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Association of CHG-SI with Incident Cardiovascular Disease Among Middle-Aged and Older Adults with Cardiovascular-Kidney-Metabolic Syndrome Stages 0-3: Findings from CHARLS

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Abstract

Background The cardiovascular-kidney-metabolic (CKM) syndrome stages 0–3 encompass individuals without established cardiovascular disease (CVD) but with varying levels of cardiometabolic and renal risk. Whether metabolic burden considered together with muscle-related physiological status is associated with subsequent CVD remains unclear. We therefore examined the association of a combined index

integrating the cholesterol-HDL-glucose (CHG) index and the sarcopenia index (SI) with incident CVD.

Methods Using data from the China Health and Retirement Longitudinal Study, we included 3,734 adults with CKM stages 0-3. Associations of cumulative CHG-SI exposure and K-means-derived longitudinal profiles with incident CVD during 2015-2020 were examined using Cox proportional hazards models, with additional analyses of dose-response relationships, subgroups, mediation, discrimination, and robustness.

Results During follow-up from 2015 to 2020, 691 participants (18.5%) developed CVD. Compared with the low profile, the moderate and high profiles had higher hazards of incident CVD (adjusted HR, 1.26; 95% CI, 1.05-1.50; and HR, 1.41; 95% CI, 1.08-1.84, respectively), with a graded increase across profiles. Each 1-unit increase in cumulative CHG-SI was associated with a 2% higher hazard (adjusted HR, 1.02; 95% CI, 1.00-1.04). Baseline CHG-SI was not associated with CVD, whereas cumulative CHG-SI showed an overall linear association in restricted cubic spline analyses. Exploratory mediation proportions were 38.2% for the frailty index and 10.1% for the estimated glucose disposal rate.

Conclusions Higher cumulative CHG-SI burden and persistently higher longitudinal profiles were associated with increased CVD risk. Repeated assessment may provide

more stable longitudinal risk information than a single baseline measurement, although incremental predictive value was limited.

Keywords Cardiovascular-kidney-metabolic syndrome; Cardiovascular disease; CHG-SI; Longitudinal profiles; Cumulative exposure; Mediation analysis

Background

Cardiovascular-kidney-metabolic (CKM) syndrome was introduced by the American Heart Association to describe the close links among metabolic, kidney, and cardiovascular disorders[1,2]. CKM syndrome is classified into stages 0 to 4. Stages 0-3 represent a spectrum of CKM-related risk before the development of overt CVD. Stage 4 indicates established clinical CVD[1,3]. Because individuals with CKM stages 0-3 have not yet developed clinical CVD, this period represents an important window for cardiovascular prevention and risk assessment [1,3]. Identifying markers that reflect multiple CKM-related physiological domains may therefore help characterize cardiovascular risk before overt disease develops.

Metabolic abnormalities, especially insulin resistance and impaired glucose and lipid metabolism, are important risk factors for CVD [4-6]. These abnormalities are also closely related to skeletal muscle health. Insulin resistance may promote muscle loss. In turn, reduced muscle mass can impair glucose disposal and metabolic homeostasis[7]. This suggests a close interaction between metabolic dysfunction and poor muscle status.

The CHG index reflects glucose-lipid metabolic burden and has been associated with incident CVD [8-10]. The sarcopenia index (SI), calculated from the serum creatinine-to-cystatin C ratio, reflects muscle-related status and has also been associated with cardiovascular outcomes [11-15]. Recent studies have also combined metabolic indices with frailty-related measures for cardiovascular risk assessment [16-19]. These studies support the importance of considering metabolic abnormalities together with broader physiological vulnerability. However, frailty is a multidimensional construct and does not specifically represent muscle-related physiological status. We therefore combined CHG with SI, so that metabolic burden and muscle-related status could be examined within the same framework. Whether CHG-SI is associated with CVD in individuals with CKM stages 0-3 remains unclear.

A single CHG-SI measurement may not adequately characterize long-term exposure. Metabolic and physiological status may change over time, and a single baseline value may not fully reflect sustained burden. Previous studies have shown that cumulative CHG exposure and longitudinal CHG patterns are associated with subsequent CVD [10]. Similar findings have been reported for repeated measurements of other metabolic indices [20-23]. However, evidence remains limited on whether cumulative exposure and longitudinal profiles of a combined metabolic-muscle marker are associated with CVD in individuals with CKM stages 0-3.

Using longitudinal data from the China Health and Retirement Longitudinal Study, we investigated the association between CHG-SI and incident CVD among middle-aged and older adults with CKM stages 0-3. We focused on cumulative CHG-SI exposure and longitudinal CHG-SI profiles to better characterize long-term metabolic-muscle burden. Then we further explored potential pathways underlying this association and assessed the robustness of the findings.

Methods

Study Design and Population

This study used longitudinal data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative cohort study of Chinese adults aged 45 years and older. The baseline survey was conducted in 2011-2012 with follow-up surveys in 2013, 2015, 2018, and 2020. Details of the CHARLS study design and sampling procedures have been described previously. The study protocol was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent [24,25].

In the present study, 17,705 participants were initially enrolled at the CHARLS baseline survey (Wave 1). Participants were sequentially excluded as follows: 393 participants aged <45 years or missing age data; 3,980 with missing or implausible BMI values (BMI <12 or >60 kg/m^2) or missing education/residential information; 6,044 with insufficient baseline data for calculation of CHG-SI; 150 with missing information

required for CKM staging; 1,001 with prior clinical CVD at baseline (CKM stage 4); and 219 without follow-up information. After these exclusions, 5,918 participants with CKM stages 0-3 were included in the baseline analyses.

For longitudinal analyses, participants without CHG-SI data in 2015 (n=1,837) or who developed CVD before 2015 (n=347) were further excluded. The final longitudinal cohort included 3,734 participants who were free of clinical CVD through 2015. Follow-up continued from 2015 to 2020. The participant selection process is shown in Figure 1.

Definition of CKM Syndrome Stages 0-3

CKM stages were defined according to the American Heart Association framework [1,2]. Stage 0 indicated the absence of CKM risk factors. Stage 1 included overweight or abdominal obesity or impaired glycemic status. Stage 2 was characterized by metabolic disorders, including diabetes, hypertension, metabolic syndrome, or dyslipidemia, or by chronic kidney disease (CKD). Stage 3 represented subclinical CVD or its risk equivalent. Detailed definitions and diagnostic criteria for CKM stages 0-3 are provided in Supplementary Table S1.

Ascertainment of Incident Cardiovascular Disease

Incident CVD was defined as the first occurrence of physician-diagnosed heart disease or stroke during follow-up, based on standardized CHARLS questionnaires. Heart

disease included myocardial infarction, coronary heart disease, angina, congestive heart failure, or other heart-related conditions. For the baseline analyses, participants were followed from 2011-2012 to 2020. For the longitudinal analyses, 2011-2015 was used as the exposure assessment period, and participants who developed CVD during this period were excluded. Follow-up for incident CVD then continued from 2015 to 2020. Time to event was defined as the first follow-up wave reporting CVD, with event-free participants censored at their last available follow-up.

Assessment of CHG, SI, and CHG-SI

Fasting venous blood samples were collected and assayed according to standardized CHARLS protocols. FBG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), serum creatinine, and cystatin C were used to calculate CHG-SI [24].

The cholesterol, high-density lipoprotein, and glucose (CHG) index was calculated as follows [8]:

$$CHG=ln[\frac{TC(mg/dL)\times FBG(mg/dL)}{2\times HDL\text{-}C(mg/dL)}].$$

The sarcopenia index (SI) is conventionally calculated as follows [10,11]:

$$SI=\frac{serum\ creatinine}{cystatin\ C}\times 100.$$

The unscaled serum creatinine-to-cystatin C ratio was used, and CHG-SI was calculated as:

$$\text{CHG-SI}=\frac{\text{CHG}}{\textit{serum creatinine/cystatin C}}.$$

Higher CHG-SI values therefore reflect a higher CHG level and/or a lower creatinine-to-cystatin C ratio.

CHG-SI was calculated at baseline (2011-2012) and in 2015. Cumulative CHG-SI exposure was estimated from the two measurements using a time-weighted approach [10,22,23]:

$$\text{Cumulative CHG-SI}=\frac{\text{CHG-SI}_{2012}+\text{CHG-SI}_{2015}}{2}\times(2015-2012).$$

For supplementary baseline analyses, CHG-SI was examined as both a continuous variable and according to quartiles. CHG and SI were dichotomized according to their respective median values and cross-classified into four groups, with the low CHG/high SI group serving as the reference category.

Potential Covariates

Covariates included sociodemographic factors (age, sex, marital status, residential area, and education), lifestyle factors (smoking, alcohol consumption, sleep duration, and BMI), and clinical factors including hypertension, diabetes, and COPD. Laboratory measurements included serum uric acid, C-reactive protein (CRP), and renal biomarkers, including estimated glomerular filtration rate (eGFR) calculated according to the CKD-EPI equation [26].

Hypertension was defined by physician diagnosis, antihypertensive medication use, or blood pressure≥140/90 mmHg. Diabetes was defined by FBG≥126 mg/dL, HbA1c≥6.5%, physician diagnosis, or glucose-lowering medication use. Variables directly involved in CHG-SI calculation were not simultaneously included in the fully adjusted model to reduce potential overadjustment and mathematical coupling.

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges (IQRs), and categorical variables as frequencies and percentages. Differences in baseline characteristics across longitudinal CHG-SI profile groups were compared using the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Longitudinal CHG-SI profiles were identified using K-means clustering based on standardized CHG-SI values at baseline and in 2015. Three clusters were selected according to clustering performance and stability and were classified as low, moderate, and high CHG-SI profiles.

Cox proportional hazards regression models were used to examine the associations of cumulative CHG-SI and longitudinal CHG-SI profiles with incident CVD. The low profile was used as the reference group. Model 1 was unadjusted; Model 2 was adjusted for age, gender, education level, marital status, and location; and Model 3 was

additionally adjusted for BMI, sleep duration, smoking status, alcohol consumption, hypertension, diabetes mellitus, COPD, serum uric acid, and CRP. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported and the proportional hazards assumption was assessed using Schoenfeld residuals [27,28]. Restricted cubic spline models were used to examine dose-response relationships [29], and Kaplan-Meier curves with log-rank tests were used to compare CVD-free survival. Subgroup and interaction analyses were performed according to age, sex, BMI, hypertension, diabetes, and CKM stage. The incremental predictive value of CHG-SI-related measures was additionally assessed using Harrell's C-index, AUC, NRI, and IDI [30,31].

Exploratory mediation analyses were performed to examine frailty index (FI) and estimated glucose disposal rate (eGDR) as potential mediators of the association between cumulative CHG-SI and incident CVD. FI was constructed from 32 health deficits according to established methods [32], with details provided in Supplementary Table S2. eGDR was calculated as follows [33]:

$$eGDR=21.158-(0.09\times WC)-(3.407\times HT)-(0.551\times HbA1c)$$

Cumulative CHG-SI was used as the exposure, and 2015 FI and eGDR were examined separately as mediators. Mediation models were adjusted for the covariates included in Model 3, and indirect effects were estimated using 500 bootstrap simulations [34]. These analyses were considered exploratory

Sensitivity analyses included analyses of unimputed data, separate heart disease and stroke outcomes, exclusion of participants with baseline hypertension or diabetes, additional adjustment for medication use and frailty, alternative definitions of smoking and alcohol consumption, and IPTW Cox models [35]. Missing covariate data in the primary analyses were handled using multiple imputation by chained equations (MICE) with five imputed datasets combined according to Rubin's rules[36]. All statistical analyses were performed using R version 4.5.3, with two-sided $P<0.05$ considered statistically significant.

Results

Baseline Characteristics of Study Participants

A total of 3,734 participants with CKM stages 0-3 were included in the longitudinal analysis, of whom 691 (18.5%) developed incident CVD during follow-up. The median age was 58.0 years (IQR, 52.0-65.0 years), and 53.9% were women. K-means clustering identified three longitudinal CHG-SI profiles: low, moderate, and high (Figure 2). The low, moderate, and high profiles included 1,646 (44.1%), 1,677 (44.9%), and 411 (11.0%) participants, respectively. CHG-SI levels decreased from baseline to 2015 in all three profiles, while their relative ordering remained unchanged, with the low, moderate, and high profiles consistently representing progressively higher CHG-SI levels. Baseline characteristics according to these profiles are shown in Table 1. Compared with participants in the low profile, those in the high profile were generally older and had higher prevalences of hypertension (52.6% vs. 31.2%) and diabetes (28.5%

241 vs. 10.7%). They also had higher BMI and FI, lower eGDR, and a greater proportion
242 of advanced CKM stages. The proportion of incident CVD increased across the low,
243 moderate, and high profiles (15.1%, 20.2%, and 25.3%, respectively; P<0.001).
244
245 For supplementary baseline analyses, 5,918 participants were included. Baseline
246 characteristics according to CHG-SI quartiles are presented in Supplementary Table S3,
247 and the joint distribution of CHG and SI is shown in Supplementary Table S4.
248
249 **Associations of Cumulative CHG-SI and Longitudinal Profiles with Incident CVD**
250 The associations of cumulative CHG-SI and longitudinal CHG-SI profiles with incident
251 CVD are shown in Table 2. Higher cumulative CHG-SI was consistently associated
252 with a greater hazard of incident CVD across the sequential Cox models, although the
253 association was attenuated after multivariable adjustment. In the fully adjusted model,
254 each 1-unit increase in cumulative CHG-SI was associated with a 2% higher hazard of
255 incident CVD (HR, 1.02; 95% CI, 1.00-1.04; P=0.021).
256
257 A graded association was also observed across the longitudinal CHG-SI profiles.
258 Compared with the low profile, participants in the moderate and high profiles had
259 higher hazards of incident CVD after full adjustment (moderate: HR, 1.26; 95% CI,
260 1.05-1.50; P=0.013; high: HR, 1.41; 95% CI, 1.08-1.84; P=0.012). The hazard of CVD
261 increased progressively across the low, moderate, and high profiles (P for trend=0.005).
262 Both cumulative CHG-SI and longitudinal CHG-SI profiles remained associated with

incident CVD in the fully adjusted model. Multicollinearity diagnostics are presented in Supplementary Table S6.

Table 2 Associations of Cumulative CHG-SI Exposure and Longitudinal Profiles with Incident CVD in CKM Stages 0–3

Exposure / Profile groups	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*	Model 3 HR (95% CI)	*P*
Continuous cumulative exposure						
Cumulative CHG-SI (per unit)	1.03 (1.02-1.04)	<0.001	1.02 (1.01-1.04)	<0.001	1.02 (1.00-1.04)	0.021
Profile groups						
Low Profile	Ref	-	Ref	-	Ref	-
Moderate Profile	1.38 (1.17-1.63)	<0.001	1.32 (1.11-1.58)	0.002	1.26 (1.05-1.50)	0.013
High Profile	1.82 (1.45-2.29)	<0.001	1.61 (1.24-2.08)	<0.001	1.41 (1.08-1.84)	0.012
P for trend	<0.001		<0.001		0.005	

Model 1: Unadjusted (crude model). Model 2: Adjusted for demographic characteristics, including age, gender, education level, marital status, and residence location. Model 3: Further adjusted for lifestyle factors, clinical history, and laboratory biomarkers, including body mass index (BMI), sleep duration, smoking status, alcohol consumption, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), uric acid, and C-reactive protein (CRP).

Abbreviations: CHG-SI, combined cholesterol, high-density lipoprotein, glucose, and sarcopenia index; CI, confidence interval; CKM, cardiovascular-kidney-metabolic syndrome; CVD, cardiovascular disease; HR, hazard ratio.

Dose-Response Relationships of CHG-SI with Incident CVD

Restricted cubic spline analyses are shown in Figure 3. Baseline CHG-SI was not significantly associated with incident CVD (P for overall=0.186; P for nonlinearity=0.098). In contrast, cumulative CHG-SI showed a significant overall association with incident CVD (P for overall=0.026), with no evidence of nonlinearity (P for nonlinearity=0.126). The fitted spline for cumulative CHG-SI showed an overall increasing pattern across the observed range.

CVD-Free Survival According to Longitudinal CHG-SI Profiles

Kaplan-Meier analysis showed significant differences in CVD-free survival across the longitudinal CHG-SI profiles (Figure 4; log-rank P<0.0001). Participants in the high profile consistently exhibited the lowest CVD-free survival during follow-up, followed by those in the moderate and low profiles. The survival curves remained separated across the follow-up period.

Incremental Predictive Performance of CHG-SI

The predictive performance of CHG-SI-related measures is shown in Figure 5. In the overall cohort, the AUC of the base model was 0.611, with only small changes after the addition of CHG-SI-related measures. Similar patterns were observed for Harrell's C-index and in analyses stratified by CKM stage. Adding cumulative CHG-SI modestly improved continuous NRI (0.0609; 95% CI, 0.0122-0.1091; P=0.0066). The

improvement in IDI was not significant (0.0015; 95% CI, −0.0001 to 0.0050; P=0.086). Improvements for the other CHG-SI-related measures were small or inconsistent. Overall, the incremental predictive value of CHG-SI-related measures was limited.

Subgroup Analyses

Subgroup analyses showed that the associations between longitudinal CHG-SI profiles and incident CVD (Figure 6) were broadly consistent across strata defined by age, sex, BMI, hypertension, diabetes, and CKM stage. Although the magnitude of the associations varied across individual subgroups, none of the multiplicative interaction tests reached statistical significance (P for interaction=0.963 for age, 0.502 for sex, 0.871 for BMI, 0.111 for hypertension, 0.274 for diabetes, and 0.719 for CKM stage). Thus, there was no clear evidence that the association between longitudinal CHG-SI profiles and incident CVD was modified by these demographic or clinical characteristics.

Exploratory Mediation Analyses

Exploratory mediation analyses were performed to investigate potential pathways underlying the association between cumulative CHG-SI and incident CVD (Figure 7). The estimated proportion mediated by the frailty index (FI) was 38.2%, whereas the corresponding proportion mediated by estimated glucose disposal rate (eGDR) was 10.1%. These findings suggest that frailty-related physiological vulnerability and

insulin resistance may represent potential pathways linking greater cumulative CHG-SI exposure to subsequent CVD.

Sensitivity Analyses

The main findings were generally consistent across multiple sensitivity analyses (Supplementary Tables S7-S13). In analyses using unimputed data, cumulative CHG-SI remained associated with incident CVD (HR, 1.02; 95% CI, 1.00-1.04; P=0.016), and the moderate and high profiles showed associations similar to those in the primary analysis. Results were also generally unchanged after additional adjustment for antihypertensive and glucose-lowering medication use, alternative definitions of smoking and alcohol consumption, and further adjustment for frailty.

After excluding participants with baseline hypertension or diabetes, the associations for cumulative CHG-SI and the moderate profile were attenuated. The high profile remained associated with incident CVD (HR, 1.83; 95% CI, 1.22-2.73; P=0.003). A similar pattern was observed in the IPTW analysis, in which the high profile remained significant (HR, 1.69; 95% CI, 1.08-2.65; P=0.022), while the moderate profile was attenuated (HR, 1.18; 95% CI, 0.97-1.44; P=0.100). In subtype analyses, the moderate and high profiles remained associated with heart disease after full adjustment. For stroke, the corresponding associations were attenuated and were no longer statistically significant.

Discussion

In this longitudinal study of adults with CKM stages 0-3, higher cumulative CHG-SI exposure and persistently higher CHG-SI profiles were associated with an increased risk of incident CVD. Exploratory mediation analyses further suggested that frailty and insulin resistance may partly contribute to this association. These findings support a potential link between the metabolic-muscle profile reflected by CHG-SI and subsequent cardiovascular risk.

Glucose-lipid metabolic abnormalities and poor muscle status are both closely related to cardiovascular risk [4-6,13-15]. Previous evidence has examined these two dimensions separately. A recent study in individuals with CKM stages 0-3 reported that higher CHG was associated with an increased risk of incident CVD [8], supporting the relevance of glucose-lipid metabolic burden in this population. On the muscle-related side, Han et al. reported an association between the sarcopenia index and incident cardiovascular outcomes, while broader evidence has also linked sarcopenia with increased cardiovascular risk [13-15]. Studies have also begun to integrate metabolic abnormalities with broader measures of physiological vulnerability. For example, combined CHG-frailty and insulin resistance-frailty indices have been associated with cardiovascular outcomes among individuals with CKM stages 0-3 [16,17], and similar findings have been reported for other metabolic-frailty composite indices [18,19]. These studies support the value of considering metabolic and non-metabolic vulnerability together. However, frailty represents a broad accumulation of health

deficits and does not specifically reflect muscle-related physiological status. A marker more closely related to muscle status may therefore provide complementary information beyond general frailty. Metabolic burden and muscle-related status have generally been evaluated separately. This may overlook the close interaction between metabolic dysfunction and impaired muscle-related physiological status. By combining CHG and SI, our study extends previous work from a general metabolic-frailty framework toward a more specific metabolic-muscle perspective. CHG-SI provides an integrated measure of both metabolic burden and muscle-related status and therefore offers a way to examine the metabolic-muscle axis within the same framework.

Baseline CHG-SI alone was not independently associated with CVD. In contrast, cumulative CHG-SI and persistently higher longitudinal profiles were associated with incident CVD. This pattern is consistent with previous evidence showing that cumulative or repeated metabolic measurements may better reflect sustained exposure than a single baseline assessment [10,21-23]. Cumulative CHG-SI summarizes overall exposure across repeated measurements, and longitudinal profiles capture persistent differences in CHG-SI levels over time. The exposure assessment period also preceded the subsequent CVD follow-up, providing a clearer temporal sequence between CHG-SI exposure and incident events. The dose-response analysis further supported the association between cumulative CHG-SI and incident CVD, with no clear evidence of nonlinearity. These findings were further supported by the Kaplan-Meier and subgroup analyses. Participants with persistently higher CHG-SI profiles had lower CVD-free

survival, while no significant heterogeneity was observed across major demographic or clinical subgroups. The associations were generally consistent across sensitivity analyses, with the high CHG-SI profile showing the most stable association with incident CVD.

The association between CHG-SI and CVD may involve several interconnected pathways. Insulin resistance, chronic inflammation, oxidative stress, and endothelial dysfunction may contribute to both cardiovascular injury and impaired skeletal muscle health [4,37-39,40]. Skeletal muscle is an important site of insulin-mediated glucose disposal, and impaired insulin signaling may reduce glucose uptake while adversely affecting muscle protein metabolism and muscle function [40]. Loss of muscle reserve may therefore not only reflect poor physiological status but may also contribute to worsening glucose homeostasis, creating a reciprocal relationship between metabolic dysfunction and muscle impairment. Chronic inflammation and oxidative stress may further reinforce this interaction by promoting both vascular injury and deterioration of muscle function [38,39,40]. This bidirectional interaction may link metabolic dysfunction and poor muscle status to cardiovascular risk. In addition, SI is derived from serum creatinine and cystatin C, two biomarkers closely related to renal filtration but differently influenced by muscle mass [7,11,12]. Serum creatinine is partly determined by muscle mass while cystatin C is less dependent on muscle mass and more closely reflects renal filtration. Thus, their ratio may contain information related to both muscle status and kidney physiology rather than representing muscle mass alone

[7,11,12]. These features are particularly relevant in CKM syndrome, in which cardiovascular, kidney, and metabolic abnormalities are closely interconnected [1-3]. Accordingly, CHG-SI may be useful not because it directly measures each component of CKM syndrome, but because it integrates metabolic burden with a muscle-related marker that is also influenced by renal physiology.

To further explore potential pathways, we examined insulin resistance and frailty as candidate mediators. Because CHG is derived from fasting glucose and lipid parameters, eGDR was selected as an alternative marker of insulin resistance based on waist circumference, hypertension, and HbA1c, without directly sharing the components used to calculate CHG [33,41,42]. This allowed insulin resistance to be evaluated from a related but independent perspective. FI was used to represent broader frailty-related physiological vulnerability that may partly overlap with reduced muscle reserve [20,32,43]. Together, eGDR and FI provided complementary information regarding metabolic dysfunction and reduced physiological reserve, two aspects potentially involved in the association between CHG-SI and CVD. The mediation analyses suggested that both frailty-related vulnerability and insulin resistance may partly contribute to the association between cumulative CHG-SI and incident CVD, with a larger contribution observed for frailty. However, neither mediator fully accounted for the observed association, suggesting that other pathways, including inflammation, endothelial dysfunction, oxidative stress, and kidney-related factors, may also be

involved. Because this study was observational, these mediation findings should be interpreted as exploratory and not as evidence of causal mechanisms.

The addition of CHG-SI-related measures resulted in only minor changes in AUC and C-index, indicating little improvement in overall model discrimination beyond conventional cardiovascular risk factors. Reclassification analyses showed a modest improvement in continuous NRI for cumulative CHG-SI, whereas IDI was not significantly improved [30,31]. Overall, these findings suggest that CHG-SI provides limited incremental value for conventional risk prediction. Its potential value may lie more in characterizing sustained metabolic-muscle burden than in improving conventional risk scores. CHG-SI is derived from routinely measured laboratory parameters, which may make repeated assessment feasible in longitudinal settings. Future studies should examine whether changes in CHG-SI correspond to changes in metabolic and muscle-related status and whether these changes are associated with subsequent cardiovascular outcomes.

Several limitations should be considered when interpreting these findings. The observational design does not allow causal inference, and residual or unmeasured confounding may remain despite multivariable adjustment and sensitivity analyses. CHG-SI was assessed at only two time points, which limits the ability to describe more complex changes over time; the K-means groups should therefore be regarded as data-driven longitudinal profiles rather than true developmental trajectories. In addition,

incident CVD was identified mainly from self-reported physician diagnoses of heart disease and stroke rather than through standardized event adjudication, leaving the possibility of recall bias and outcome misclassification. The interpretation of SI also warrants caution because the creatinine-to-cystatin C ratio is influenced by factors other than muscle status; accordingly, neither SI nor CHG-SI should be viewed as a direct measure of muscle mass or physiological reserve [11,12]. The mediation analyses were exploratory and may also be affected by unmeasured confounding, so the estimated indirect effects should not be interpreted as causal pathways [34]. Finally, because CHARLS mainly includes middle-aged and older Chinese adults [24], the extent to which these findings apply to younger populations or to other ethnic and geographic groups remains uncertain.

Conclusions

Among middle-aged and older adults with CKM stages 0-3, greater cumulative CHG-SI exposure and persistently higher CHG-SI profiles were associated with increased risk of incident CVD. In contrast, a single baseline CHG-SI measurement provided limited independent prognostic information. Repeated CHG-SI assessment may therefore better characterize sustained metabolic-muscle burden and provide insight into potential metabolic-muscle pathways underlying cardiovascular risk.

List of abbreviations

ACME, average causal mediation effect; ADE, average direct effect; AUC, area under the curve; BMI, body mass index; CHARLS, China Health and Retirement Longitudinal Study; CHG, cholesterol, high-density lipoprotein, and glucose index; CHG-SI, combined cholesterol-HDL-glucose and sarcopenia index; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKM, cardiovascular-kidney-metabolic; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; FI, frailty index; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; HT, hypertension status; IDI, integrated discrimination improvement; IPTW, inverse probability of treatment weighting; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MICE, multiple imputation by chained equations; NRI, net reclassification improvement; RCS, restricted cubic spline; ROC, receiver operating characteristic; SI, sarcopenia index; TC, total cholesterol; WC, waist circumference.

Declarations

Ethics Approval and Consent to Participate

The CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015 for the main survey and IRB00001052-11014 for biomarker collection). The present study was a secondary analysis of CHARLS data. Consent to participate: Written informed consent was obtained from participants by the

CHARLS study team before data collection.

Clinical trial number: not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data analyzed in this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS): 2011 Wave 1 (Baseline) (https://charls.pku.edu.cn/en/Data/a2011_CHARLS_Wave1__Baseline_.htm), 2013 Wave 2 (https://charls.pku.edu.cn/en/Data/a2013_CHARLS_Wave2.htm), 2015 Wave 3 (https://charls.pku.edu.cn/en/Data/a2015_CHARLS_Wave_3.htm), and 2020 Wave 5 (https://charls.charlsdata.com/pages/Data/2020-charls-wave5/en.html). The datasets are available through the CHARLS data portal after registration.

Competing interests

The authors declare no competing interests.

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Authors' contributions

HL and XZ contributed equally to this work. HL conceived and designed the study. HL performed the research and interpreted the data. HL and XZ conducted the statistical analysis. HL, XZ, and ZL drafted and revised the manuscript. ZL critically reviewed the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript and agreed on the journal to which the manuscript would be submitted.

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References

1. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. Circulation. 2023;148(20):1606-1635. doi: 10.1161/CIR.0000000000001184.

2. Ndumele CE, Neeland IJ, Tuttle KR, et al. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2023;148(20):1636-1664. doi: 10.1161/CIR.0000000000001186.

3. Ndumele CE, Rodriguez F, Dixon DL, et al. 2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome. J Am Coll Cardiol. 2026;87(22S):e1889-e2007. doi: 10.1016/j.jacc.2026.03.056.

4. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PWF. Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes. 2005;54(11):3252-3257. doi: 10.2337/diabetes.54.11.3252.

5. Tao LC, Xu JN, Wang TT, Hua F, Li JJ. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations. Cardiovasc Diabetol. 2022;21:68. doi: 10.1186/s12933-022-01511-x.

6. Liu X, Tan Z, Huang Y, et al. Relationship between the triglyceride-glucose index and risk of cardiovascular diseases and mortality in the general population: a systematic review and meta-analysis. Cardiovasc Diabetol. 2022;21:124. doi: 10.1186/s12933-022-01546-0.

7. Lin T, Jiang T, Huang X, et al. Diagnostic test accuracy of serum creatinine and cystatin C-based index for sarcopenia: a systematic review and meta-analysis. Age Ageing. 2024;53(1):afad252. doi:10.1093/ageing/afad252.

8. Mansoori A, Nosrati M, Dorchin M, et al. A novel index for diagnosis of type 2 diabetes mellitus: Cholesterol, High density lipoprotein, and Glucose (CHG) index. J Diabetes Investig. 2025;16(2):309-314. doi: 10.1111/jdi.14343.

9. Zhao Z, Du P, Jian M, et al. Association of cholesterol, high-density lipoprotein, and glucose index and modified indices in predicting cardiovascular diseases incidence among population with cardiovascular-kidney-metabolic syndrome stages 0-3: a nationwide prospective cohort study. BMC Cardiovasc Disord. 2026. doi:10.1186/s12872-026-06295-6.

10. Wang H, Song G, Li G, et al. Associations of cumulative exposure and dynamic trajectories of the cholesterol-HDL-glucose index and its obesity-related derivatives with cardiovascular disease: a nationwide prospective cohort study. Cardiovasc Diabetol. 2026;25:239. doi: 10.1186/s12933-026-03295-w.

11. Kashani KB, Frazee EN, Kukrálová L, et al. Evaluating Muscle Mass by Using Markers of Kidney Function: Development of the Sarcopenia Index. Crit Care Med. 2017;45(1):e23-e29. doi: 10.1097/CCM.0000000000002013.

12. Tabara Y, Kohara K, Okada Y, Ohyagi Y, Igase M. Creatinine-to-cystatin C ratio as a marker of skeletal muscle mass in older adults: J-SHIPP study. Clin Nutr. 2020;39(6):1857-1862. doi: 10.1016/j.clnu.2019.07.027.

13. Han W, Li Y, Zheng X, Zhang K. Incident cardiovascular diseases and changes in the ratio of serum creatinine to cystatin C: the sarcopenia index. Nutr Metab Cardiovasc Dis. 2026;36(3):104425. doi: 10.1016/j.numecd.2025.104425.

14. Damluji AA, Alfaraidhy M, AlHajri N, et al. Sarcopenia and Cardiovascular Diseases. Circulation. 2023;147(20):1534-1553. doi: 10.1161/CIRCULATIONAHA.123.064071.

15. Zuo X, Li X, Tang K, et al. Sarcopenia and cardiovascular diseases: A systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2023;14(3):1183-1198. doi: 10.1002/jcsm.13221.

16. Sun Z, Wang K, Guo C, et al. Association between the combined cholesterol, high-density lipoprotein, glucose index and frailty index and new-onset cardiovascular disease in individuals with cardiovascular-kidney-metabolic syndrome stages 0-3: evidence from CHARLS. Cardiovasc Diabetol. 2026. doi: 10.1186/s12933-026-03293-y.

17. Huang Y, Xu Y, Gu W, et al. Joint association of insulin resistance and frailty index with incident

ASCVD and MACE in individuals with cardiovascular-kidney-metabolic syndrome stages 0-3: a multi-cohort study. Cardiovasc Diabetol. 2026. doi: 10.1186/s12933-026-03275-0.

18. Zhao YC, Wu SQ, Li JK, et al. Predictive value of the combined triglyceride-glucose and frailty index for cardiovascular disease and stroke in two prospective cohorts. Cardiovasc Diabetol. 2025;24:318. doi: 10.1186/s12933-025-02880-9.

19. Feng X, Deng B, Pan Y, et al. Associations of cumulative exposure and dynamic trajectories of the combined atherogenic and frailty index with incident cardiometabolic multimorbidity: a longitudinal analysis based on the China Health and Retirement Longitudinal Study (CHARLS). Cardiovasc Diabetol. 2026;25:228. doi: 10.1186/s12933-026-03235-8.

20. He D, Wang Z, Li J, et al. Changes in frailty and incident cardiovascular disease in three prospective cohorts. Eur Heart J. 2024;45(12):1058-1068. doi: 10.1093/eurheartj/ehad885.

21. Li H, Zuo Y, Qian F, et al. Triglyceride-glucose index variability and incident cardiovascular disease: a prospective cohort study. Cardiovasc Diabetol. 2022;21:105. doi: 10.1186/s12933-022-01541-5.

22. Tai S, Fu L, Zhang N, et al. Association of the cumulative triglyceride-glucose index with major adverse cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol. 2022;21:161. doi: 10.1186/s12933-022-01599-1.

23. Domanski MJ, Wu CO, Tian X, et al. Association of Incident Cardiovascular Disease With Time Course and Cumulative Exposure to Multiple Risk Factors. J Am Coll Cardiol. 2023;81(12):1151-1161. doi: 10.1016/j.jacc.2023.01.024.

24. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol. 2014;43(1):61-68. doi: 10.1093/ije/dys203.

603 25. Chen X, Crimmins E, Hu PP, et al. Venous Blood-Based Biomarkers in the China Health and
604 Retirement Longitudinal Study: Rationale, Design, and Results From the 2015 Wave. Am J
605 Epidemiol. 2019;188(11):1871-1877. doi: 10.1093/aje/kwz170.
606 26. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate.
607 Ann Intern Med. 2009;150(9):604-612. doi: 10.7326/0003-4819-150-9-200905050-00006.
608 27. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika.
609 1982;69(1):239-241. doi: 10.1093/biomet/69.1.239.
610 28. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted
611 residuals. Biometrika. 1994;81(3):515-526. doi: 10.1093/biomet/81.3.515.
612 29. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med. 1989;8(5):551-
613 561. doi: 10.1002/sim.4780080504.
614 30. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive
615 ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat
616 Med. 2008;27(2):157-172. doi: 10.1002/sim.2929.
617 31. Pencina MJ, D'Agostino RB Sr, Demler OV. Novel metrics for evaluating improvement in
618 discrimination: net reclassification and integrated discrimination improvement for normal
619 variables and nested models. Stat Med. 2012;31(2):101-113. doi: 10.1002/sim.4348.
620 32. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating
621 a frailty index. BMC Geriatr. 2008;8:24. doi: 10.1186/1471-2318-8-24.
622 33. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin
623 resistance in type 1 diabetes? Diabetes. 2000;49(4):626-632. doi: 10.2337/diabetes.49.4.626.
624 34. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. Psychol Methods.

2010;15(4):309-334. doi: 10.1037/a0020761.

35. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-3679. doi: 10.1002/sim.6607.

36. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011;45(3):1-67. doi: 10.18637/jss.v045.i03.

37. Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. Diabetes Metab Res Rev. 2006;22(6):423-436. doi: 10.1002/dmrr.634.

38. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol. 2009;6(6):399-409. doi: 10.1038/nrcardio.2009.55.

39. Soehnlein O, Libby P. Targeting inflammation in atherosclerosis—from experimental insights to the clinic. Nat Rev Drug Discov. 2021;20(8):589-610. doi: 10.1038/s41573-021-00198-1.

40. Mesinovic A, Zengin A, De Courten B, Ebeling PR, Scott D. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. Diabetes Metab Syndr Obes. 2019;12:1057-1072. doi:10.2147/DMSO.S186600.

41. Ren X, Jiang M, Han L, Zheng X. Estimated glucose disposal rate and risk of cardiovascular disease: evidence from the China Health and Retirement Longitudinal Study. BMC Geriatr. 2022;22(1):968. doi: 10.1186/s12877-022-03689-x.

42. Zhang Z, Zhao L, Lu Y, Xiao Y, Zhou X. Insulin resistance assessed by estimated glucose disposal rate and risk of incident cardiovascular diseases among individuals without diabetes: findings from a nationwide, population based, prospective cohort study. Cardiovasc Diabetol. 2024;23:194. doi: 10.1186/s12933-024-02256-5.

43. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-762. doi: 10.1016/S0140-6736(12)62167-9.

Table

Table 1 Baseline Characteristics of Participants Based on Longitudinal Profiles of CHG-SI

Characteristics	Overall (n=3734)	Low Profile (n=1646)	Moderate Profile (n=1677)	High Profile (n=411)	*P*
Age, years	58.00 [52.00, 65.00]	57.00 [50.00, 63.00]	59.00 [53.00, 66.00]	63.00 [57.00, 70.00]	<0.001

Gender, n (%)					<0.001
Female	2011 (53.9)	531 (32.3)	1118 (66.7)	362 (88.1)	
Male	1723 (46.1)	1115 (67.7)	559 (33.3)	49 (11.9)	
Marital, n (%)					<0.001
Unmarried	557 (14.9)	196 (11.9)	273 (16.3)	88 (21.4)	
Married	3177 (85.1)	1450 (88.1)	1404 (83.7)	323 (78.6)	
Location, n (%)					0.196
Rural	3538 (94.8)	1548 (94.0)	1596 (95.2)	394 (95.9)	
Urban	196 (5.2)	98 (6.0)	81 (4.8)	17 (4.1)	
Education, n (%)					<0.001
Illiterate	1109 (29.7)	344 (20.9)	563 (33.6)	202 (49.1)	
Primary school	1579 (42.3)	722 (43.9)	707 (42.2)	150 (36.5)	
High school or above	1046 (28.0)	580 (35.2)	407 (24.3)	59 (14.4)	
Smoking status, n (%)					<0.001
Never	2322 (62.2)	801 (48.7)	1171 (69.8)	350 (85.2)	
Current	1133 (30.3)	678 (41.2)	402 (24.0)	53 (12.9)	
Past	279 (7.5)	167 (10.1)	104 (6.2)	8 (1.9)	
Alcohol consumption, n (%)					<0.001
None of these	2481 (66.4)	896 (54.4)	1230 (73.3)	355 (86.4)	
Drink less than once a	294 (7.9)	166 (10.1)	109 (6.5)	19 (4.6)	

month					
Drink more than once a month	959 (25.7)	584 (35.5)	338 (20.2)	37 (9.0)	
Hypertension, n (%)	1411 (37.8)	514 (31.2)	681 (40.6)	216 (52.6)	<0.001
Diabetes, n (%)	575 (15.4)	176 (10.7)	282 (16.8)	117 (28.5)	<0.001
COPD, n (%)	351 (9.4)	162 (9.8)	145 (8.6)	44 (10.7)	0.314
BMI, kg/m^2	23.05 [20.84, 25.60]	22.62 [20.57, 25.07]	23.19 [21.06, 25.83]	24.17 [21.43, 27.16]	<0.001
Waist circumference, cm	84.40 [78.00, 92.00]	83.10 [77.03, 90.00]	85.00 [78.20, 92.10]	88.80 [81.00, 96.15]	<0.001
SBP, mmHg	126.67 [114.00, 141.67]	123.67 [112.00, 137.00]	128.67 [115.33, 143.33]	133.67 [120.00, 153.00]	<0.001
DBP, mmHg	74.33 [67.00, 83.00]	74.00 [66.67, 81.67]	74.67 [67.33, 84.00]	75.33 [69.00, 84.33]	0.002
Sleep time, hours	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]	6.00 [5.00, 8.00]	0.004
Glucose, mg/dL	102.24 [94.32, 112.32]	101.07 [93.78, 109.76]	102.60 [94.50, 112.86]	106.92 [97.29, 126.09]	<0.001
Hba1c, %	5.10 [4.90, 5.40]	5.10 [4.80, 5.40]	5.10 [4.90, 5.40]	5.30 [5.00, 5.70]	<0.001
TG, mg/dL	104.43 [74.34, 153.99]	94.69 [68.14, 138.95]	108.86 [79.65, 157.53]	123.90 [90.27, 191.16]	<0.001
TC, mg/dL	190.98 [167.40, 215.72]	187.89 [165.85, 211.08]	192.91 [168.17, 220.75]	195.23 [170.68, 224.81]	<0.001
LDL-C, mg/dL	114.05 [93.56, 137.63]	110.95 [92.40, 132.22]	117.53 [94.72, 142.27]	117.91 [93.56, 145.75]	<0.001

HDL-C, mg/dL	49.48 [40.59, 59.92]	51.42 [42.91, 62.63]	48.71 [40.59, 58.76]	44.85 [35.57, 54.32]	<0.001
Uric acid, mg/dL	4.24 [3.51, 5.08]	4.49 [3.72, 5.42]	4.03 [3.40, 4.82]	4.01 [3.27, 4.84]	<0.001
Serum creatinine, mg/dL	0.75 [0.64, 0.87]	0.82 [0.72, 0.94]	0.70 [0.62, 0.80]	0.62 [0.53, 0.71]	<0.001
CRP, mg/L	0.97 [0.53, 1.96]	0.84 [0.49, 1.74]	1.04 [0.56, 2.00]	1.33 [0.75, 2.77]	<0.001
Frailty index	0.11 [0.06, 0.20]	0.11 [0.05, 0.17]	0.12 [0.07, 0.21]	0.15 [0.10, 0.24]	<0.001
Frailty status, n(%)					<0.001
Healthy	1531 (41.0)	779 (47.3)	642 (38.3)	110 (26.8)	
Pre-frail	1692 (45.3)	715 (43.4)	774 (46.2)	203 (49.4)	
Frail	511 (13.7)	152 (9.2)	261 (15.6)	98 (23.8)	
eGDR	9.98 [7.33, 11.13]	10.34 [7.73, 11.25]	10.14 [7.51, 11.17]	9.92 [7.29, 11.13]	<0.001
CHG_{2012}	5.27 [5.03, 5.56]	5.18 [4.96, 5.46]	5.31 [5.08, 5.58]	5.49 [5.21, 5.80]	<0.001
SI_{2012}	0.78 [0.68, 0.89]	0.87 [0.78, 0.97]	0.73 [0.66, 0.81]	0.57 [0.51, 0.66]	<0.001
$CHG\text{-}SI_{2012}$	6.81 [5.93, 7.82]	5.98 [5.36, 6.61]	7.33 [6.65, 8.00]	9.46 [8.60, 10.62]	<0.001
$CHG\text{-}SI_{2015}$	5.67 [4.87, 6.58]	4.78 [4.34, 5.21]	6.25 [5.80, 6.79]	8.00 [7.28, 9.03]	<0.001
Cumulative $CHG\text{-}SI_{2012\text{-}2015}$	18.71 [16.57, 21.42]	16.26 [15.03, 17.36]	20.33 [19.16, 21.79]	26.10 [24.84, 28.45]	<0.001
CHG and SI joint groups, n (%)					<0.001
Low CHG + High SI	866 (23.2)	690 (41.9)	173 (10.3)	3 (0.7)	
High CHG + High SI	1066 (28.5)	597 (36.3)	442 (26.4)	27 (6.6)	
Low CHG + Low SI	1006 (26.9)	293 (17.8)	589 (35.1)	124 (30.2)	

High CHG + Low SI	796 (21.3)	66 (4.0)	473 (28.2)	257 (62.5)	
CKM stage, n (%)					<0.001
Stage 0	328 (8.8)	205 (12.5)	107 (6.4)	16 (3.9)	
Stage 1	674 (18.1)	343 (20.8)	285 (17.0)	46 (11.2)	
Stage 2	1616 (43.3)	619 (37.6)	795 (47.4)	202 (49.1)	
Stage 3	1116 (29.9)	479 (29.1)	490 (29.2)	147 (35.8)	
New-onset CVD, n (%)	691 (18.5)	249 (15.1)	338 (20.2)	104 (25.3)	<0.001

665 **Abbreviations**: BMI, body mass index; CHG, cholesterol, high-density lipoprotein, glucose index; CKM,

666 cardiovascular-kidney-metabolic syndrome; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein;

667 CVD, cardiovascular disease; DBP, diastolic blood pressure; eGDR, estimated glucose disposal rate; HbA1c,

668 glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol;

669 SBP, systolic blood pressure; SI, sarcopenia index; TC, total cholesterol; TG, triglycerides.

Figure

Figure Legends:

Figure 1 Flowchart of the Sample Selection Process

Figure 2 Identification and Characterization of Longitudinal CHG-SI Profiles Using K-means Clustering Analysis. (A) Elbow plot used to evaluate the optimal number of clusters. (B) Scatter plot showing the distribution and separation of the identified clusters based on standardized CHG-SI measurements at baseline and 2015. (C) Longitudinal profiles showing mean CHG-SI levels from baseline to 2015 across the low, moderate, and high profiles. (D) Density plots showing the distributions of CHG-SI across the identified profiles at baseline and in 2015, respectively. Three clusters were identified and categorized as low, moderate, and high longitudinal CHG-SI profiles.

Figure 3 Baseline and Cumulative CHG-SI Associations with Incident CVD in CKM Stages 0–3: Restricted Cubic Splines. The left and right panels show the associations of baseline CHG-SI and cumulative CHG-SI with incident CVD, respectively. Solid lines represent hazard ratios (HRs), and shaded areas represent the corresponding 95% confidence intervals (CIs). The horizontal dashed line indicates the reference value of HR=1.0, and histograms show the distributions of the corresponding CHG-SI measures. Models were adjusted for age, sex, education level,

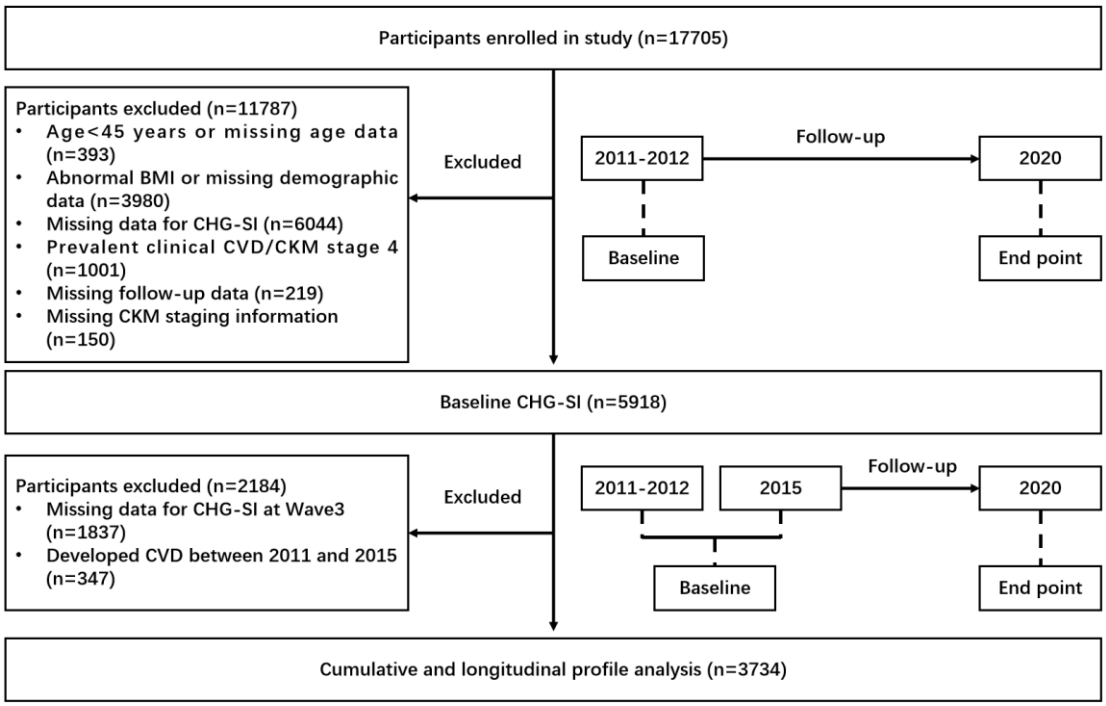
marital status, residential area, BMI, sleep duration, smoking status, alcohol consumption, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, serum uric acid, and C-reactive protein.

Figure 4 Kaplan-Meier Curves for CVD-Free Survival According to Baseline CHG-SI-Related Groups and Longitudinal CHG-SI Profiles. The three panels show CVD-free survival according to the four baseline joint CHG and SI groups, baseline CHG-SI quartiles, and the low, moderate, and high longitudinal CHG-SI profiles, respectively. The baseline analyses included follow-up from 2011–2012 through 2020, whereas the longitudinal profile analysis included follow-up from 2015 through 2020. Differences between groups were assessed using the log-rank test.

Figure 5 Receiver Operating Characteristic Curves Evaluating the Discriminatory Performance of CHG-SI-Related Measures for Incident Cardiovascular Disease. The three panels show ROC curves for the overall longitudinal cohort, participants with CKM stages 0–1, and participants with CKM stages 2–3, respectively. ROC curves compare the base model with models additionally incorporating CHG, SI, baseline CHG-SI, or cumulative CHG-SI. The base model included age, sex, BMI, smoking status, alcohol consumption, hypertension, diabetes mellitus, and C-reactive protein. Corresponding area under the curve (AUC) values are shown in the panel legends.

Figure 6 Subgroup Analyses of the Associations Between Longitudinal CHG-SI Profiles and Incident Cardiovascular Disease. Forest plots show hazard ratios (HRs) and 95% confidence intervals (CIs) for the moderate and high longitudinal CHG-SI profiles compared with the low profile across subgroups defined by age, sex, BMI, hypertension, diabetes, and CKM stage. P values for interaction were derived from multiplicative interaction terms incorporated into the Cox regression models.

Figure 7 Exploratory Mediation by Frailty and Estimated Glucose Disposal Rate Between Cumulative CHG-SI and Incident CVD. The figure illustrates exploratory mediation analyses examining frailty index (FI) and estimated glucose disposal rate (eGDR) as potential mediators of the association between cumulative CHG-SI exposure and incident CVD. The indirect effects through FI and eGDR are presented together with the corresponding estimated proportions mediated, while the average direct effect (ADE) and total effect are also shown in the figure. Mediation analyses were adjusted for age, sex, education level, marital status, residential area, BMI, sleep duration, smoking status, alcohol consumption, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, serum uric acid, and C-reactive protein. These analyses were exploratory and should not be interpreted as evidence of causal mediation.



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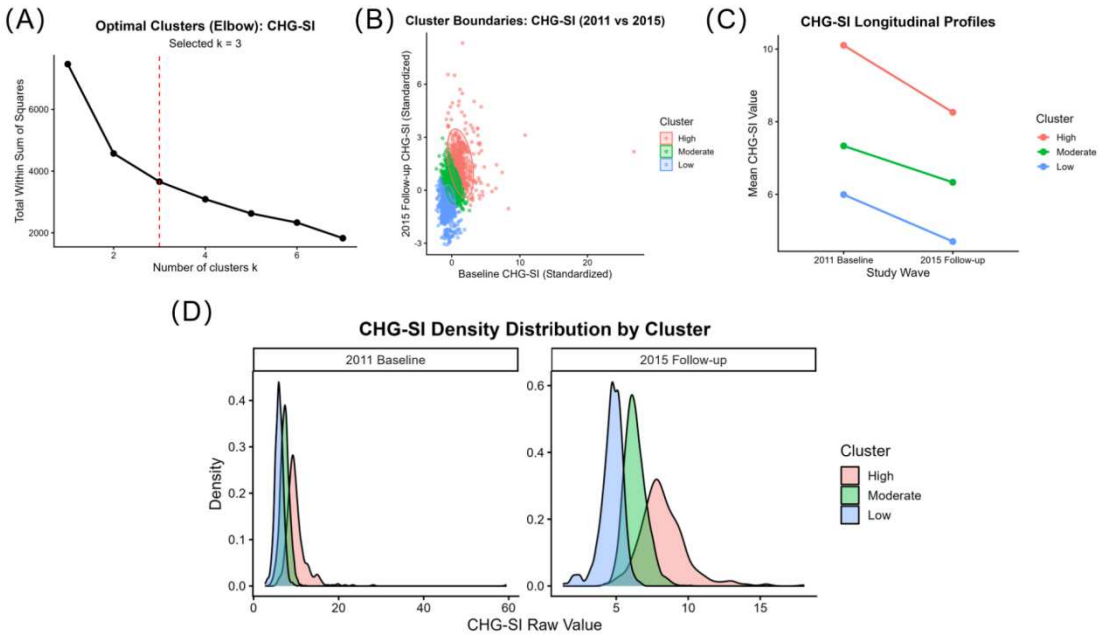
734 **Figure 1**

735



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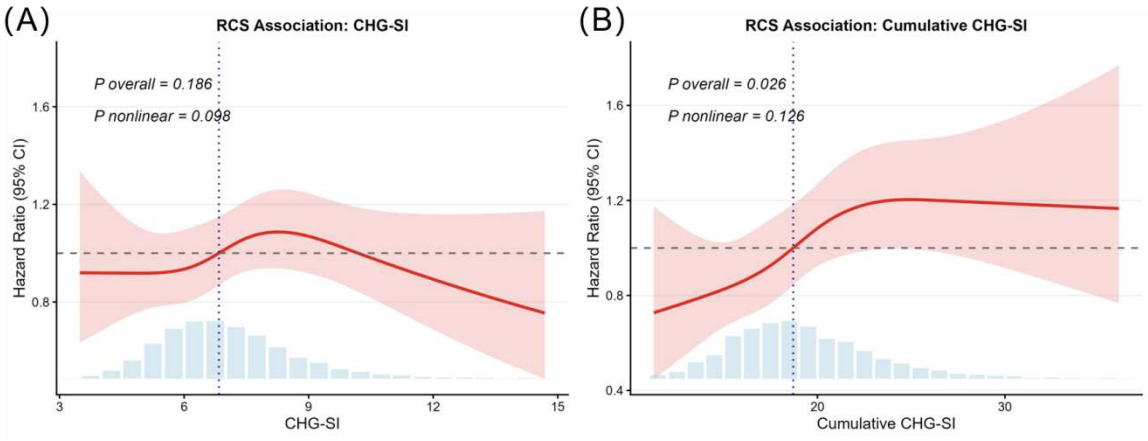
737 **Figure 2**



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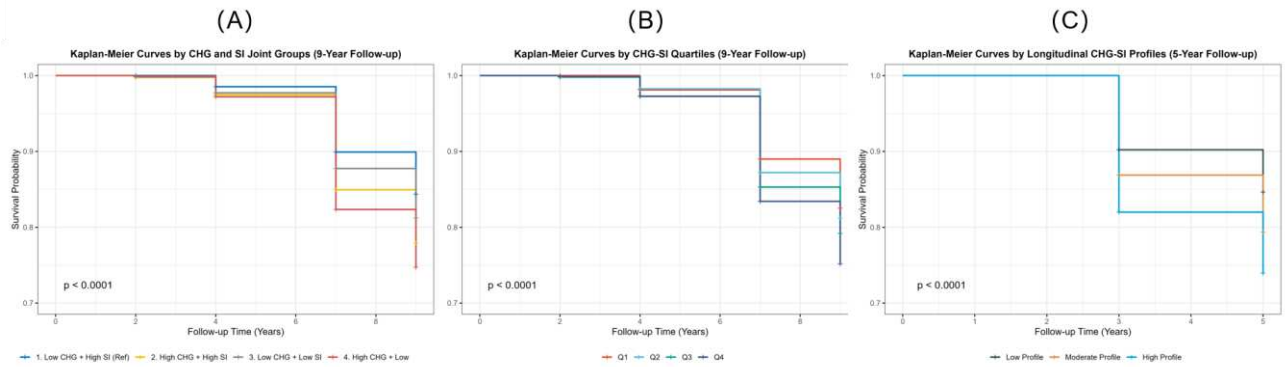
739 **Figure 3**



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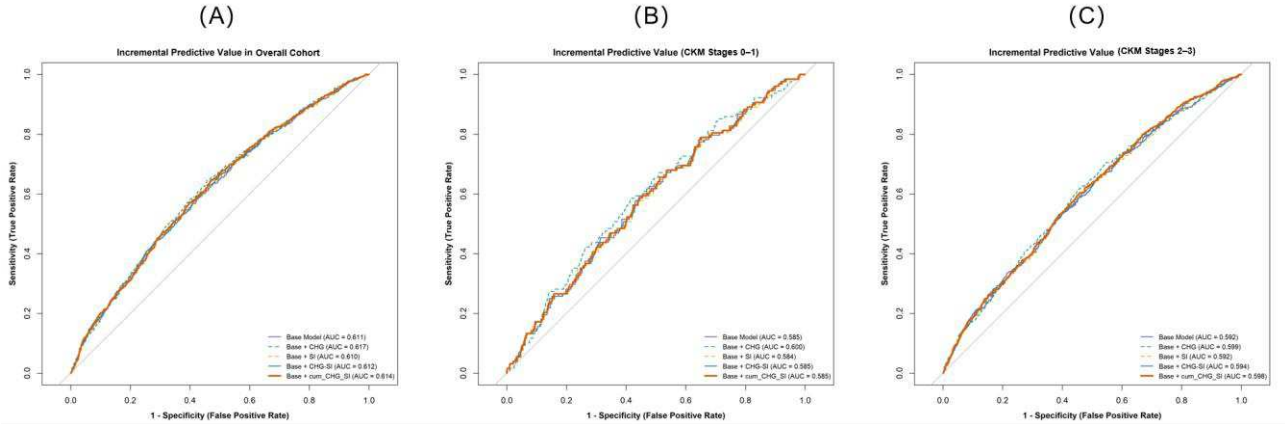
741 **Figure 4**



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743 **Figure 5**

744

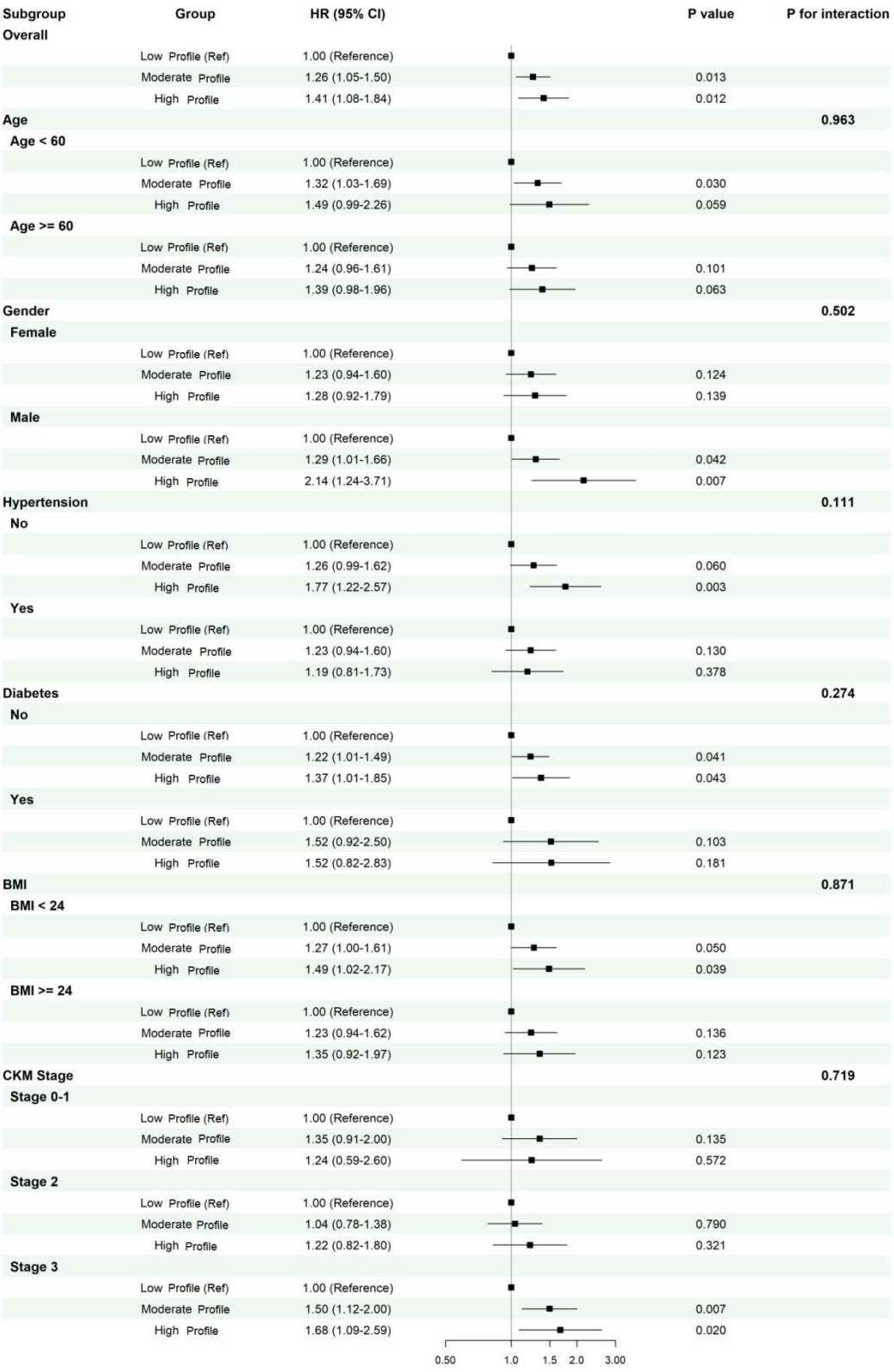
Subgroup
Group
HR (95% CI)
P value
P for interaction
Overall
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.26 (1.05-1.50) 0.013
High Profile 1.41 (1.08-1.84) 0.012
Age 0.963
Age < 60
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.32 (1.03-1.69) 0.030
High Profile 1.49 (0.99-2.26) 0.059
Age >= 60
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.24 (0.96-1.61) 0.101
High Profile 1.39 (0.98-1.96) 0.063
Gender 0.502
Female
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.23 (0.94-1.60) 0.124
High Profile 1.28 (0.92-1.79) 0.139
Male
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.29 (1.01-1.66) 0.042
High Profile 2.14 (1.24-3.71) 0.007
Hypertension 0.111
No
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.26 (0.99-1.62) 0.060
High Profile 1.77 (1.22-2.57) 0.003
Yes
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.23 (0.94-1.60) 0.130
High Profile 1.19 (0.81-1.73) 0.378
Diabetes 0.274
No
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.22 (1.01-1.49) 0.041
High Profile 1.37 (1.01-1.85) 0.043
Yes
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.52 (0.92-2.50) 0.103
High Profile 1.52 (0.82-2.83) 0.181
BMI 0.871
BMI < 24
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.27 (1.00-1.61) 0.050
High Profile 1.49 (1.02-2.17) 0.039
BMI >= 24
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.23 (0.94-1.62) 0.136
High Profile 1.35 (0.92-1.97) 0.123
CKM Stage 0.719
Stage 0-1
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.35 (0.91-2.00) 0.135
High Profile 1.24 (0.59-2.60) 0.572
Stage 2
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.04 (0.78-1.38) 0.790
High Profile 1.22 (0.82-1.80) 0.321
Stage 3
Low Profile (Ref) 1.00 (Reference)
Moderate Profile 1.50 (1.12-2.00) 0.007
High Profile 1.68 (1.09-2.59) 0.020
0.50
1.0
1.5
2.0
3.00

Figure 6

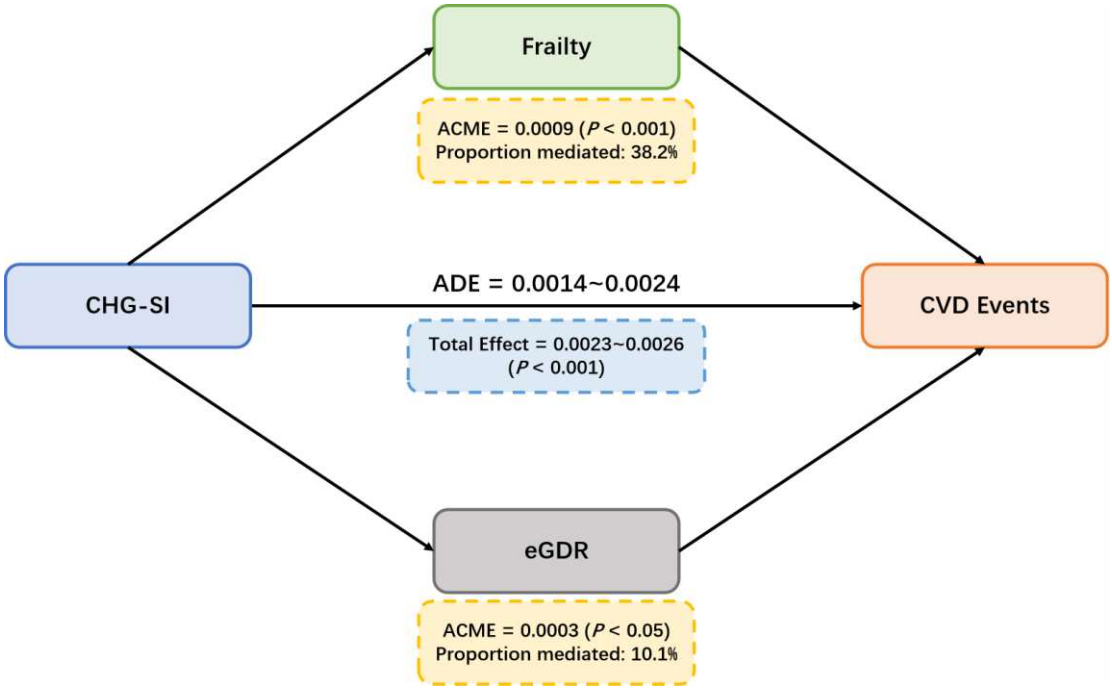
Frailty
ACME = 0.0009 (P < 0.001)
Proportion mediated: 38.2%
CHG-SI
ADE = 0.0014~0.0024
CVD Events
Total Effect = 0.0023~0.0026
(P < 0.001)
eGDR
ACME = 0.0003 (P < 0.05)
Proportion mediated: 10.1%

Figure 7

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS113.docx