

Bidirectional association between gastrointestinal disease and cardiovascular disease: the mediating role of depressive symptoms

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Abstract

Background

Gastrointestinal (GI) disease and cardiovascular disease (CVD) are major contributors to global morbidity and mortality. However, longitudinal population-based evidence regarding their bidirectional relationship and the potential psychological and metabolic-inflammatory mechanisms underlying the gut–heart axis remains limited.

Methods

We analyzed five waves (2011–2020) of the China Health and Retirement Longitudinal Study (CHARLS), including 13,730 participants without baseline CVD and 12,450 without baseline GI disease. Cox proportional hazards models estimated bidirectional associations, and mediation analyses assessed the contribution of depressive symptoms (CESD-10 scores) and the C-reactive protein–glucose–triglyceride index (CTI). Sensitivity and subgroup analyses were additionally performed.

Results

Baseline GI disease was associated with incident CVD (HR 1.44, 95% CI 1.32–1.57), and baseline CVD was associated with incident GI disease (HR 1.46, 95% CI 1.30–1.64). Depressive symptoms partially mediated both associations, accounting for 20.6% of the total effect of GI disease on incident CVD and 26.4% of the total effect of CVD on incident GI disease, whereas CTI did not significantly mediate either pathway. The association between baseline CVD and incident GI disease was significant among women (HR 1.51, 95% CI 1.25–1.81) but not men (P for interaction = 0.01). Findings were robust across sensitivity analyses.

Conclusions

GI disease and CVD were bidirectionally associated in middle-aged and older Chinese adults. Depressive symptoms may represent a shared psychological pathway underlying the gut–heart axis, whereas CTI did not play a major mediating role. These findings suggest the clinical importance of integrated gastrointestinal, cardiovascular, and psychological health management in aging populations.

What is currently known about this topic?

<p>GI disease and CVD are increasingly recognized as interconnected conditions. Depressive symptoms are common in both diseases.</p> <p>Existing evidence has mainly focused on unidirectional associations.</p>
<p>What is the key research question?</p>
<p>Are GI disease and CVD bidirectionally associated over time, and do depressive symptoms or metabolic-inflammatory dysregulation mediate these associations?</p>
<p>What is new?</p>
<p>This study demonstrates a bidirectional association between GI disease and CVD in a nationally representative longitudinal cohort.</p> <p>Depressive symptoms partially mediated both directions, whereas CTI did not significantly mediate either pathway.</p> <p>The association between CVD and incident GI disease was observed primarily among women.</p>
<p>How might this study influence clinical practice?</p>
<p>These findings highlight the clinical relevance of the gut–heart axis and underscore the need for integrated, system-level approaches to the prevention and long-term management of gastrointestinal, cardiovascular, and psychological health in aging populations.</p>

Introduction

Gastrointestinal (GI) diseases and cardiovascular disease (CVD) constitute two primary global health burdens, contributing substantially to escalating morbidity, mortality, and long-term healthcare utilization worldwide^[1–3]. CVD has emerged as an important cause of morbidity and mortality among patients with chronic digestive disorders, a relationship particularly evident in populations with inflammatory bowel disease (IBD)^[4–6]. Recent prospective evidence indicates that common GI diseases, including gastritis and peptic ulcer disease, are associated with an increased risk of incident CVD^[7, 8]. Several shared pathological mechanisms, including systemic inflammation, dyslipidemia, gut microbial dysbiosis, immune activation, and neuroendocrine dysregulation, may collectively promote endothelial dysfunction, atherosclerotic progression, and cardiac impairment^[9, 10]. Conversely, CVD may also contribute to the development or exacerbation of GI diseases through impaired splanchnic perfusion, intestinal ischemia, venous congestion, neurohormonal activation, and adverse gastrointestinal effects of long-term cardiovascular medications^[11, 12]. Accumulating evidence supports a complex bidirectional interplay between the gastrointestinal system and the cardiovascular system, mediated through inflammatory, metabolic, neuroendocrine, and hemodynamic pathways—a concept increasingly recognized as the gut–heart axis^[13–15]. Such interactions may be particularly important in middle-aged and older adults, among whom multimorbidity and declining organ functional reserve are highly prevalent^[16].

Despite growing mechanistic insights into the gut–heart axis, high-quality population-based longitudinal evidence remains limited. Previous studies have primarily focused on the impact of GI disease on

cardiovascular outcomes^[5, 7], whereas the reciprocal influence of CVD on GI health has received comparatively less attention. In addition, many existing studies have relied on cross-sectional designs or selected clinical populations, limiting the ability to establish temporal relationships and reducing generalizability to the broader population. Importantly, GI diseases are highly heterogeneous, and evidence regarding common non-malignant GI conditions, such as gastritis and peptic ulcer disease, remains insufficient compared with the relatively well-studied inflammatory bowel disease. Therefore, high-quality longitudinal studies systematically evaluating the bidirectional association between GI disease and CVD in the general middle-aged and older population are still lacking.

Among the potential mechanisms linking GI disease and CVD, depressive symptoms may represent an important yet underexplored pathway. Depressive symptoms are highly prevalent in individuals with GI disorders and have also been recognized as an independent risk factor for CVD, with evidence suggesting bidirectional relationships between depression and both conditions^[17–19]. Mechanistically, depressive symptoms may dysregulate the hypothalamic–pituitary–adrenal (HPA) axis and induce chronic low-grade inflammation, which can influence gastrointestinal motility, visceral sensitivity, vascular function, and cardiovascular regulation^[20, 21]. They may also modulate neurotransmitter signaling, including serotonin, contributing to gut–brain interactions^[22, 23]. Thus, psychological mechanisms may constitute an important yet underappreciated component of the gut–heart axis. To our knowledge, no large-scale prospective cohort study has yet examined whether depressive symptoms mediate the bidirectional association between GI disease and CVD in a general population.

To address these gaps, we used longitudinal data from the nationally representative China Health and Retirement Longitudinal Study (CHARLS) from 2011 to 2020 to investigate the bidirectional temporal association between GI disease and CVD. We further examined whether depressive symptoms mediated these associations. We further explored the potential mediating roles of depressive symptoms and C-reactive protein–glucose–triglyceride index (CTI) in this relationship. This design enabled an examination of the dynamic interplay between GI disease and CVD over time and aims to provide population-based evidence to inform the integrated management of these common chronic conditions in an aging population.

Methods

Study population

Data for this cohort study were derived from five waves of the China Health and Retirement Longitudinal Study (CHARLS) conducted between 2011 and 2020. CHARLS targets Chinese residents aged 45 years and older, with the primary objective of investigating population aging and monitoring longitudinal changes in health status among middle-aged and older adults^[24]. The present analysis employed de-identified, publicly available CHARLS data, which had received prior ethical approval from the Biomedical Ethics Review Committee of Peking University (IRB00001052–11015), and all participants provided

written informed consent. The present analysis utilized de-identified, publicly available CHARLS data. Detailed information about the CHARLS study is available <https://charls.pku.edu.cn/index.htm>.

Participants were excluded from the 2011 baseline wave if they were aged < 45 years, had a history of cancer, or had missing or non-positive follow-up time (≤ 0 years), yielding 16,323 eligible participants. For the analysis of GI disease with incident CVD, participants with prevalent CVD at baseline or missing incident CVD status were further excluded, resulting in 13,730 participants. For the analysis of CVD with incident GI disease, participants with prevalent GI disease at baseline or missing incident GI status were excluded, resulting in 12,450 participants. Sample selection is illustrated in Supplementary Figure S1.

Assessment of GI disease and CVD

Consistent with previous studies^[25, 26], GI disease and CVD diagnoses were determined based on doctor-confirmed self-reported medical histories recorded during survey interviews. Specifically, incident GI disease was ascertained using the question: “Have you been diagnosed with stomach or other digestive disease (excluding tumors and cancers) by a doctor?” Incident CVD was ascertained using the question: “Has a doctor ever told you that you have had a heart attack, angina, coronary heart disease, heart failure, other heart problems, or a stroke?” To reduce potential recall bias, participants were additionally asked, “Are you currently receiving any treatment (e.g., traditional Chinese medicine, Western medicine, or other therapies) for GI disease or CVD or their complications?” GI disease and CVD status were subsequently classified as “yes” or “no” based on self-reported diagnosis.

Assessment of depressive symptoms

Depressive symptoms were evaluated using the 10-item short form of the Center for Epidemiologic Studies Depression Scale (CESD-10) administered in the 2011 wave^[27]. This scale is a commonly used self-reported tool for assessing depression in general populations. Each item is scored on a 4-point scale from 0 (rarely or none of the time) to 3 (most or all of the time), yielding a total score ranging from 0 to 30. A total score of 10 or higher was used to define clinically significant depressive symptoms in descriptive and subgroup analyses. For mediation analyses, the CESD-10 total score was treated as a continuous variable.

Covariates

Covariates included in this study encompassed age, sex, place of residence (urban or rural), educational attainment (Less than high school versus high school or above), marital status (married versus other), body mass index (BMI), smoking status (never/ever), drinking status (never/ever), C-reactive protein (CRP), uric acid (UA), triglycerides (TG), fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and glycated hemoglobin (HbA1c). The CTI was defined as $0.412 \times \ln [\text{CRP (mg/L)}] + \ln [\text{TG (mg/dL)} \times \text{FPG (mg/dL)} / 2]$ ^[28]. Hypertension was

defined as self-reported diagnosis, use of antihypertensive medication, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg. Diabetes was defined as self-reported diagnosis, use of antidiabetic medication, fasting plasma glucose > 126 mg/dL (in confirmed fasting participants), or glycosylated haemoglobin A1c (HbA1c) $\geq 6.5\%$ ^[26].

Statistical analysis

Continuous variables were summarized as mean $\pm$ standard deviation (SD) or median [interquartile range, IQR] as appropriate based on distribution. Differences between groups were assessed using t-tests or Mann–Whitney U test as appropriate. Categorical variables were presented as frequencies (percentages) and evaluated using the chi-square test.

We examined whether death occurred prior to the outcome of interest to determine the need for competing-risk modeling. Because no deaths occurred before the onset of the outcome, no evidence suggested that death substantially competed with the outcome. Accordingly, multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the bidirectional associations between GI disease and CVD. Cumulative incidence of CVD and GI disease was estimated using the Kaplan–Meier method, and differences between groups were compared using the log-rank test.

Missing values in baseline covariates were assumed to be missing at random and were handled using multiple imputation by chained equations (MICE) with 20 imputed datasets, as recommended in prior longitudinal studies^[29]. Predictive mean matching was applied to continuous variables and logistic regression to binary variables. Three models were fitted: Model 1 unadjusted; Model 2 adjusted for age and sex; Model 3 additionally adjusted for residence, education, marital status, smoking, drinking, BMI, hypertension, and diabetes. No substantial violation of the proportional hazards assumption was observed based on Schoenfeld residual tests. Restricted cubic splines with three knots were used to flexibly model the potential non-linear effect of age (results shown in Supplementary Figure S2).

Subgroup analyses were performed stratified by sex, age, smoking, drinking, hypertension, diabetes, and depression status. Multiplicative interactions were tested by adding product terms to the fully adjusted Cox models.

Mediation analyses were conducted to examine whether CESD-10 and CTI served as mediators in the bidirectional associations between GI disease and CVD. Structural equation modeling with full information maximum likelihood (SEM-FIML) was used to handle missing data, adjusting for all covariates in Model 3. The original CESD-10 and CTI were standardized to make coefficients comparable. For each direction, we estimated the indirect effect (ACME), direct effect (ADE), total effect, and proportion mediated with 95% confidence intervals derived from robust standard errors. Statistical significance of mediation effects was determined based on whether the 95% confidence interval of the indirect effect excluded zero. Because a significant sex interaction was observed in the subgroup

analysis (the association of CVD with incident GI disease was significant only in women), we additionally performed an exploratory mediation analysis restricted to female participants, after removing sex from the covariate list.

To ensure the robustness of the results, a series of sensitivity analyses were conducted. Sensitivity analysis 1 was a complete-case analysis (excluding participants with missing data on any covariate or outcome). Sensitivity analysis 2 excluded participants who developed the outcome within the first 2 years of follow-up to reduce reverse causation. Sensitivity analysis 3 excluded obese participants ($\text{BMI} \geq 28 \text{ kg/m}^2$) to minimize the potential influence of undiagnosed metabolic dysfunction. Sensitivity analysis 4 additionally adjusted for CRP and UA. Sensitivity analysis 5 additionally adjusted for LDL-C and HDL-C. Sensitivity analysis 6 used a Fine-Gray subdistribution hazard model treating death as a competing event. E-values were calculated to quantify the robustness of the findings to potential unmeasured confounding (Supplementary Table S5).

All statistical analyses were performed using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of the cohorts are presented in Table 1 and Table 2. For the primary analysis assessing the association between GI disease and incident CVD, a total of 13,730 participants were included, with a mean (SD) age of 58.6 (9.4) years. For the primary analysis assessing the association between CVD and incident GI disease, 12,450 participants were included, with a mean (SD) age of 59.1 (9.5) years. Compared with participants without GI disease, those with GI disease were more likely to be women, reside in rural areas, have lower educational attainment, higher CESD-10 scores, and lower hypertension prevalence (all $P < 0.05$); they were also more likely to be ever drinkers (62.1% vs. 59.1%, $P = 0.005$). No significant differences were observed for age, smoking status, or diabetes prevalence (all $P > 0.05$). Participants with baseline CVD were more likely to be older (62.6 vs. 58.6), have hypertension (63.5% vs. 35.8%) and diabetes (21.8% vs. 10.9%), and have higher CESD-10 scores (9 vs. 6) than those without CVD. Additionally, they were less likely to be ever drinkers (36.2% vs. 40.9%, $P < 0.001$). They were also less likely to be ever smokers (38.0% vs. 40.9%, $P = 0.035$). Detailed distributions of inflammatory and metabolic biomarkers are provided in Supplementary Tables S1–S2. The proportions of missing data for baseline covariates are summarized in Supplementary Table S3.

Table 1
Baseline characteristics by GI disease status (participants without CVD at baseline, complete-case analysis)

Parameters	GI disease			<i>P</i>
	Overall	No	Yes	
(n = 13,730)	(n = 10,999)	(n = 2,731)		
Age, years	58.6 ± 9.4	58.6 ± 9.4	58.4 ± 9.1	0.669
Age group, n (%)				0.219
< 65	10340 (75.3%)	8258 (75.1%)	2082 (76.2%)	
≥ 65	3390 (24.7%)	2741 (24.9%)	649 (23.8%)	
Sex, n (%)				< 0.001
Female	6926 (50.4%)	5436 (49.4%)	1490 (54.6%)	
Male	6804 (49.6%)	5563 (50.6%)	1241 (45.4%)	
Residence, n (%)				< 0.001
Urban	5175 (37.7%)	4262 (38.7%)	913 (33.4%)	
Rural	8555 (62.3%)	6737 (61.3%)	1818 (66.6%)	
Education, n (%)				< 0.001
High school and above	4583 (33.5%)	3795 (34.6%)	788 (28.9%)	
Less than high school	9112 (66.5%)	7171 (65.4%)	1941 (71.1%)	
Marital status, n (%)				0.051
Unmarried	1632 (11.9%)	1337 (12.2%)	295 (10.8%)	
Married	12079 (88.1%)	9643 (87.8%)	2436 (89.2%)	
Smoking, n (%)				0.054
Never	8111 (59.5%)	6443 (59.1%)	1668 (61.1%)	
Ever	5520 (40.5%)	4460 (40.9%)	1060 (38.9%)	
Drinking, n (%)				0.005
Never	8134 (59.7%)	6442 (59.1%)	1692 (62.1%)	
Ever	5484 (40.3%)	4451 (40.9%)	1033 (37.9%)	
Data are presented as mean ± SD for normally distributed continuous variables, median [interquartile range] for skewed continuous variables, and n (%) for categorical variables. GI, gastrointestinal; CVD, cardiovascular disease; BMI, body mass index; SD, standard deviation; IQR, interquartile range.				

Parameters	GI disease			<i>P</i>
	Overall	No	Yes	
(n = 13,730)	(n = 10,999)	(n = 2,731)		
BMI (kg/m ²)	23.3 ± 3.5	23.4 ± 3.6	22.7 ± 3.4	< 0.001
Hypertension, n (%)				< 0.001
No	8959 (65.3%)	7070 (64.3%)	1889 (69.2%)	
Yes	4771 (34.7%)	3929 (35.7%)	842 (30.8%)	
Diabetes, n (%)				0.279
No	12256 (89.3%)	9802 (89.1%)	2454 (89.9%)	
Yes	1474 (10.7%)	1197 (10.9%)	277 (10.1%)	
CESD-10 score	7 [3–12]	6 [3–11]	9 [5–14]	< 0.001
Data are presented as mean ± SD for normally distributed continuous variables, median [interquartile range] for skewed continuous variables, and n (%) for categorical variables. GI, gastrointestinal; CVD, cardiovascular disease; BMI, body mass index; SD, standard deviation; IQR, interquartile range.				

Table 2

Baseline characteristics by CVD status (participants without GI disease at baseline, complete-case analysis)

Parameters	CVD			P
	Overall	No	Yes	
(n = 12,450)	(n = 10,961)	(n = 1,489)		
Age, years	59.1 ± 9.5	58.6 ± 9.4	62.6 ± 9.5	< 0.001
Age group, n (%)				< 0.001
< 65	9126 (73.3%)	8233 (75.1%)	893 (60%)	
≥ 65	3324 (26.7%)	2728 (24.9%)	596 (40%)	
Sex, n (%)				< 0.001
Female	6224 (50%)	5419 (49.4%)	805 (54.1%)	
Male	6226 (50%)	5542 (50.6%)	684 (45.9%)	
Residence, n (%)				< 0.001
Urban	4993 (40.1%)	4239 (38.7%)	754 (50.6%)	
Rural	7457 (59.9%)	6722 (61.3%)	735 (49.4%)	
Education, n (%)				0.919
High school and above	4298 (34.6%)	3782 (34.6%)	516 (34.8%)	
Less than high school	8117 (65.4%)	7149 (65.4%)	968 (65.2%)	
Marital status, n (%)				< 0.001
others	1568 (12.6%)	1330 (12.2%)	238 (16%)	
Married	10866 (87.4%)	9615 (87.8%)	1251 (84%)	
Smoking, n (%)				0.035
Never	7352 (59.5%)	6430 (59.1%)	922 (62%)	
Ever	5013 (40.5%)	4448 (40.9%)	565 (38%)	
Drinking, n (%)				< 0.001
Never	7370 (59.7%)	6424 (59.1%)	946 (63.8%)	
Data are presented as mean ± SD for normally distributed continuous variables, median [interquartile range] for skewed continuous variables, and n (%) for categorical variables.				
GI, gastrointestinal; CVD, cardiovascular disease; BMI, body mass index; SD, standard deviation; IQR, interquartile range.				

Parameters	CVD			<i>P</i>
	Overall	No	Yes	
(n = 12,450)	(n = 10,961)	(n = 1,489)		
Ever	4981 (40.3%)	4444 (40.9%)	537 (36.2%)	
BMI (kg/m ²)	23.6 ± 3.7	23.4 ± 3.6	24.6 ± 4	< 0.001
Hypertension, n (%)				< 0.001
No	7584 (60.9%)	7040 (64.2%)	544 (36.5%)	
Yes	4866 (39.1%)	3921 (35.8%)	945 (63.5%)	
Diabetes, n (%)				< 0.001
No	10931 (87.8%)	9767 (89.1%)	1164 (78.2%)	
Yes	1519 (12.2%)	1194 (10.9%)	325 (21.8%)	
CESD-10 score	6 [3–11]	6 [3–11]	9 [4–14]	< 0.001
Data are presented as mean ± SD for normally distributed continuous variables, median [interquartile range] for skewed continuous variables, and n (%) for categorical variables.				
GI, gastrointestinal; CVD, cardiovascular disease; BMI, body mass index; SD, standard deviation; IQR, interquartile range.				

Bidirectional association between GI disease and CVD

During a median follow-up of up to 9 years, 3,206 participants developed incident CVD in the GI disease cohort, and 2,849 participants developed incident GI disease in the CVD cohort. Kaplan–Meier curves demonstrated that participants with baseline GI disease had a higher cumulative incidence of CVD compared with those without GI disease (Fig. 1A). Similarly, participants with baseline CVD exhibited a higher cumulative incidence of GI disease during follow-up (Fig. 1B).

In multivariable Cox proportional hazards models (Table 3), baseline GI disease was significantly associated with an increased risk of incident CVD. Compared with participants without GI disease, the fully adjusted HR for incident CVD was 1.44 (95% CI: 1.32–1.57, *P* < 0.001). Likewise, baseline CVD was independently associated with a higher risk of incident GI disease, with a fully adjusted HR of 1.46 (95% CI: 1.30–1.64, *P* < 0.001). The associations were consistent across the three models (Model 1 unadjusted, Model 2 adjusted for age and sex, and Model 3 fully adjusted) (Table 3, Fig. 2).

Table 3
Longitudinal bidirectional association of GI disease with CVD.

Variables	HR (95%CI)					
	Model 1	P	Model 2	P	Model 3	P
GI disease and new-onset CVD risk						
GI disease						
No	Reference		Reference		Reference	
Yes	1.33 (1.23–1.45)	< 0.001	1.33 (1.23–1.45)	< 0.001	1.44 (1.32–1.57)	< 0.001
CVD and new-onset GI disease risk						
CVD						
No	Reference		Reference		Reference	
Yes	1.37 (1.22–1.53)	< 0.001	1.34 (1.2–1.5)	< 0.001	1.46 (1.3–1.64)	< 0.001
Model 1 was unadjusted for covariates. Model 2 was adjusted for age and gender. Model 3: additionally adjusted for rural, education, marital status, smoking, drinking, BMI, hypertension, and diabetes. <i>P</i> -values from pooled analyses of 20 imputed datasets. HR, hazard risk; CI, confidence interval; GI,gastrointestinal; CVD, cardiovascular diseases.						

Subgroup analyses

As shown in Fig. 3, the association between GI disease and incident CVD was generally consistent across predefined subgroups. A significant interaction was observed for hypertension status (*P* for interaction = 0.0344), with a stronger association among participants without hypertension (HR: 1.55, 95% CI: 1.34–1.79) than among those with hypertension (HR: 1.23, 95% CI: 1.04–1.45). No other significant interactions were identified (all *P* for interaction > 0.05). For the association between CVD and incident GI disease (Fig. 6), a significant interaction by sex was observed (*P* for interaction = 0.0088). The association was significant among women (HR: 1.51, 95% CI: 1.25–1.81, *P* < 0.001) but not among men (HR: 1.00, 95% CI: 0.76–1.31, *P* = 0.995). A significant interaction was also observed for drinking status (*P* for interaction = 0.006), with a stronger association among ever drinkers (HR: 1.54, 95% CI: 1.12–2.10) than never drinkers (HR: 1.22, 95% CI: 0.99–1.52). No other significant interactions were detected (all *P* > 0.05).

Mediation analyses

As shown in Table 1, Table 2, and Supplementary Tables S1–S2, participants with GI disease had higher CESD-10 scores and slightly lower CTI levels compared with those without GI disease, whereas

participants with CVD had higher CESD-10 scores and slightly higher CTI levels compared with those without CVD. Based on these observations, we conducted structural equation modeling with full information maximum likelihood (SEM-FIML) to evaluate the potential mediating roles of CESD-10 and CTI in the bidirectional association between GI disease and CVD.

For the full cohort, CESD-10 partially mediated the association between GI disease and incident CVD (average causal mediation effect [ACME] = 0.013, 95% CI: 0.010–0.016, $P < 0.001$; proportion mediated 20.6%, 95% CI: 12.8%–28.5%) and also partially mediated the association between CVD and incident GI disease (ACME = 0.017, 95% CI: 0.013–0.021, $P < 0.001$; proportion mediated 26.4%, 95% CI: 14.9%–38.1%) (Fig. 5; Supplementary Table S4). In contrast, CTI did not significantly mediate either association, as the 95% confidence intervals of ACME included zero (Supplementary Table S5).

Because a significant sex interaction was observed for the association of CVD with incident GI disease, we performed an exploratory analysis restricted to women. In this subgroup, CESD-10 remained a significant partial mediator of the CVD→GI disease association (ACME = 0.024, 95% CI: 0.017–0.030, $P < 0.001$; proportion mediated 24.5%, 95% CI: 13.7%–35.2%) (Supplementary Figure S3).

Sensitivity analyses

The bidirectional associations between GI disease and CVD remained robust across multiple sensitivity analyses, including complete-case analysis, exclusion of early events and participants with obesity, additional adjustment for inflammatory and lipid biomarkers, competing-risk modeling, and E-value analysis (Table 4; Fig. 6; Supplementary Tables S6). Additional adjustment for CRP and UA or for LDL-C and HDL-C did not materially change the effect estimates, indicating that the observed associations were not substantially explained by inflammatory or lipid metabolic factors. Fine–Gray competing-risk models yielded results consistent with the primary Cox analyses. Furthermore, E-value analyses suggested that relatively strong unmeasured confounding would be required to fully attenuate the observed associations.

Table 4
Sensitivity analysis.

Variables	GI disease and new-onset CVD risk		CVD and new-onset GI disease risk	
	HR (95%CI)	P	HR (95%CI)	P
Sensitivity analysis 1				
GI disease			CVD	
No	Reference		No	Reference
Yes	1.403(1.26,1.57)	< 0.001	Yes	1.35(1.16,1.58) < 0.001
Sensitivity analysis 2				
GI disease			CVD	
No	Reference		No	Reference
Yes	1.346(1.19,1.52)	< 0.001	Yes	1.381(1.17,1.63) < 0.001
Sensitivity analysis 3				
GI disease			CVD	
No	Reference		No	Reference
Yes	1.473(1.31,1.66)	< 0.001	Yes	1.428(1.21,1.69) < 0.001
Sensitivity analysis 4				
GI disease			CVD	
No	Reference		No	Reference
Yes	1.396(1.25,1.56)	< 0.001	Yes	1.351(1.16,1.58) < 0.001
Sensitivity analysis 5				
Sensitivity analysis 1: Complete-case analysis (excluding participants with missing data for any covariate or outcome). Sensitivity analysis 2: Exclusion of participants who developed the outcome within the first 2 years of follow-up (to reduce reverse causation). Sensitivity analysis 3: Exclusion of obese participants (body mass index ≥ 28 kg/m ²). Sensitivity analysis 4: Additional adjustment for C-reactive protein (CRP) and uric acid (UA) in complete cases with non-missing values. Sensitivity analysis 5: Additional adjustment for low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol in complete cases with non-missing values. Sensitivity analysis 6: Competing risk analysis using Fine-Gray subdistribution hazard model, treating death as a competing event.				
HR, hazard ratio; CI, confidence interval; GI, gastrointestinal; CVD, cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; UA, uric acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein.				

Variables	GI disease and new-onset CVD risk		CVD and new-onset GI disease risk		
	HR (95%CI)	P		HR (95%CI)	P
Sensitivity analysis 1					
GI disease			CVD		
No	Reference		No	Reference	
Yes	1.412(1.26,1.58)	< 0.001	Yes	1.349(1.15,1.58)	< 0.001
Sensitivity analysis 6 (Competing risk)					
GI disease			CVD		
No	Reference		No	Reference	
Yes	1.40 (1.25–1.56)	< 0.001	Yes	1.35 (1.16–1.57)	< 0.001
Sensitivity analysis 1: Complete-case analysis (excluding participants with missing data for any covariate or outcome). Sensitivity analysis 2: Exclusion of participants who developed the outcome within the first 2 years of follow-up (to reduce reverse causation). Sensitivity analysis 3: Exclusion of obese participants (body mass index ≥ 28 kg/m²). Sensitivity analysis 4: Additional adjustment for C-reactive protein (CRP) and uric acid (UA) in complete cases with non-missing values. Sensitivity analysis 5: Additional adjustment for low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol in complete cases with non-missing values. Sensitivity analysis 6: Competing risk analysis using Fine-Gray subdistribution hazard model, treating death as a competing event.					
HR, hazard ratio; CI, confidence interval; GI, gastrointestinal; CVD, cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; UA, uric acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein.					

Discussion

In this nationally representative prospective cohort study of middle-aged and older Chinese adults, we observed a robust bidirectional association between GI disease and CVD over up to 9 years of follow-up. Individuals with baseline GI disease had a significantly increased risk of incident CVD, whereas those with baseline CVD were also at higher risk of subsequent GI disease, independent of multiple demographic, behavioral, and clinical factors. These associations remained consistent across subgroup and sensitivity analyses, supporting the robustness of the findings. In addition, mediation analyses indicated that depressive symptoms partially mediated both directions of the association, suggesting that psychological factors may represent an important shared pathway underlying the gut–heart axis.

Our findings extend previous epidemiological evidence by demonstrating a bidirectional temporal association between GI disease and CVD in a nationally representative middle-aged and older population. Previous longitudinal studies have primarily examined the association between GI disorders and subsequent cardiovascular outcomes^[7, 30, 31]. More recently, growing evidence from large-scale

prospective cohorts, including analyses from the UK Biobank, has suggested that the association between GI disease and CVD may be bidirectional^[32]. Our study corroborates these bidirectional associations and further extends them to a Chinese population by identifying depressive symptoms as a shared psychological pathway linking GI disease and CVD. In addition, our findings highlight the relevance of common, non-malignant GI conditions frequently encountered in aging adults and primary care settings, and suggest potential sex-specific differences in the association between CVD and subsequent GI disease.

The observed association between GI disease and incident CVD is biologically plausible and consistent with current understanding of the gut–heart axis^[33]. GI disease have been linked to alterations in gut microbiota composition, increased intestinal permeability, and chronic low-grade inflammation, which may collectively promote systemic inflammation, oxidative stress, endothelial dysfunction, and atherosclerotic progression^[34–36]. Gastrointestinal dysfunction may influence neuroendocrine and autonomic regulation through bidirectional communication between the gut and central nervous system, thereby contributing to adverse cardiovascular outcomes^[37, 38]. Importantly, these mechanisms are unlikely to be restricted to severe or highly specific gastrointestinal disease and may also operate in common GI diseases frequently encountered in the general population.

Conversely, the strong association between baseline CVD and subsequent GI disease highlights the often underrecognized impact of cardiovascular dysfunction on gastrointestinal health. Reduced cardiac output, impaired splanchnic perfusion, venous congestion, and neurohormonal activation may collectively contribute to intestinal ischemia, mucosal injury, and disruption of gut barrier integrity^[39, 40]. In addition, systemic inflammation and long-term cardiovascular medication exposure may further increase gastrointestinal vulnerability^[41, 42]. These mechanisms are consistent with emerging evidence that cardiovascular dysfunction can impair intestinal perfusion and barrier integrity^[43], leading to subclinical intestinal injury that may precede overt gastrointestinal manifestations and remain clinically underrecognized for prolonged periods.

Our mediation analyses further suggest that depressive symptoms may represent a partially shared pathway linking GI disease and CVD. Depressive symptoms partially mediated both the association of GI disease with incident CVD and the association of CVD with subsequent GI disease. The proportion mediated was higher for the association of CVD with incident GI disease than for the reverse association, suggesting that psychological distress may play a relatively larger role in cardiovascular-related gastrointestinal vulnerability. Individuals with CVD frequently experience chronic symptom burden, neurohormonal dysregulation, and impaired quality of life, which may contribute to depressive symptoms and subsequently affect gastrointestinal function through alterations in gut–brain signaling and visceral sensitivity^[44–46]. Conversely, although GI disease may also contribute to depressive symptoms^[47], its cardiovascular consequences are likely driven by multiple biological pathways beyond psychological factors alone^[48].

In contrast, CTI did not significantly mediate either association. Although CTI has been proposed as a composite biomarker reflecting systemic inflammation and insulin resistance^[49], our findings suggest that metabolic-inflammatory dysregulation alone may not fully explain the bidirectional gut–heart relationship in this population. Notably, participants with GI disease had slightly lower baseline CTI levels than those without GI disease (as shown in Supplementary Tables S1), which may partly account for the absence of a significant positive mediation effect for the association of GI disease with incident CVD. By contrast, the consistent partial mediation observed for depressive symptoms supports the potential involvement of psychological and neurohormonal pathways. Nevertheless, the mediation effects were only partial, indicating that additional biological, behavioural, and psychosocial mechanisms are likely involved.

Given the significant sex interaction in the association between CVD and incident GI disease, we further conducted an exploratory mediation analysis in women. Depressive symptoms remained a significant partial mediator in female participants, suggesting that psychological distress may play a particularly important role in the pathway linking CVD to subsequent GI disease among women. This finding is consistent with previous evidence indicating that women are more susceptible to depressive symptoms and disorders involving gut-brain interactions^[50]. Sex-related differences in hormonal regulation, autonomic function, and stress responsiveness may further contribute to increased gastrointestinal susceptibility in women^[51]. Nevertheless, these subgroup findings should be interpreted cautiously given the exploratory nature of the analyses.

From a clinical and public health perspective, these findings highlight the need for greater awareness of the bidirectional relationship between GI disease and CVD in middle-aged and older adults. Individuals with GI disease may warrant closer attention to cardiovascular risk, whereas patients with established CVD may benefit from increased vigilance regarding gastrointestinal health, particularly among women. The observed mediation effect of depressive symptoms further supports the importance of integrating psychological assessment into the management of patients with coexisting gastrointestinal and cardiovascular conditions. Collectively, these findings support a more integrated and multidisciplinary approach to gastrointestinal, cardiovascular, and psychological health in aging populations, rather than traditional organ-specific disease models.

Using a large nationally representative cohort with repeated follow-up enabled the assessment of bidirectional temporal associations between GI disease and CVD in middle-aged and older adults. Furthermore, the integration of mediation analyses provided additional insight into potential psychological and metabolic-inflammatory pathways underlying the gut–heart association, thereby extending current understanding beyond conventional organ-specific or inflammation-focused models. Nevertheless, several limitations should be considered when interpreting these findings. First, GI disease and CVD were identified based on self-reported physician diagnoses without medical record verification, which may have introduced recall bias and disease misclassification, particularly for asymptomatic or subclinical conditions. Second, both GI disease and CVD were analyzed as heterogeneous entities without stratification by specific etiologies, disease severity, or clinical subtypes,

limiting mechanistic specificity of the observed associations. Different GI and cardiovascular conditions may involve distinct biological pathways and risk profiles. Third, although extensive covariates were adjusted for, residual confounding from unmeasured factors, including dietary habits, medication use, and physical activity, cannot be completely excluded. Fourth, depressive symptoms and CTI were assessed only at baseline and therefore may not capture temporal variability or dynamic changes over follow-up. Future studies incorporating repeated assessments and time-varying mediation analyses may help further clarify the dynamic mechanisms underlying gut–heart interactions. Fifth, owing to the observational design, causal relationships and mediation effects should be interpreted cautiously. Finally, as the study population consisted predominantly of middle-aged and older Chinese adults, the generalizability of these findings to other ethnic and cultural populations requires further validation.

Conclusions

In this prospective, nationally representative cohort of middle-aged and older Chinese adults, GI disease and CVD were bidirectionally associated. Depressive symptoms partially mediated both associations, whereas CTI did not significantly mediate either pathway. The association between CVD and incident GI disease was observed primarily among women, suggesting potential sex-related heterogeneity. Collectively, these findings support the concept of a bidirectional gut–heart axis and highlight the importance of psychological pathways in linking gastrointestinal and cardiovascular health.

Abbreviations

ACME

Average causal mediation effect

ADE

Average direct effect

BMI

Body mass index

CHARLS

China Health and Retirement Longitudinal Study

CESD-10

10-item Center for Epidemiologic Studies Depression Scale

CI

Confidence interval

CRP

C-reactive protein

CTI

C-reactive protein–glucose–triglyceride index

CVD

Cardiovascular disease

FPG

Fasting plasma glucose
GI
Gastrointestinal
HbA1c
Glycated hemoglobin
HDL-C
High-density lipoprotein cholesterol
HR
Hazard ratio
LDL-C
Low-density lipoprotein cholesterol
MICE
Multiple imputation by chained equations
SHR
Subhazard ratio
TyG
Triglyceride-glucose
UA
Uric acid

Declarations

Ethics approval and consent to participate

The CHARLS study protocol was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052–11015). All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

RZ conceptualized and designed the study, performed the statistical analyses, and drafted the original manuscript. LY and QJ contributed to data curation, literature review, and methodology validation. LXJ and LX assisted with data interpretation and prepared the tables and figures. ZG supervised the project and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript for submission.

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Data Availability

The datasets supporting the conclusions of this study are publicly available from the China Health and Retirement Longitudinal Study (CHARLS) repository at <https://charls.pku.edu.cn/>.

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Figures

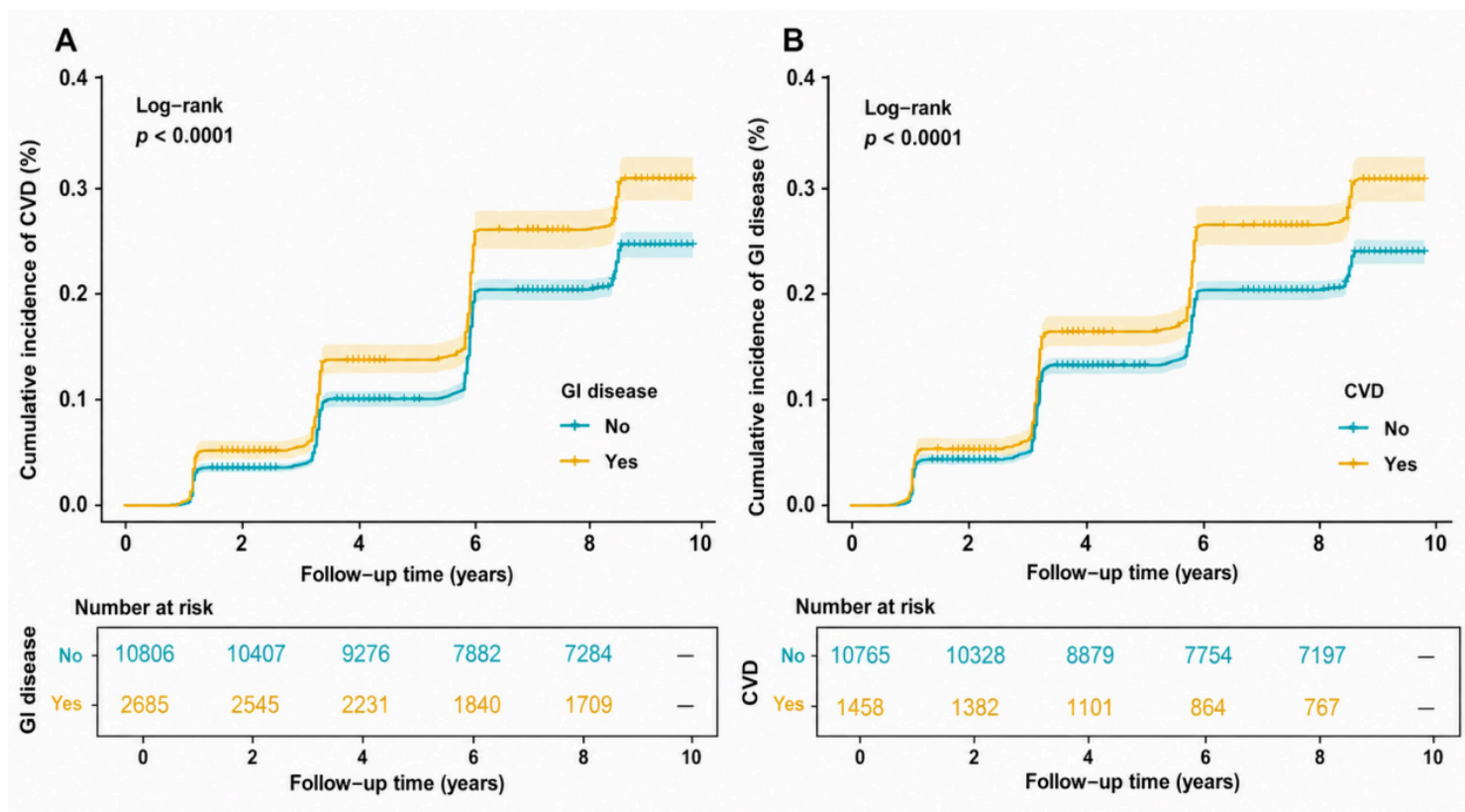


Figure 1

Kaplan–Meier curves for the bidirectional associations between GI disease and CVD. (A) Cumulative incidence of CVD according to baseline GI disease status. (B) Cumulative incidence of GI disease according to baseline CVD status. Shaded areas represent 95% confidence intervals. GI, gastrointestinal; CVD, cardiovascular diseases.

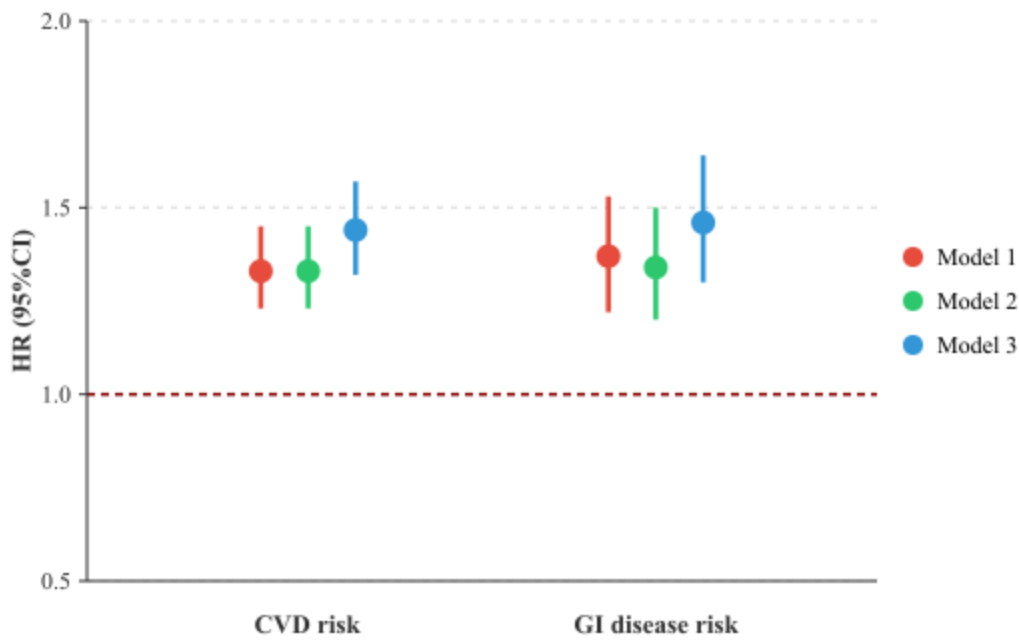


Figure 2

Longitudinal bidirectional association of GI disease with CVD in different models. HR, hazard risk; CI, confidence interval; GI, gastrointestinal; CVD, cardiovascular diseases.

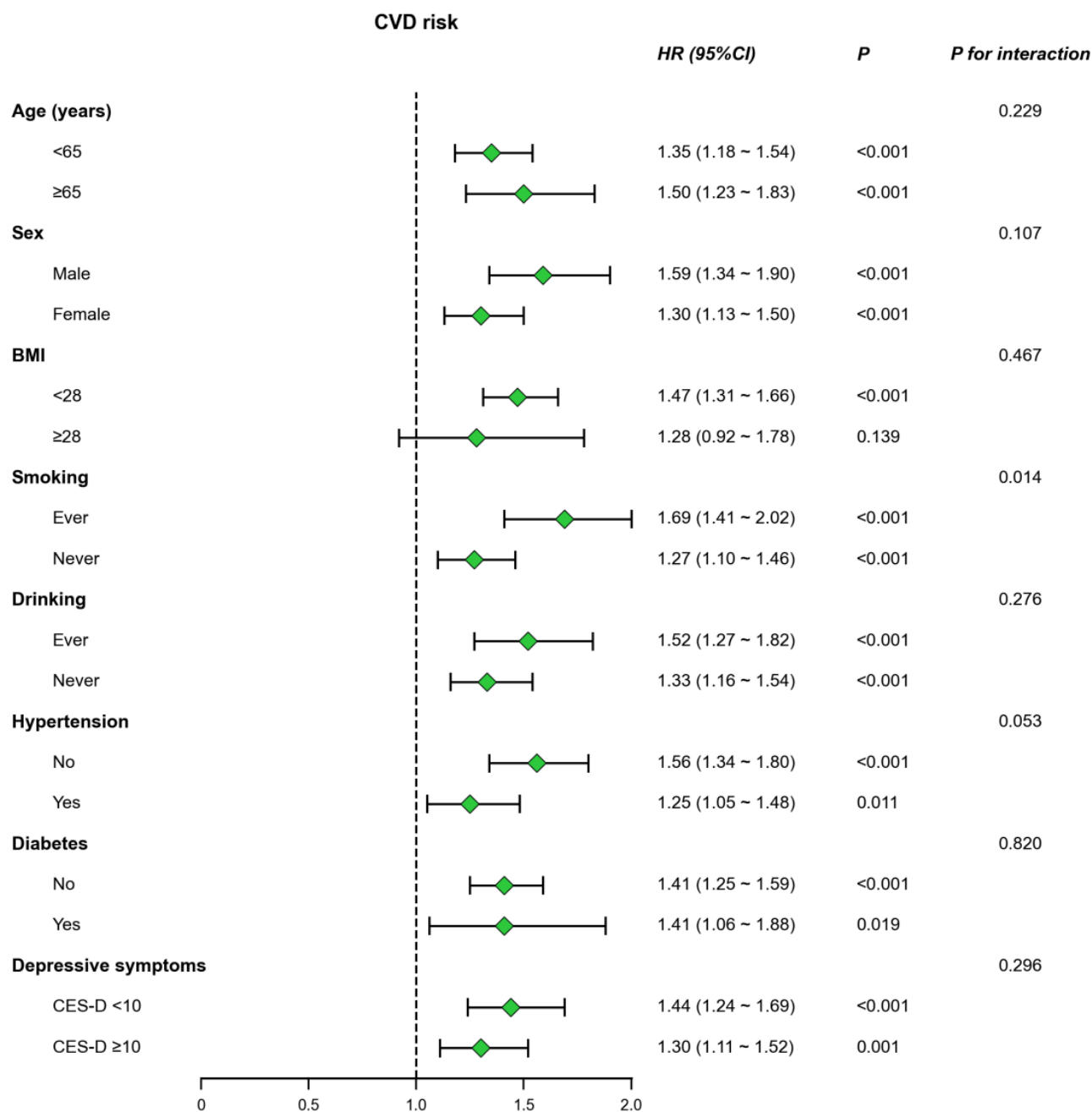


Figure 3

Subgroup analysis for the association between GI disease and new-onset CVD. HR, hazard risk; CI, confidence interval; GI,gastrointestinal; CVD, cardiovascular diseases.

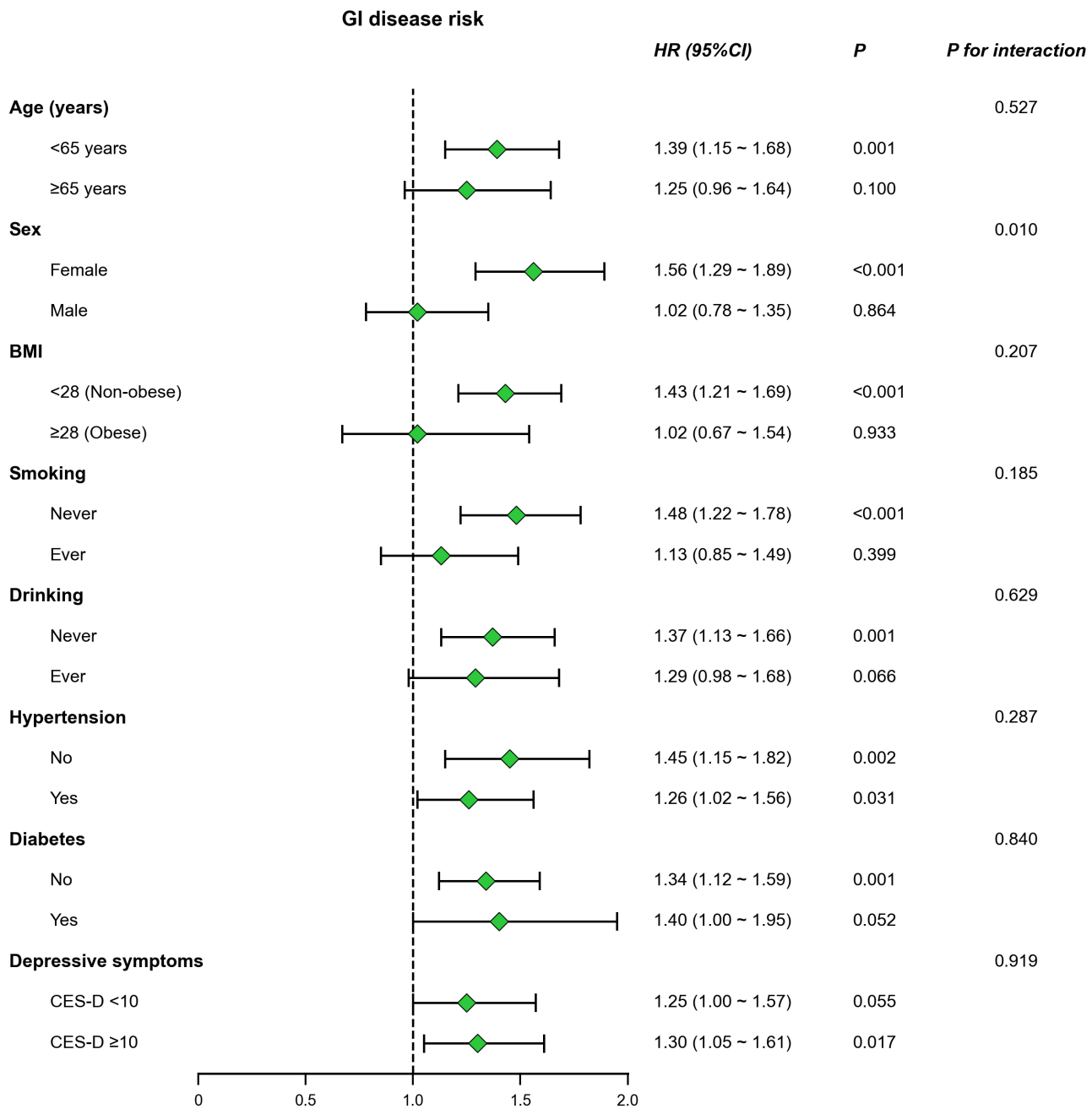


Figure 4

Subgroup analysis for the association between CVD and new-onset GI disease. HR, hazard risk; CI, confidence interval; GI,gastrointestinal; CVD, cardiovascular diseases.

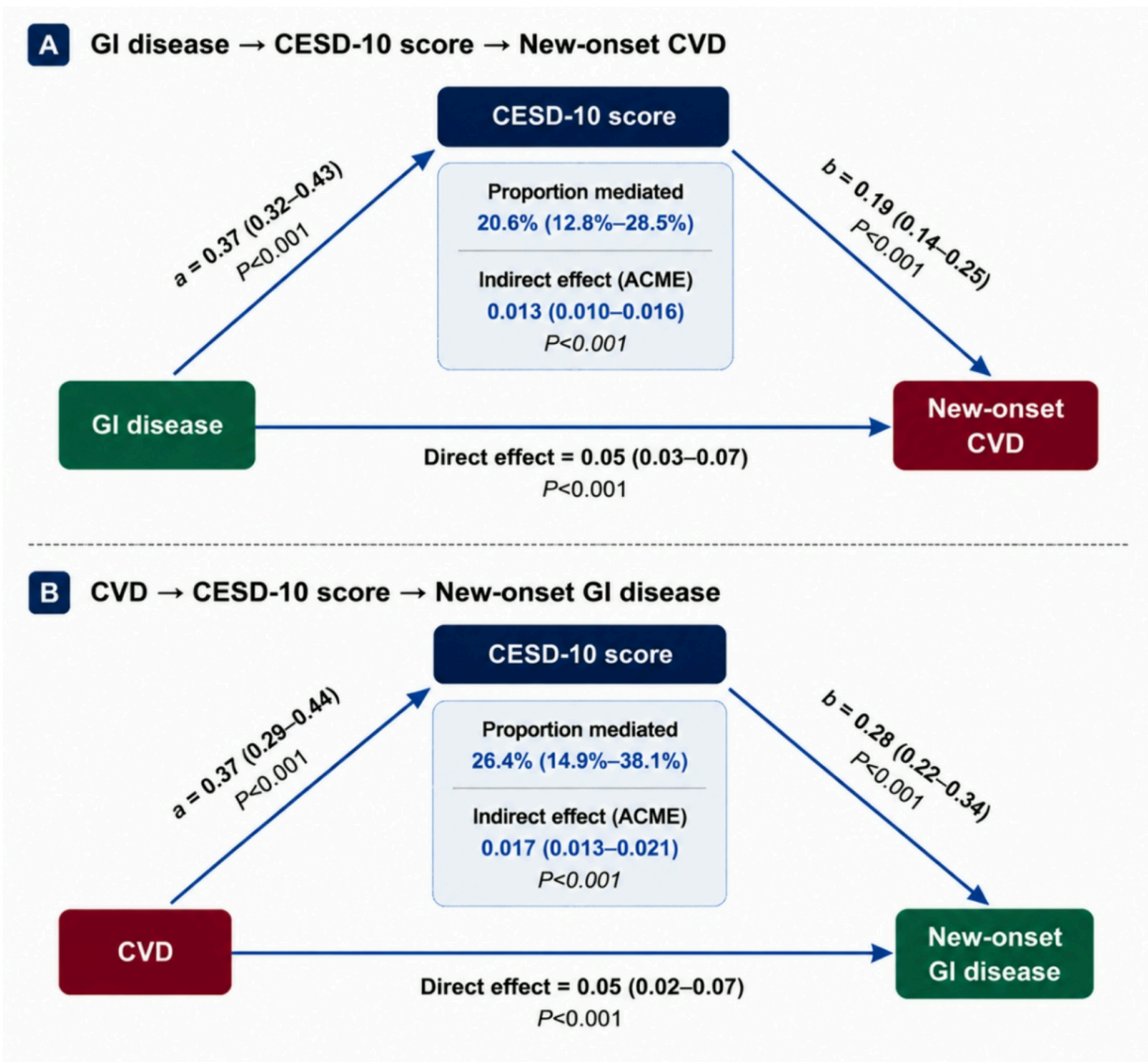


Figure 5

Mediation analysis of CESD-10 in the bidirectional GI–CVD association.

Effect estimates (95% CI) were obtained from SEM with FIML, adjusted for all covariates in Model 3. Both indirect effects were significant (95% CI did not include zero). GI, gastrointestinal disease; CVD, cardiovascular disease; CESD-10, 10-item Center for Epidemiologic Studies Depression Scale; ACME, average causal mediation effect.

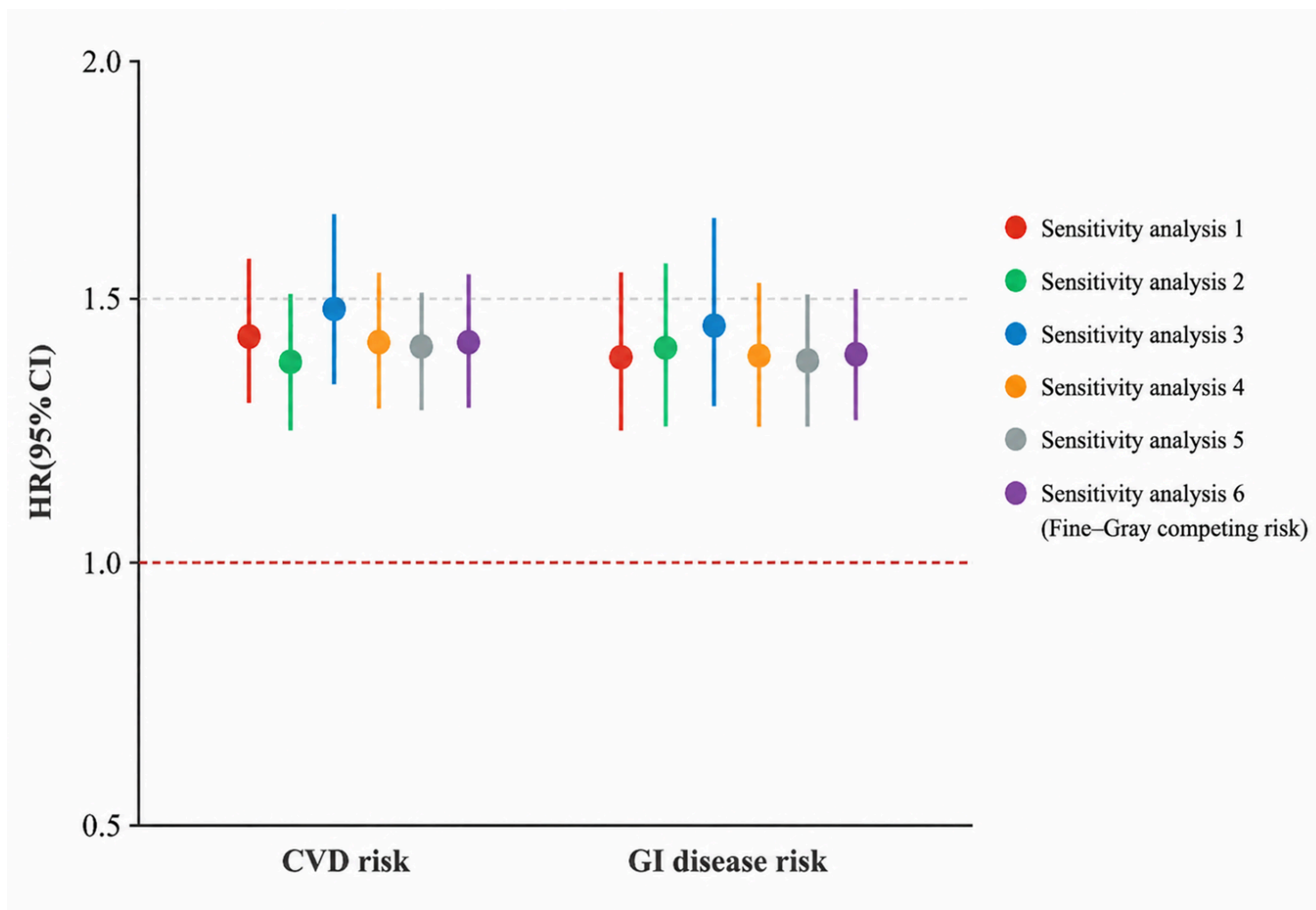


Figure 6

Longitudinal bidirectional association of GI disease with CVD in different

sensitivity analyses. HR, hazard risk; CI, confidence interval; GI,gastrointestinal; CVD, cardiovascular diseases.

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