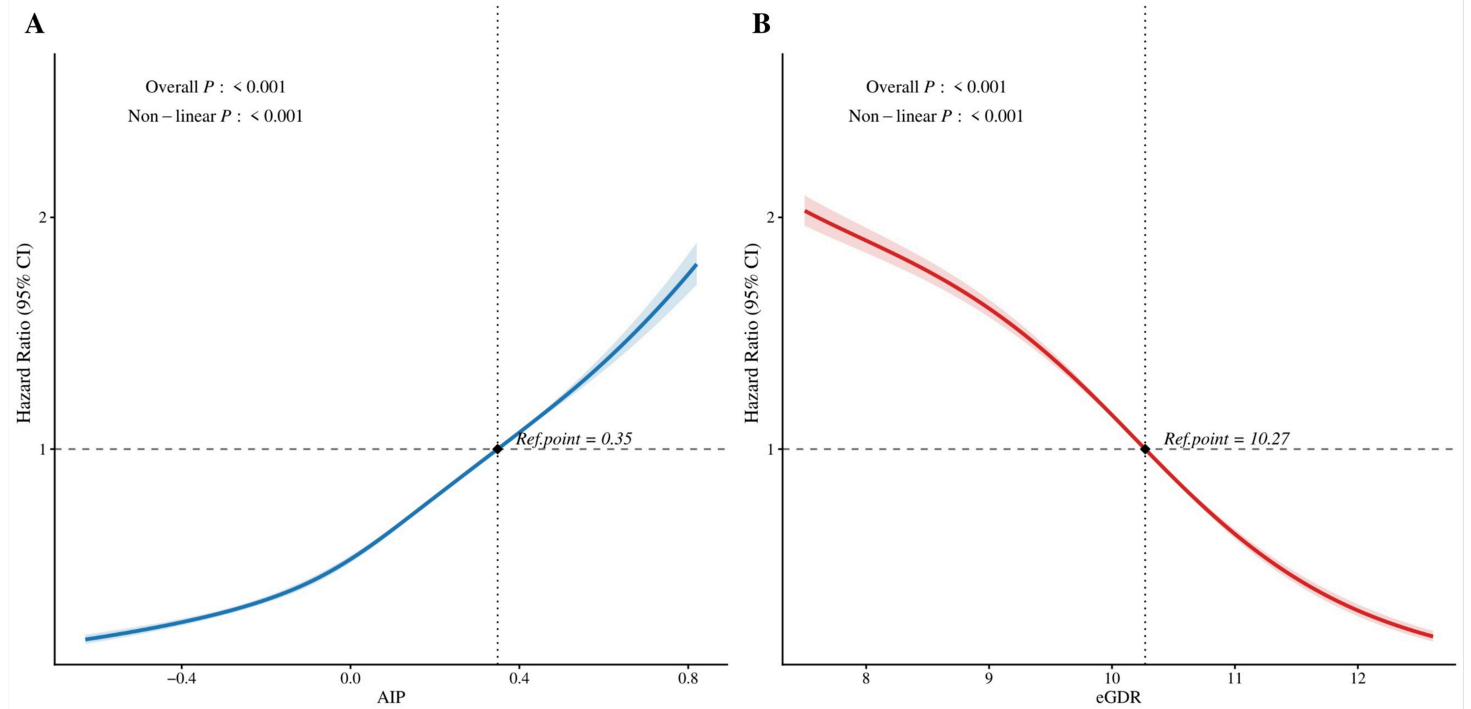


Figure 1

Associations of AIP and eGDR with incident CRMM. Forest plots show the individual and joint associations in UK Biobank and CHARLS. HRs are presented for high versus low AIP, low versus high eGDR, and the four joint phenotypes (G1, low AIP/high eGDR [reference]; G2, high AIP/high eGDR; G3, low AIP/low eGDR; G4, high AIP/low eGDR) across the crude model, Model 1 (age and sex), and Model 2 (fully adjusted). (A) UK Biobank; (B) CHARLS.

UKB



CHARLS

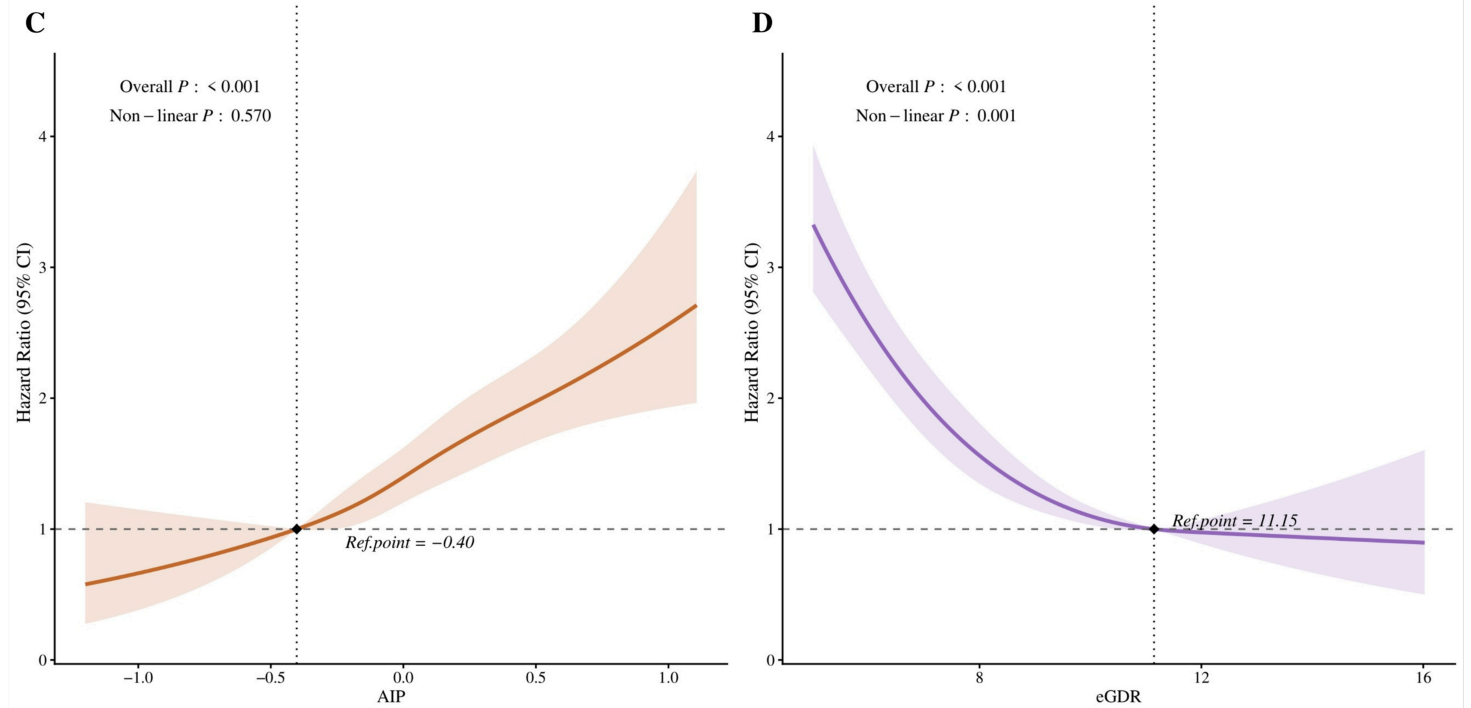


Figure 2

Continuous associations of AIP and eGDR with incident CRMM. Restricted cubic spline curves are shown for UK Biobank (A, B) and CHARLS (C, D). Dashed horizontal lines indicate HR=1. Dotted vertical lines mark threshold points identified in the piecewise regression. (A) AIP in UK Biobank; (B) eGDR in UK Biobank; (C) AIP in CHARLS; (D) eGDR in CHARLS.

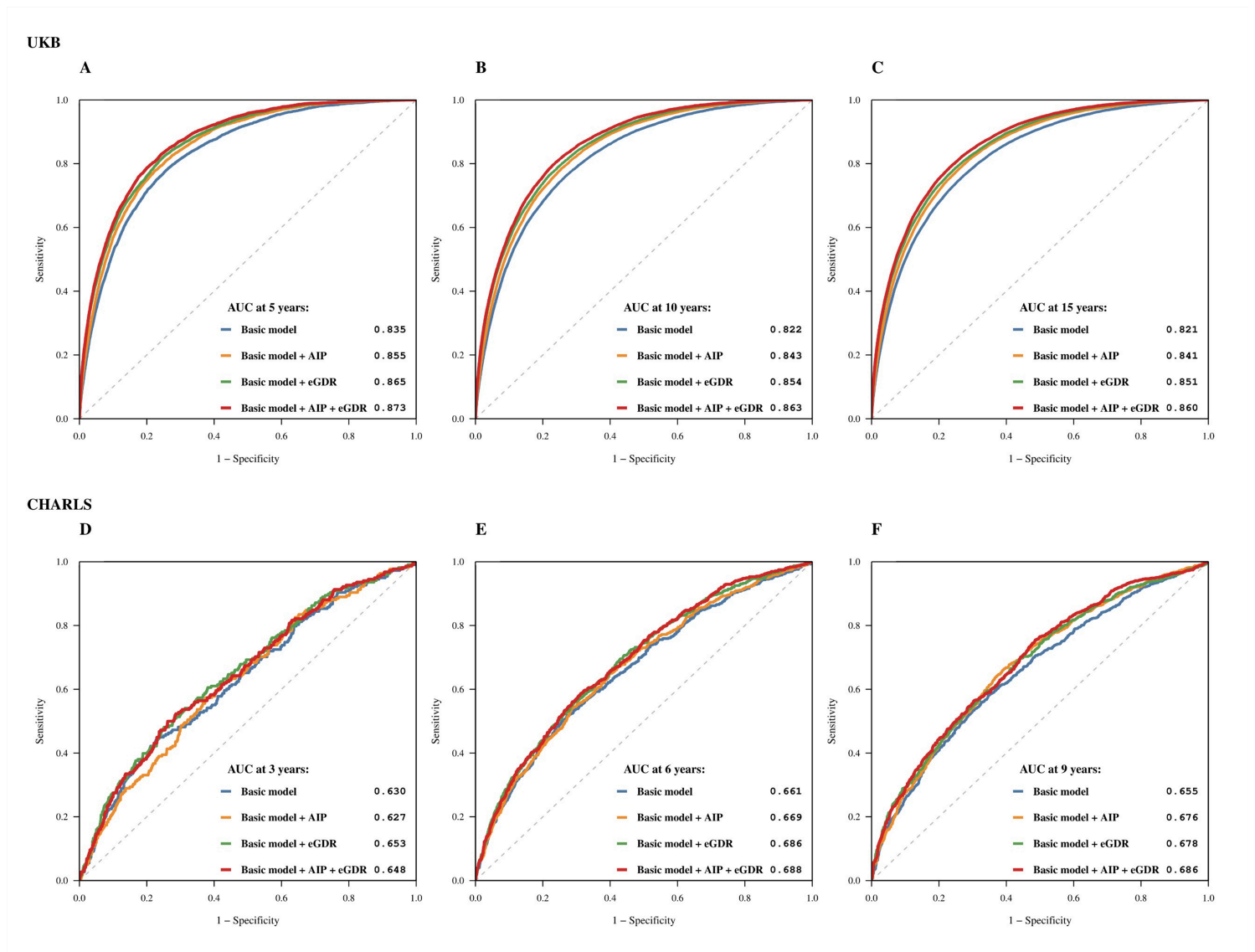


Figure 3

Time-dependent ROC curves for incident CRMM. Exploratory curves compare the basic model with models additionally including AIP, eGDR, or both markers in UK Biobank and CHARLS. (A) UK Biobank at 5 years; (B) UK Biobank at 10 years; (C) UK Biobank at 15 years; (D) CHARLS at 3 years; (E) CHARLS at 6 years; (F) CHARLS at 9 years.

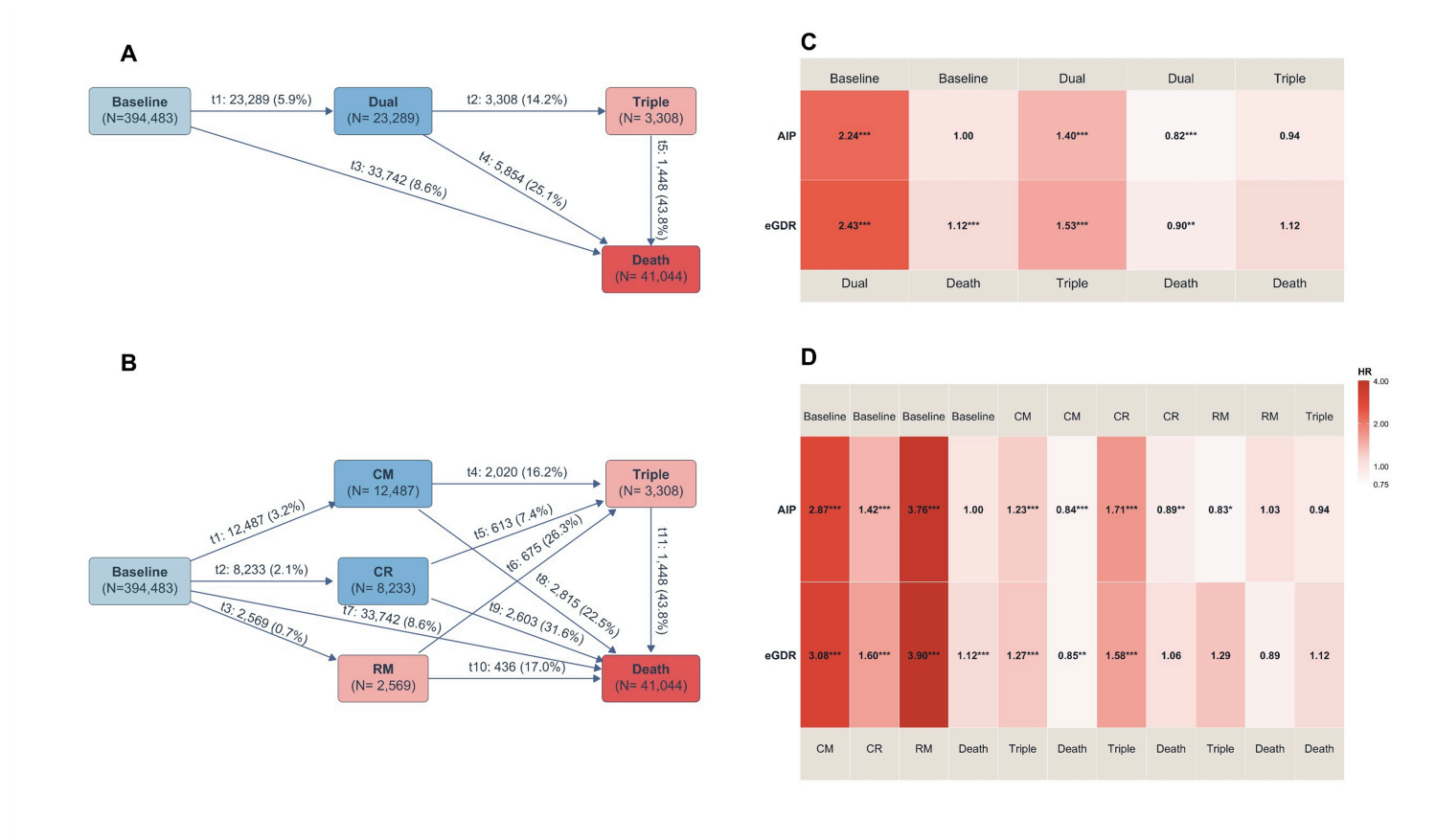


Figure 4

Multistate transitions and exposure-specific hazard ratios. Coarse and detailed transition diagrams and corresponding heatmaps show transition-specific associations for AIP and eGDR in UK Biobank. The no-CRMM starting state includes participants with zero or one component disease. (A) Coarse transition diagram; (B) detailed transition diagram; (C) transition-specific HRs for the coarse model; (D) transition-specific HRs for the detailed model.

Abbreviations: AIP, atherogenic index of plasma; CI, confidence interval; CKD, chronic kidney disease; CM, cardiometabolic disease (CVD and/or T2D); CR, cardio-renal disease (CVD and/or CKD); CRMM, cardio-renal-metabolic multimorbidity; CVD, cardiovascular disease; eGDR, estimated glucose disposal rate; HR, hazard ratio; RM, renal-metabolic disease (CKD and/or T2D); T2D, type 2 diabetes; UKB, UK Biobank.

Supplementary Files

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