

Associations of C-reactive protein-triglyceride-glucose index and Cholesterol- high-density lipoprotein-glucose index with heart disease risk in individuals with cardiovascular-kidney-metabolic syndrome stages 0-3: a cohort study from CHARLS

Qichao Dong

Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University

Meiling Jiang

Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University

Xinyi Zheng

Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University

Zewen Yang

Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University

XinLei Wu

Department of Cardiology, The First Affiliated Hospital of Wenzhou Medical University

Hong Yu

yuvascular@zju.edu.cn

Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University

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Abstract

Background

Although the C-reactive protein-triglyceride-glucose index (CTI) and cholesterol-high-density lipoprotein-glucose index (CHG) have both been implicated in adverse cardiovascular outcomes, their comparative predictive performance for incident heart disease among individuals with cardiovascular-kidney-metabolic (CKM) syndrome stages 0–3 remains to be elucidated.

Methods

We analyzed 6,740 participants with CKM syndrome stages 0–3 from the China Health and Retirement Longitudinal Study (CHARLS) database. Stratified Cox regression models were constructed to examine the associations of CTI and CHG with incident heart disease. Restricted cubic spline (RCS) analysis was applied to explore potential nonlinear relationships. Kaplan-Meier curves were plotted to compare heart disease-free survival across groups, and time-dependent receiver operating characteristic (ROC) analyses were performed to evaluate the discriminatory performance of CTI and CHG. Causal mediation analysis was conducted to assess the mediating role of systolic blood pressure (SBP). Subgroup and sensitivity analyses were undertaken to verify the robustness of our findings.

Results

Over a 9-year follow-up period, 1,229 participants (18.2%) developed heart disease. In fully adjusted models, compared with the lowest quartile, participants in the highest quartile of CTI exhibited a 35% elevated risk of heart disease (HR = 1.35, 95% CI: 1.14–1.60), while those in the highest quartile of CHG showed a 19% elevated risk (HR = 1.19, 95% CI: 1.01–1.41). Both indices demonstrated positive linear associations with heart disease risk, with cumulative incidence increasing progressively across ascending quartiles. CTI exhibited slightly superior discriminatory performance compared to CHG at the 2- and 4-year follow-up time points. SBP mediated 16.4% of the association between CTI and heart disease, and 18.0% of the association between CHG and heart disease. Subgroup and sensitivity analyses consistently supported the robustness of these findings.

Conclusions

Both CTI and CHG are independently associated with incident heart disease in individuals with CKM syndrome stages 0–3. CTI demonstrates modestly superior predictive performance, particularly during early follow-up, suggesting that incorporating inflammatory biomarkers may enhance heart disease risk stratification beyond metabolic indicators alone.

Introduction

In 2023, the American Heart Association (AHA) first introduced the concept of cardiovascular-kidney-metabolic (CKM) syndrome. The CKM syndrome identifies the interconnections of metabolic abnormalities, kidney impairment, and cardiovascular disease (CVD) ^[1, 2]. This syndrome is categorized into stages 0–4 according to disease progresses. The early stages of CKM syndrome (stages 0–3) precede the onset of heart failure (HF) and atherosclerotic cardiovascular disease (ASCVD). This stage provides an opportunity for early intervention and risk reduction in CVD ^[3]. Research demonstrates that 86% of adults in China meet standards for stages 0–3, and nearly 90% of U.S adults suffer from stages 1 or above, showing the large prevalence of early-stage CKM syndrome ^[4–6]. Consequently, it is important to identify effective biomarkers to assess heart disease hazard in people with CKM syndrome stages 0–3.

Insulin resistance (IR) and inflammation are widely recognized as central mechanisms in the development of CKM syndrome ^[7, 8]. They contribute to endothelial dysfunction, oxidative stress, and abnormal lipid metabolism, promoting the development of ASCVD and HF eventually ^[9]. Therefore, increasing attention has been directed toward composite metabolic-inflammatory indicators that may capture metabolic dysregulation and inflammatory burden. Recently, many researchers have focused on composite biomarkers that combine glucose and lipid metabolism, among which the triglyceride-glucose (TyG) index is the most representative ^[10, 11]. The C-reactive protein-triglyceride-glucose (CTI) index, which combines C-reactive protein (CRP) and the TyG index, has been confirmed to be associated with hypertension, stroke, and CVD outcomes ^[12].

However, most prior studies have focused on the association of CTI with stroke or composite CVD outcomes, rather than with heart disease, specifically ASCVD and HF^[13]. Heart disease and stroke are not the same condition and they involve different biological pathways and risk factors. As a result, results obtained from combined CVD endpoints may not be fully applicable when the goal is to predict heart disease specifically ^[14, 15]. The cholesterol-high-density lipoprotein-glucose (CHG) index, a novel glycolipid metabolic index incorporating HDL-C, can identify type 2 diabetes and metabolic dysfunction more accurately than conventional TyG-related markers ^[16–18]. Nevertheless, there is still little research on its predictive significance for heart disease especially in persons with early-stage CKM syndrome.

As two promising markers, CTI and CHG have not been specifically evaluated for predicting incident heart disease (rather than stroke or composite CVD) in early-stage CKM syndrome. Therefore, we used data from the China Health and Retirement Longitudinal Study (CHARLS) to compare their predictive performance for incident heart disease risk stratification in this population. These findings may offer further information to facilitate the early identification of persons with early-stage CKM syndrome that are at elevated risk for heart disease.

Materials and methods

Study population and design

Our cohort research comprised Chinese adults and utilized data from the CHARLS database^[19]. 17,708 individuals were enrolled in the 2011 baseline survey. We excluded participants at baseline based on the following criteria: (1) age < 45 years; (2) pre-existing heart disease; (3) meeting criteria for CKM stage 4 or having incomplete CKM information; (4) missing requisite variables for the calculation of CTI and CHG; and (5) lack of follow-up data on incident heart disease. After applying these exclusions, 6,740 participants were included in the final analytic cohort. The participant screening and follow-up process is illustrated in Fig. 1.

Assessment of CHG and CTI

The CTI and CHG indices were derived from five biochemical markers: triglycerides (TG), CRP, FPG, TC and HDL-C. The calculation of CTI was conducted as follows: $CTI = 0.412 \times \ln(CRP [mg/L]) + \ln(TG [mg/dL] \times FPG [mg/dL]/2)$ ^[20]. CHG was computed using the equation: $CHG = \ln[TC (mg/dL) \times FPG (mg/dL)/(2 \times HDL-C (mg/dL))]$ ^[21].

Definition of CKM syndrome stages 0–4

The CKM syndrome categorizes the condition into five progressive stages. Stage 0 is a normal condition. Stage 1 means obesity or prediabetes. Stage 2 is characterized by metabolic risk factors or CKD. Stage 3 is defined as subclinical CVD accompanied by CKD or metabolic disorders. Stage 4 comprises clinical CVD associated with CKD or metabolic disorders^[1]. Comprehensive definitions are included in Supplementary Table S1.

Outcome definition and assessment

This study assessed the development of heart disease as the primary outcome in persons with stage 0–3 CKM syndrome. Throughout the follow-up phase (Wave 2–5), new cases of heart disease were discovered using self-reported physician diagnoses. Specifically, heart disease was identified if a participant reported a doctor's diagnosis of heart problems or current receipt of heart disease treatment^[22].

Study Variables and Definitions

At baseline, professional interviewers gathered participant information through standardized questions. Information, including age, gender, living environment, educational attainment, marital status, tobacco use, and alcohol use, was documented. Anthropometric measurements were performed according to recognized protocols to evaluate height, weight, and blood pressure. Participants supplied prior

physician-diagnosed conditions and current pharmacological treatments. Furthermore, fasting plasma blood specimens were obtained for laboratory assessment of metabolic and inflammatory biomarkers [19, 23].

DM, hypertension, dyslipidemia, and CKD were defined using internationally recognized laboratory-based diagnostic criteria, supplemented by self-reported medication use and physician diagnoses [24].

Missing Data Handling and Data Preparation

A majority of variables exhibited relatively low percentages of missing data (Table S2). To maintain statistical robustness, we imputed missing values using multiple imputation by chained equations (MICE). During data preprocessing, extreme values were identified in variables used for calculating CTI and CHG. To mitigate the influence of outliers and enhance robustness, the continuous variables used to calculate CTI and CHG were winsorized at the 1st and 99th percentiles prior to computing these indices (Figure S1).

Statistical analysis

As for baseline characteristics, continuous variables are expressed as mean (SD) or median (IQR), and categorical variables as number (%). The t-test, Mann-Whitney U test, and chi-square test were applied for comparisons, as appropriate. The Lilliefors test and Q-Q plots were utilized to evaluate normality. Multicollinearity was evaluated utilising generalised variance inflation factors (GVIFs); all $GVIF^{(1/[2 \times DF])}$ values were below 2, signifying the absence of significant collinearity (Tables S3 and S4).

When analyzing the associations of CTI and CHG with incident heart disease in individuals with CKM stages 0–3, three covariate-adjusted models, with covariate selection guided by clinical relevance, were employed: Model 1 was unadjusted; Model 2 was adjusted for age, sex, geographic location, tobacco use, and body mass index (BMI); and Model 3 was expanded to include LDL-C, uric acid (UA), and renal function markers (eGFR, BUN, Cr) in addition to the variables in Model 2. Variables directly included in the calculation of CTI and CHG were not entered as covariates.

Cox regression was used to derive HRs and 95% CIs for incident heart disease, and we checked the proportional hazards assumption via Schoenfeld residuals. These variables were included as stratification factors in the primary analysis since violations were found for alcohol intake, marital status, and educational level in some models. The proportional hazards assumption was met for the other factors upon stratification.

Utilizing Kaplan-Meier procedures based on the CTI and CHG quartiles, the cumulative event rates were computed at 2,4,7, and 9 years. Restricted cubic spline (RCS) was used within a stratified Cox framework to evaluate possible nonlinear correlations. When deciding on a configuration with four knots at the 5,35,65, and 95th percentiles, respectively, we used the Bayesian information criteria. The presence or absence of non-linearity was then confirmed using a likelihood ratio test. We evaluated prediction

capability by creating time-dependent receiver operating characteristic (ROC) curves at four follow-up time points. To further investigate potential differences in AUCs, we employed a two-sided bootstrap test.

To determine if SBP mediated the relationships between CTI and CHG and incident heart disease among people with CKM stages 0–3, a regression-based causal mediation analysis was performed. The distribution of mediation effects was estimated using 1,000 bootstrap resamples in the analysis. The percentile approach provided CIs and P values; total, controlled direct effect (CDE), and pure natural indirect effect (PNIE), along with the proportion mediated, were reported on the HR scale.

Age, sex, education, tobacco and alcohol use and marital status, were the predetermined variables for the subgroup analysis. Sensitivity tests were undertaken to confirm the consistency of the key findings. The analyses were repeated among participants with complete data only, using the original values without Winsorization, and after excluding individuals who developed heart disease within the first two years of follow-up. We also calculated E-values for unmeasured confounding and refitted the models using multivariable logistic regression.

All statistical analyses were conducted utilizing R software version 4.5.2. All tests were bilateral, and $P < 0.05$ was deemed statistically significant.

Results

Participant characteristics

The study population consisted of 6,740 individuals with CKM syndrome stages 0–3 after the eligibility screening process (Fig. 1). Baseline data is summarized in Table 1. The mean age was 58.6 years (SD = 9.2), and 3,551 participants (52.7%) were female. During follow-up, which extended for up to 9 years, 1,229 participants developed heart disease for the first time, yielding a cumulative incidence of 18.2%.

As shown in Table 1, individuals who developed heart disease were generally older, higher likelihood of being female, living in rurality, while tobacco intake and drinking were less common in this group. Participants who developed heart disease had higher rates of hypertension, DM, and dyslipidemia (all $P < 0.05$).

At baseline, individuals who later experienced heart disease generally presented with a less favorable cardiometabolic profile. SBP, DBP, FPG, HbA1c, TG, TC, LDL-C, and CRP values were all elevated, whereas HDL-C, eGFR, BUN, and UA levels were relatively reduced (all $P < 0.05$). Moreover, both CHG and CTI scores showed higher average values in participants who went on to develop heart disease during follow-up. CKM stage 2 was more common among participants who experienced heart disease during follow-up.

Associations of CTI and CHG with incident heart disease in participants with CKM stages 0–3

Across stratified Cox regression models, higher CTI and CHG values were linked to a greater likelihood of developing heart disease during follow-up among participants with early-stage CKM syndrome (Table 2). A 1-SD rise in CTI correlated with a 12% elevated risk of incident heart disease in the unadjusted model (Model 1: HR = 1.12, 95% CI: 1.06–1.19, $P < 0.001$). The connection persisted as significant following adjustments for demographic and clinical variables in Model 2 (HR = 1.09, 95% CI: 1.03–1.15, $P = 0.002$) and Model 3 (HR = 1.10, 95% CI: 1.04–1.17, $P = 0.001$). Each 1-SD rise in CHG corresponded to a 10% elevated risk of heart disease in Model 1 (HR = 1.10, 95% CI: 1.04–1.16, $P < 0.001$). The link persisted as statistically significant in Model 2 (HR = 1.08, 95% CI: 1.02–1.14, $P = 0.006$) and Model 3 (HR = 1.08, 95% CI: 1.02–1.15, $P = 0.008$).

Individuals classified in the top quartile of either index experienced a substantially greater risk of heart disease than those in the bottom quartile. In the fully adjusted model, the HR for CTI-Q4 was 1.35 (95% CI: 1.14–1.60, $P < 0.001$), whereas the HR for CHG-Q4 was 1.19 (95% CI: 1.01–1.41, $P = 0.049$). Trend analyses also showed significant dose-response relationships for both indices (CTI: P for trend < 0.001 ; CHG: P for trend = 0.022).

Cumulative incidence of heart disease according to CTI and CHG levels

Kaplan-Meier survival curves are shown in Fig. 2. As shown in Fig. 2A, cumulative heart disease risk increased significantly progressively with increasing CTI quartiles in individuals with early-stage CKM syndrome, (log-rank $\chi^2 = 21.963$, $P < 0.001$). Comparable findings were found for CHG (Fig. 2B) (log-rank $\chi^2 = 11.941$, $P = 0.008$).

Restricted cubic spline analysis of CTI, CHG, and incident heart disease risk

RCS analysis models indicated an approximately linear increase in heart disease risk across the CTI spectrum (Figs. 3A-3C). The overall relationships were significant across unadjusted, moderately adjusted, and thoroughly adjusted models (all P for overall association < 0.05), with no indication of nonlinearity (P for nonlinearity = 0.443, 0.622, and 0.813, respectively).

Similarly, CHG had a positively and approximately linear correlation with incident heart disease in individuals with early-stage CKM syndrome (Figs. 3D-3F). The overall associations were significant across all models (all P for overall association < 0.05), with no significant nonlinear associations detected (P for nonlinearity = 0.483, 0.426, and 0.297, respectively).

Predictive performance of CTI and CHG for incident heart disease

Across the follow-up period, CTI consistently yielded slightly larger AUC values than CHG, suggesting a modest advantage in risk discrimination (Fig. 4).

For CTI, the AUC values were 0.554 (95% CI: 0.520–0.589) at 2 years, 0.541 (95% CI: 0.515–0.566) at 4 years, 0.541 (95% CI: 0.521–0.561) at 7 years, and 0.540 (95% CI: 0.524–0.555) at 9 years.

Corresponding AUC values for CHG were 0.516 (95% CI: 0.481–0.549), 0.519 (95% CI: 0.494–0.546), 0.532 (95% CI: 0.515–0.552), and 0.534 (95% CI: 0.517–0.550), respectively.

Bootstrap analyses indicated that the differences in AUC between CTI and CHG were statistically significant at 2 years ($P = 0.02$) and 4 years ($P = 0.04$), whereas no significant differences were observed at 7 years ($P = 0.25$) or 9 years ($P = 0.37$).

Mediation of SBP in the CTI, CHG and heart disease association

Causal mediation analysis (Fig. 5) revealed that SBP strongly mediated the relationships between CTI, CHG, and the occurrence of heart disease in individuals with early-stage CKM syndrome. For CTI, the total effect was an HR of 1.13 (95% CI: 1.04–1.21, $P = 0.004$), with a CDE of 1.11 (95% CI: 1.02–1.19, $P = 0.008$) and a PNIE of 1.02 (95% CI: 1.01–1.03, $P = 0.002$), corresponding to a mediation proportion of 16.4% (95% CI: 5.4%–44.2%, $P = 0.006$). For CHG, the total effect was significant (HR = 1.22, 95% CI: 1.05–1.39, $P = 0.012$), with a CDE of 1.18 (95% CI: 1.02–1.35, $P = 0.028$) and a PNIE through SBP of 1.03 (95% CI: 1.01–1.05, $P < 0.001$). The proportion mediated was 18.0% (95% CI: 5.8%–58.3%, $P = 0.012$). These findings suggest that SBP accounts for roughly one-sixth to one-fifth of the overall impact of CTI and CHG on the occurrence of heart disease.

Subgroup analyses

Strata characterized by sex, educational level, residential area, smoking status, and alcohol intake did not exhibit any significant interactions with the association between CTI and incident heart disease. This association was largely consistent across all strata (all P for interaction > 0.05). However, there were notable interactions regarding marital status and age (P for interaction = 0.039 and 0.012, respectively). In individuals under the age of 60, there was a strong correlation between higher CTI levels and an increased risk of heart disease (HR = 1.18, 95% CI: 1.07–1.30, $P < 0.001$), but this correlation was weaker and no longer statistically significant in those 60 and older (HR = 1.04, 95% CI: 0.93–1.16, $P = 0.487$). There was a positive connection between CTI and heart disease risk among married participants (HR = 1.14, 95% CI: 1.06–1.26, $P < 0.001$), but no significant association was seen among single, divorced, or widowed adults (HR = 0.95, 95% CI: 0.75–1.21, $P = 0.647$) when the data was evaluated by marital status stratification. Figure 6 shows that the correlation between CTI and the risk of heart disease in people

with CKM stages 0–3 is larger in younger and married participants, suggesting that age and marital status may moderate this link.

Analyses for CHG subgroups are shown in Fig. 7. The correlation between CHG and the risk of heart disease remained largely unchanged when broken down by demographic variables such as age, sex, education, marital status, smoking status, and alcohol consumption (all *P* for interaction > 0.05).

Sensitivity analyses

Several sensitivity analyses supported the primary findings. Results were robust in complete-case analysis (Table S5), without Winsorization (Table S6), after excluding first 2-year heart disease events (Table S7), and in E-value analyses, which indicated strong unmeasured confounding would be needed to explain the associations (Table S8). Reanalysis using multivariable logistic regression yielded similar results (Table S9). Together, these analyses confirmed the robustness of the main conclusions.

Discussion

To our knowledge, our research is the first to directly compare the predictive performance of CTI and CHG in persons with early-stage CKM syndrome for incident heart disease, rather than stroke or composite CVD outcomes^[13, 22]. After analysis of long-term follow-up data, we found independent associations between CTI and CHG and incident heart disease in adults with CKM syndrome stages 0–3. Moreover, CTI consistently showed modestly stronger predictive performance than CHG, particularly during the first 4 years of follow-up. Furthermore, SBP played a mediating role in these correlations, indicating that hypertension may represent an important link between metabolic inefficiency and ischemic heart disease.

Recently, many researchers have focused on composite biomarkers that combine glucose and lipid metabolism, among which the TyG index is the most representative. Prior research from large population-based cohorts has linked increased TyG to an increased risk of CVD, stroke, and mortality^[25–27]. Combined with TyG and CRP, CTI improves predictive value in risk of CVD, stroke and hypertension than TyG^[28]. CHG, a novel glycolipid metabolic index incorporating HDL-C, has been shown to sometimes outperform the TyG index in predictive performance in CVD or stroke^[29–31]. Likewise, the introduction of the CKM stages 0–3 concept aims to redirect attention from managing overt CVD to early prevention based on metabolic risk. However, previous studies have primarily focused on stroke or composite CVD outcomes, and few have separately examined incident heart disease, especially among the CKM stages 0–3 population.

Several biological mechanisms may underlie the observed associations. Both CTI and CHG contain glucose and lipid related components that are closely associated with IR. Chronic IR relates to endothelial dysfunction, oxidative stress, vascular remodeling, and atherosclerosis^[9, 32, 33]. CTI may provide additional prognostic information because it incorporates CRP that has been implicated in

atherosclerotic disease progression^[34, 35]. HDL-C and TC are components of CHG, which may mainly represent the atherogenic burden associated with lipids^[36–38].

It is also worth noting that CTI's advantage was mostly obviously in the first four years. An explanation is that a single baseline inflammatory measurement tends to capture short-term risk rather well, but over time, its predictive power fades as aging, lifestyle shifts, medication use, and other risk factors accumulate. That would naturally narrow the gap between CTI and CHG with longer follow-up.

In the mediation analysis, SBP explained approximately 16%-18% of these associations. Evidence suggests that IR and inflammation damage the blood vessels, and thereby increase blood pressure, ultimately causing cardiac damage^[39]. Although causal relationships cannot be established from the present study, the findings suggest that blood pressure management may be particularly important among individuals with early-stage CKM syndrome.

These findings may have clinical implications. CTI and CHG are inexpensive and accessible, making them valuable for extensive screening and risk assessment. The risk of heart disease increased with higher CTI and CHG levels. This finding supports early interventions to control blood glucose, lipids, blood pressure, body weight, and lifestyle factors.

The results of subgroup analyses were generally consistent with the primary findings. Demographic and lifestyle factors did not significantly modify the CHG-heart disease link. This suggests the association remained stable across strata. The CTI-heart disease link was similar across most subgroups. However, stronger associations were observed among participants younger than 60 years, suggesting that inflammatory-metabolic dysfunction may play a greater role during the earlier stages of heart disease development. Stronger associations were also observed among married participants, while the underlying mechanism remains ambiguous. This finding, due to the absence of a matching interaction for CHG and the lack of a definitive biological explanation, should be treated with caution and necessitates validation in future research.

Several strengths of the present study merit consideration. First, this is among the first prospective studies to directly compare CTI and CHG for predicting incident heart disease in individuals with CKM syndrome stages 0–3, which provides more disease-specific evidence for risk assessment. Second, a relatively long follow-up period strengthens the reliability of the observed associations. Third, we employed multiple analytical approaches to confirm the robustness of the findings. Finally, mediation analysis provided additional insight into the potential role of blood pressure regulation in individuals with adverse inflammatory-metabolic profiles.

Limitations are as follows. Heart disease status was determined mainly from self-reported physician diagnoses, which may have introduced some degree of recall bias and outcome misclassification. In addition, although a broad range of covariates was included in the analyses, residual confounding cannot be completely excluded. Because CTI and CHG were assessed only at baseline, the changes in these biomarkers could not be evaluated. In addition, the study population was restricted to Chinese

adults aged ≥ 45 years, which may constrain the applicability of the findings. Finally, the overall discriminatory ability of both biomarkers remained modest. Therefore, CTI and CHG may be better regarded as complementary tools that provide different but potentially useful information for heart disease risk stratification.

Conclusion

In this cohort of adults with CKM syndrome stages 0–3, both CTI and CHG were independently associated with incident heart disease. CTI showed a modest advantage over CHG in predicting future risk during the first four years of follow-up. The observed difference may reflect the additional contribution of inflammatory burden to heart disease development. Mediation analyses indicated that SBP explained part of these relationships. These findings support the potential use of CTI and CHG as simple and readily obtainable markers for heart disease stratification in individuals with early-stage CKM syndrome.

Abbreviations

CTI

C-reactive protein-triglyceride-glucose index

CHARLS

China Health and Retirement Longitudinal Study

CKM

Cardiovascular-kidney-metabolic syndrome

CHG

Cholesterol-high-density lipoprotein-glucose index

RCS

Restricted cubic spline

HR

Hazard ratio

CI

Confidence interval

ROC

Receiver operating characteristic

SBP

Systolic blood pressure

CVD

Cardiovascular disease

AHA

American Heart Association

SD

Standard deviation

ASCVD
Atherosclerotic cardiovascular disease
TC
Total cholesterol
IR
Insulin resistance
TyG
Triglyceride-glucose index
HF
Heart failure
FPG
Fasting plasma glucose
HDL-C
High-density lipoprotein cholesterol
CRP
C-reactive protein
TG
Triglycerides
DM
Diabetes mellitus
DBP
Diastolic blood pressure
HbA1c
Glycated hemoglobin A1c
CKD
Chronic kidney disease
MICE
Multiple imputation by chained equations
eGFR
Estimated glomerular filtration rate
IQR
Interquartile range
Cr
Creatinine
BMI
Body mass index
BUN
Blood urea nitrogen
AUC
Areas under the curve

UA
Uric Acid
CDE
Controlled direct effect
PNIE
Pure natural indirect effect

Declarations

Ethical approval and consent to participate

Ethical approval for this study protocol was granted by the Biomedical Ethics Review Committee of Peking University (household survey: IRB00001052-11015; blood samples: IRB00001052-11014). All participants gave written informed consent prior to enrolment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310009, China.

²State Key Laboratory of Transvascular Implantation Devices, Hangzhou, 310009, China.

³Heart Regeneration and Repair Key Laboratory of Zhejiang province, Hangzhou, 310009, China.

⁴Transvascular Implantation Devices Research Institute, Hangzhou, 310053, China.

⁵Binjiang Institute of Zhejiang University, Hangzhou, 310053, China.

⁶Department of Cardiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, 325035, China.

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Author Contribution

[Qichao Dong]: Data curation, Writing original draft, Formal analysis, Investigation, Methodology, Visualization. [Meiling Jiang]: Data curation, Writing original draft, Investigation, Methodology, Visualization. [Xinyi Zheng]: Data curation, Writing original draft, Investigation, Methodology. [Zewen Yang]: Data curation, Writing original draft, Methodology, Visualization. [XinLei Wu]: Review & Editing, Supervision. [Hong Yu]: Review & Editing, Supervision, Resources. All authors reviewed the manuscript and approved the final manuscript.

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Data Availability

The CHARLS database, which this study used, is accessible to the public via the project's website (<http://charls.pku.edu.cn>).

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Tables

Tables are available in the Supplementary Files section.

Figures

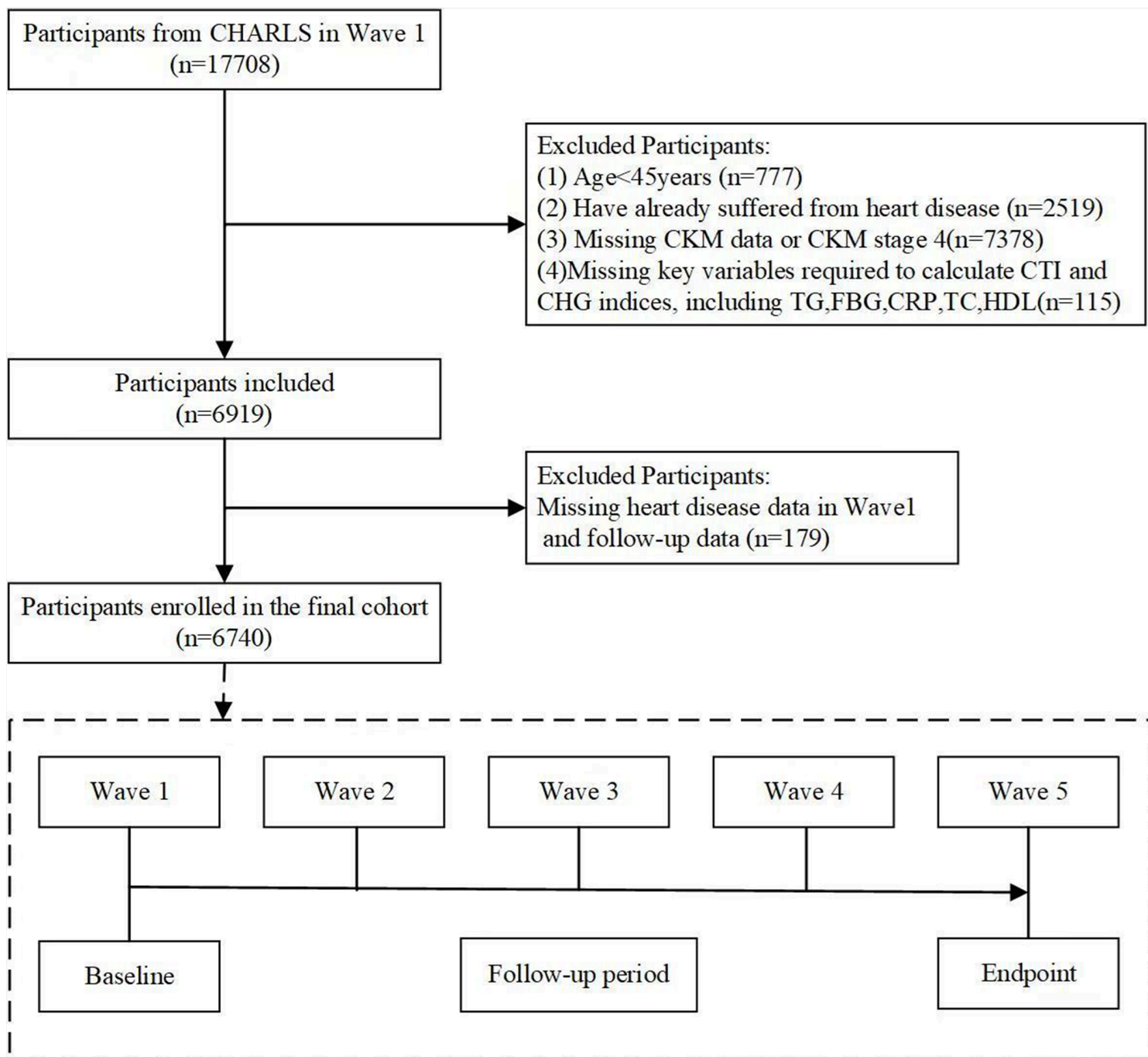


Figure 1

The flowchart of this study CHARLS: the China Health and Retirement Longitudinal Study; CKM: cardiovascular-kidney-metabolic syndrome; CTI: C-reactive protein-triglyceride-glucose, CHG: Cholesterol-high-density lipoprotein-glucose, CRP: C-reactive protein, FPG: fasting plasma glucose, HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglycerides;

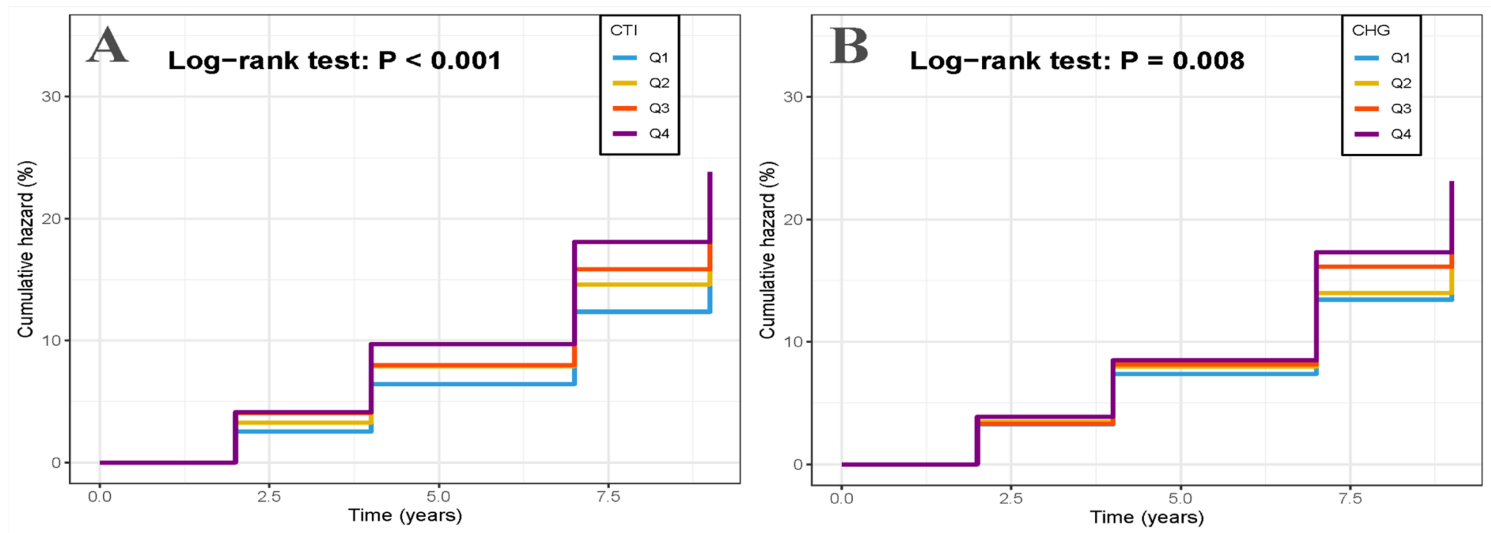


Figure 2

Kaplan-Meier cumulative heart disease incidence in CKM 0-3 by CTI and CHG quartiles. (A) CTI: C-reactive protein-triglyceride-glucose, (B) CHG: Cholesterol-high-density lipoprotein-glucose;

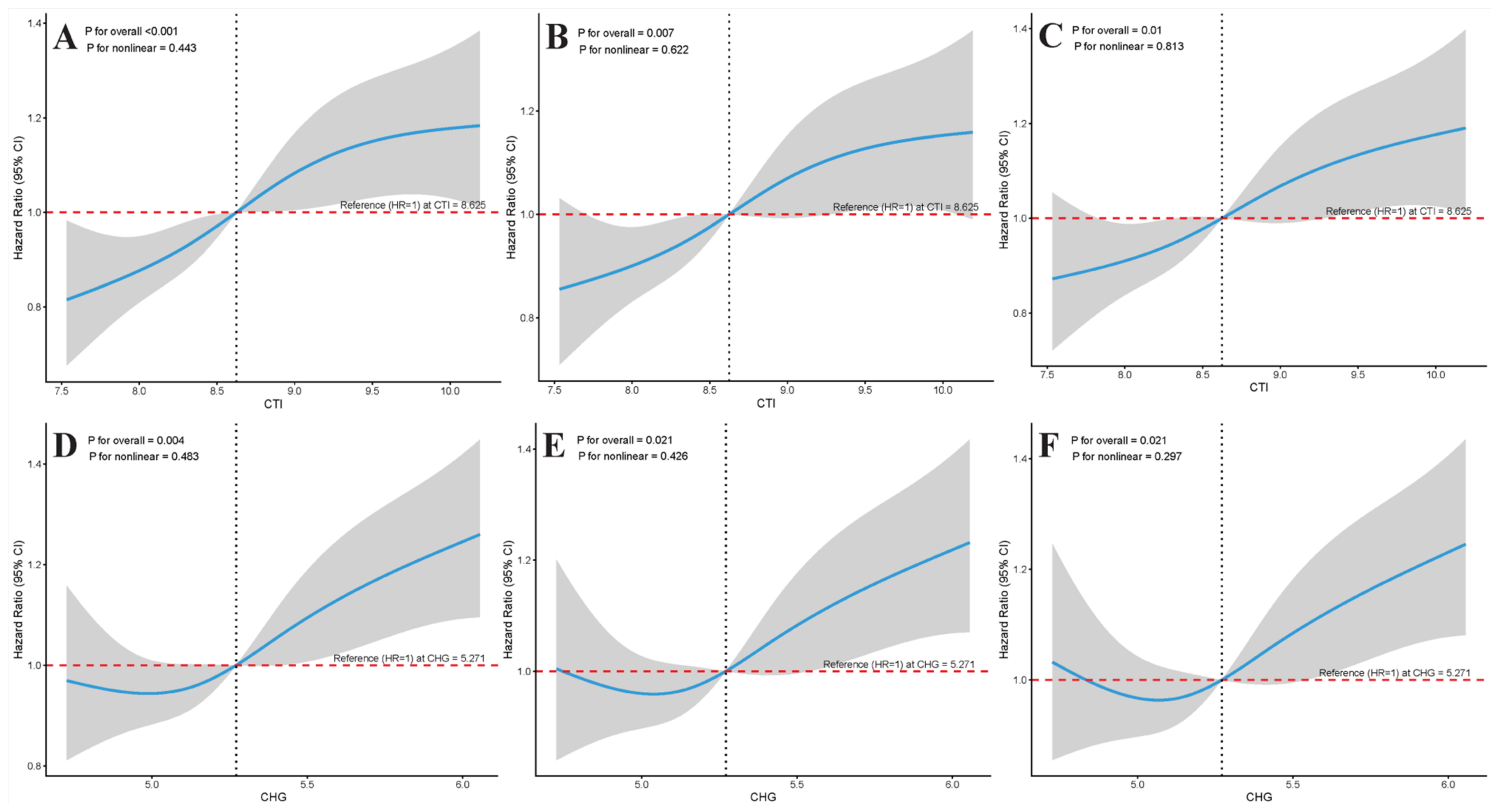


Figure 3

RCS curves of adjusted CTI/CHG index association with incident heart disease in CKM stages 0-3.

Figures A, B, and C respectively represent the dose-response association relationship between the CTI index in Model 1,2,3 and the risk of developing heart disease in patients with CKM syndrome at stages 0 - 3. Figures D, E, and F respectively represent the dose-response association relationship between the

CHG index in Model 1,2,3 and the risk of developing heart disease in patients with CKM syndrome at stages 0 - 3. Model 1: non-adjusted; Model 2: adjusted for age, gender, location, smoking status and BMI; Model 3: adjusted for age, gender, location, smoking status and BMI, LDL_C, eGFR, Cr, BUN, UA. Solid lines denote estimated HRs, while shaded areas indicate 95% CIs. RCS, restricted cubic spline; CTI, C-reactive protein-triglyceride-glucose; CHG, cholesterol-high-density lipoprotein-glucose; CI, confidence interval.

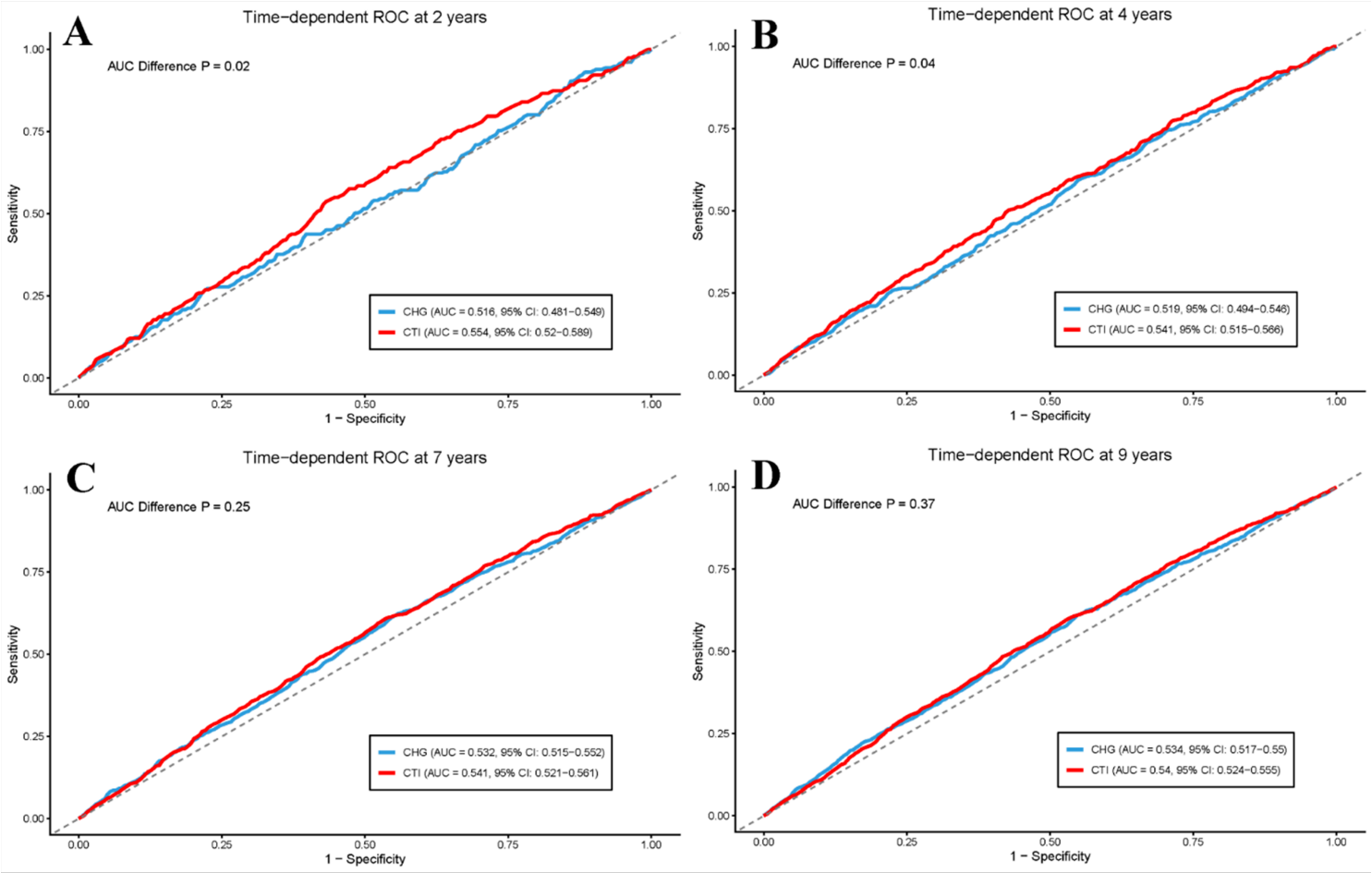


Figure 4

ROC curves comparing CTI/CHG for heart disease events in CKM 0-3. At 2 years (A), 4 years (B), 7years(C) and 9years (D) follow-up. P values for AUC differences were obtained from a subject-level nonparametric bootstrap. Analyses were derived from the fully adjusted model (Model 3). Fully adjusted models included: age, gender, location, smoking status and BMI, LDL_C, eGFR, Cr, BUN and UA. CTI, C-reactive protein-triglyceride-glucose; CHG, cholesterol-high-density lipoprotein-glucose; AUC, area under the curve; CI, confidence interval.

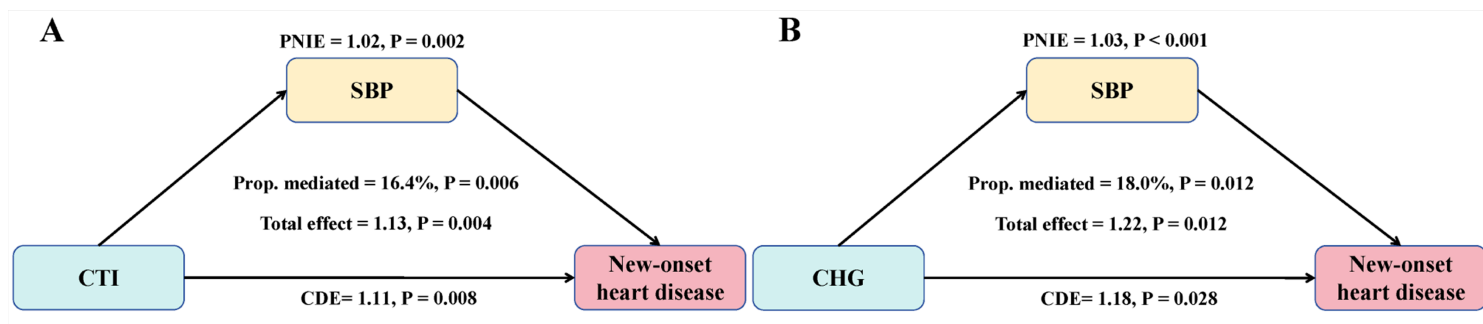


Figure 5

Mediation of SBP between CTI/CHG and incident heart disease in CKM 0-3. (A) CTI: C-reactive protein-triglyceride-glucose, (B) CHG: Cholesterol-high-density lipoprotein-glucose; Analyses were derived from the fully adjusted model (Model 3). Fully adjusted models included: age, gender, location, smoking status and BMI, LDL_C, eGFR, Cr, BUN and UA. CTI, C-reactive protein-triglyceride-glucose; CHG, cholesterol-high-density lipoprotein-glucose; PNIE, pure natural indirect effect; CDE, controlled direct effect.

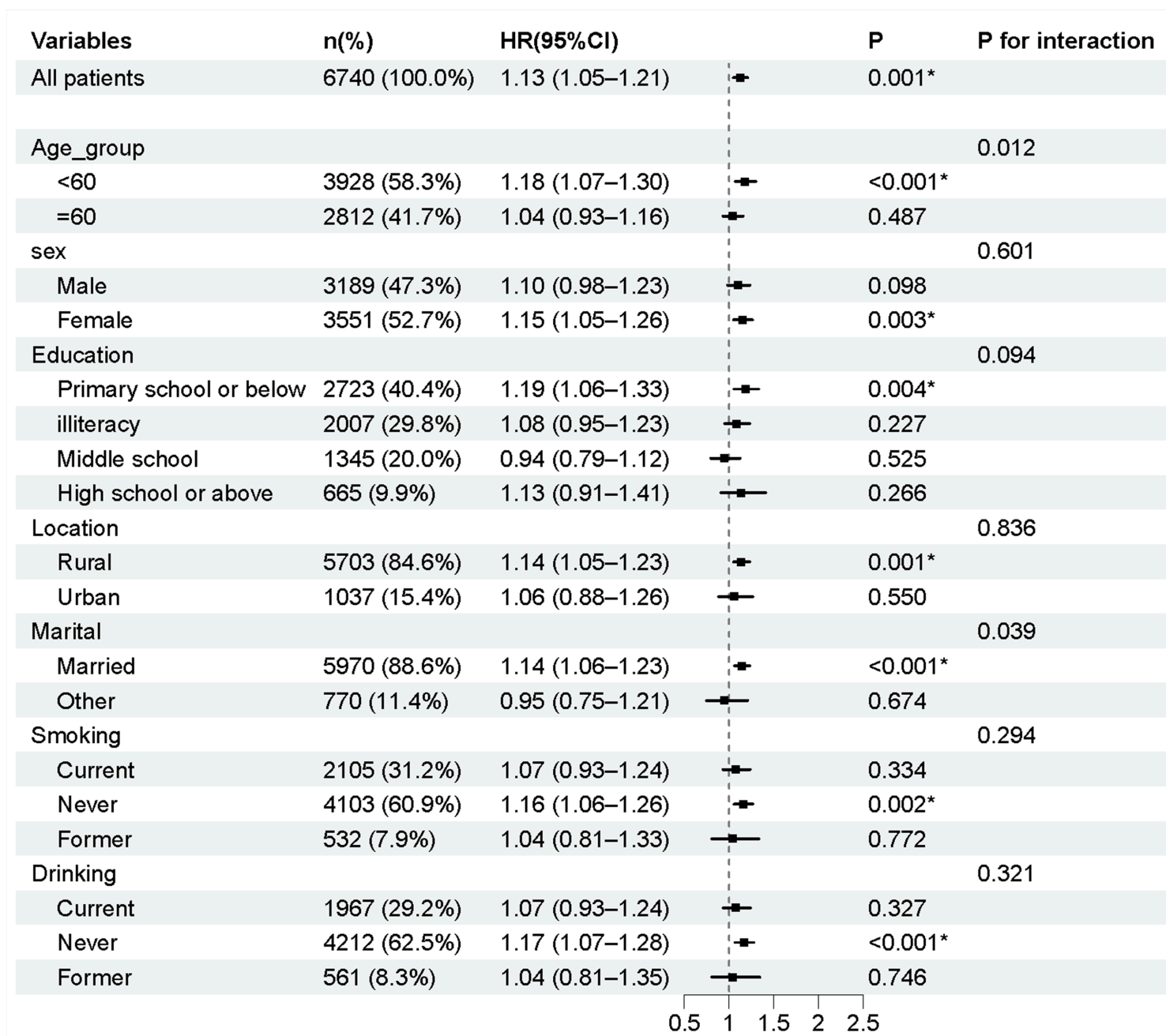


Figure 6

Subgroup analysis of CTI in predicting heart disease risk in CKM 0-3.

Hazard ratios (HRs, squares) and 95% confidence intervals (CIs, horizontal lines). Analyses were derived from the fully adjusted model (Model 3) with the stratification variable itself excluded from adjustment. Fully adjusted models included: age, gender, location, smoking status and BMI, LDL_C, eGFR, Cr, BUN and UA. HR: hazard ratio, CI: confidence interval.

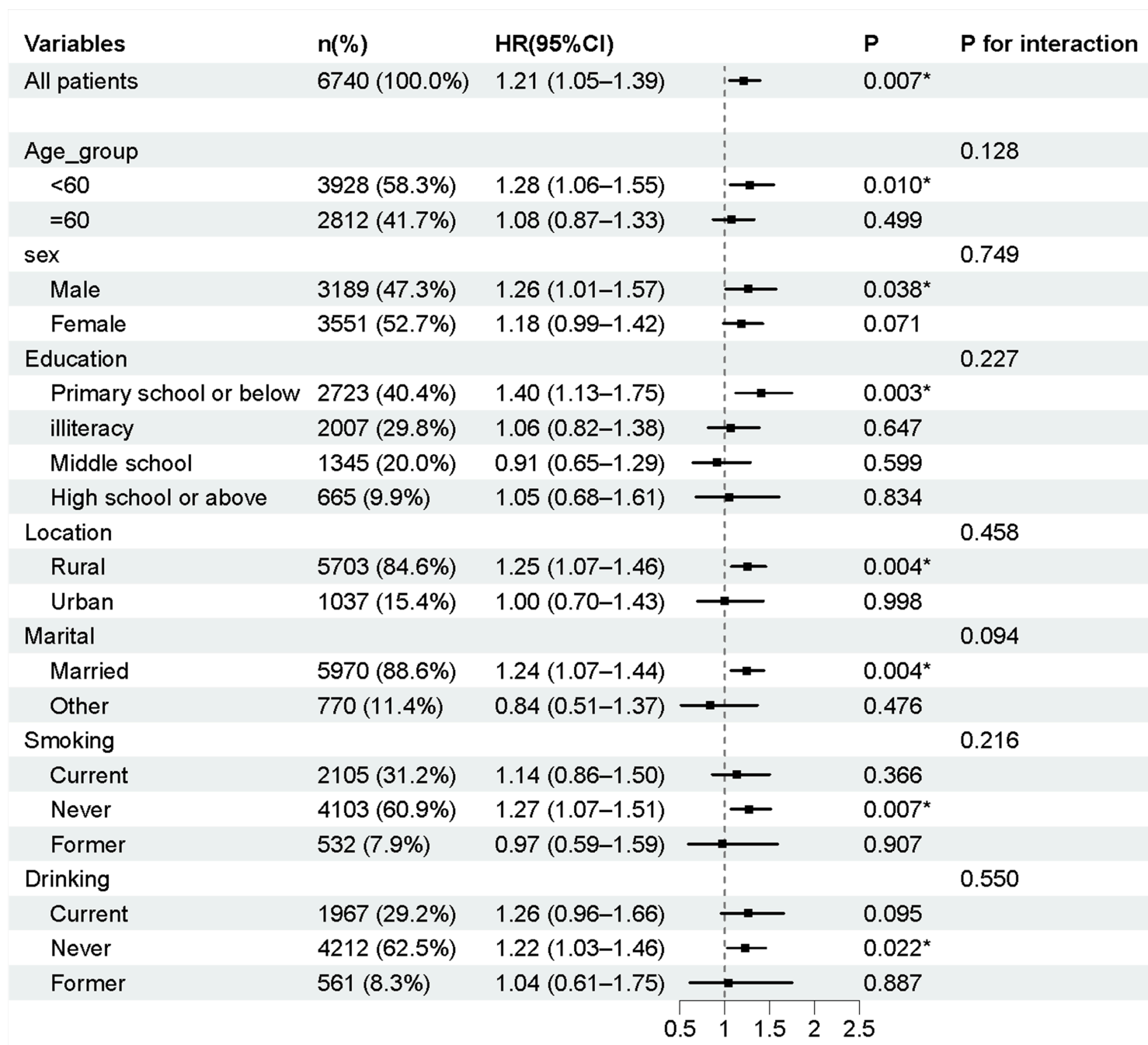


Figure 7

Subgroup analysis of CHG in predicting heart disease risk in CKM 0-3.

Hazard ratios (HRs, squares) and 95% confidence intervals (CIs, horizontal lines). Analyses were derived from the fully adjusted model (Model 3) with the stratification variable itself excluded from adjustment. Fully adjusted models included: age, gender, location, smoking status and BMI∕LDL_C, eGFR, Cr, BUN and UA. HR: hazard ratio, CI: confidence interval.

Supplementary Files

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