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Association between C-reactive protein-triglyceride-glucose index and the progress of frailty: two nationwide prospective cohort studies

Zhenyu Liu
liuzhenyu200210@163.com
Ruijin Hospital https://orcid.org/0009-0007-0565-0781
Zhi-Ran Yue
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Fangjun Xu
Rui-Yan Zhang
Ruijin Hospital

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Abstract

Introduction: Frailty, a global health burden, is driven by chronic inflammation and metabolic dysfunction. The C-reactive protein-triglyceride-glucose index (CTI) is a novel composite marker reflecting both burdens. However, its longitudinal impact on frailty progression remains unknown.

Methods: Data from two nationwide prospective cohorts, CHARLS (China) and ELSA (UK), were utilized. Frailty was measured via a cumulative deficit frailty index (FI). Multivariable Cox models and linear mixed-effects models (LMM) examined risks of incident frailty and rates of FI progression, respectively. Restricted cubic splines (RCS) explored dose-response relationships.

Results: A total of 6,524 participants from CHARLS and 3,026 from ELSA were included. Cox regression showed the highest CTI tertile (T3) significantly increased incident frailty risk compared to the lowest (T1) (CHARLS: HR=1.16, 95% CI 1.02–1.31; ELSA: HR=1.27, 95% CI 1.06–1.51). LMM analyses revealed T3 was associated with faster FI progression (CHARLS: β= 0.281, 95% CI 0.150–0.413; ELSA: β= 0.319, 95% CI 0.233–0.405). RCS analyses visualized linear positive dose-response relationships for both incidence and progression. Subgroup analyses demonstrated that the association between elevated CTI and accelerated FI progression was generally robust across most strata, including age, obesity, and diabetes status.

Conclusions: The CTI serves as a robust and independent predictor of both incident frailty and accelerated frailty progression in older adults. Our findings suggest that the composite burden of metabolic and inflammatory dysregulation is a fundamental driver of physiological decline. Monitoring the CTI may offer a valuable strategy for early risk identification and targeted intervention.

Introduction

Frailty is an increasing global health burden [1], with major implications, especially for cardiometabolic disorders [2]. Against the backdrop of global aging and the increasing prevalence of chronic diseases, the incidence of frailty is expected to increase significantly [3]. Importantly, frailty is multidimensional and consists of physiological, psychological, and social factors [4–6]. The frailty index (FI), developed by Rockwood *et al*. [7], operationalizes this syndrome as a cumulative measure of multidimensional health deterioration, which is distinct from specific phenotypic definitions. Moreover, frailty is inherently dynamic, which means that individuals potentially revert between non-frail and frail states [8]. Therefore, we can identify interventions and key impact indicators to reverse or slow frailty. This dynamic nature implies that we can find interventions and key impact indicators to reverse or slow the progression of frailty.

Elucidating the pathophysiological underpinnings of frailty is essential for identifying such predictive biomarkers. Accumulating evidence implicates chronic low-grade inflammation and insulin resistance (IR) as pivotal mechanisms underpinning the pathogenesis of frailty [9–11]. The convergence of 'inflammaging' and metabolic dysfunction exerts a synergistic deleterious effect, precipitating oxidative stress, endothelial dysfunction, and systemic physiological dysregulation [12]. While C-reactive protein (CRP) and the triglyceride-glucose (TyG) index serve as established surrogate markers for systemic inflammation and IR, respectively, the novel C-reactive protein-triglyceride-glucose index (CTI) combines these domains into a unified composite metric. By reflecting the concomitant burden of metabolic and inflammatory derangements, the CTI has the potential to become a more sensitive indicator for capturing the subclinical physiological dysregulation driving clinical decline.

Current epidemiological evidence concerning CTI has been confined predominantly to its prognostic utility for all-cause mortality and cardiovascular disease (CVD) incidence [13–15]. However, its relationship with the dynamic evolution of frailty remains uninvestigated. To address this gap, the present study utilized data from two large-scale, nationwide prospective cohort studies: the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Aging (ELSA). We aimed to elucidate the associations between the CTI and the dynamic trajectories of frailty. Specifically, we hypothesized that elevated CTI levels accelerate the progression of frailty, whereas lower CTI levels are associated with the mitigation of decline or a greater likelihood of reversal to a robust state.

Methods

Study Design and Population

This study utilized data drawn from two large-scale, nationwide prospective cohort studies: the CHARLS [16] and the ELSA [17]. Detailed descriptions of the sampling methods and study designs for both cohorts are provided in the Supplementary Methods. For the CHARLS analysis, data from Wave 1 (2011) through Wave 4 (2018) were included, with Wave 1 serving as the baseline assessment. In the ELSA cohort, data from Wave 2 (2004) to Wave 10 (2022) were utilized, with Wave 2 designated the baseline. Ethical approval was granted by the Institutional Review Board of Peking University for CHARLS and the London Multi-Centre Research Ethics Committee for ELSA. Informed

written consent was obtained from all participants prior to enrollment. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [18].

The participant selection process is illustrated in Fig. 1. Initially, 17,261 participants aged ≥ 45 years from the CHARLS and 12,207 from the ELSA were screened. Eligibility criteria required complete data on both the exposure and outcome variables at baseline. Consequently, participants were sequentially excluded if they had missing data on the FI or the CTI. This resulted in 7,787 individuals in the CHARLS and 3,358 in the ELSA being included in the baseline analyses. For the longitudinal frailty progression analyses, we further excluded participants who lacked reassessment of the FI during the follow-up period, yielding final analytical samples of 6,524 participants in the CHARLS and 3,026 participants in the ELSA.

Variables and Data Measurement

Exposure: The CTI was calculated as a composite marker combining systemic inflammation and metabolic status. On the basis of fasting plasma glucose (FPG), triglyceride (TG), and CRP levels, the CTI was determined using the following formula: $CTI = 0.412 \times \lg(CRP[mg/L]) + \lg[(TG\ [mg/dL] \times FPG\ [mg/dL])/2]$. To examine dose–response relationships, participants were categorized into tertiles (T1–T3) on the basis of the distribution of the CTI. In the CHARLS cohort, the cutoff values were defined as T1 ≤ 8.40, 8.40 < T2 < 9.08, and T3 ≥ 9.08. In the ELSA cohort, the cutoff values were T1 ≤ 8.54, 8.54 < T2 < 9.25, and T3 ≥ 9.25.

Outcome: Frailty was operationalized via a cumulative deficit model, which was constructed as an FI following standard procedures. The FI comprises 31 health deficits available in both cohorts, covering chronic comorbidities, sensory impairments, self-rated general health, functional limitations, mobility difficulties, depression, and cognitive function (**Supplemental Table 1**). Items 1–28 were coded as binary variables, where a score of 1 was assigned to the presence of a deficit (such as a self-reported diagnosis of a condition or difficulty performing a task) and 0 indicated its absence. For self-reported general health, a response of "poor" or "fair" was coded as a deficit. Depressive symptoms were evaluated using the Center for Epidemiologic Studies Depression Scale (CES-D), with a deficit defined as a total score > 10 on the CESD-10 in the CHARLS or ≥ 4 on the CESD-8 in the ELSA. Cognitive function was assessed based on memory and orientation tests, which were treated as continuous variables ranging from 0 to 1, with higher values indicating worse cognitive performance. The FI score for each participant was calculated as the unweighted sum of deficits divided by the total number of items considered, multiplied by 100 to yield a score between 0 and 100. We permitted a missing data rate of up to 10% for FI items; in such cases, the denominator was adjusted to the number of non-missing items to calculate the score [19]. Consistent with previous studies, frailty was defined as an FI ≥ 25. The FI was assessed at baseline and at each follow-up wave to monitor frailty progression.

Covariates: To control for potential confounding factors, a comprehensive set of covariates was harmonized between the CHARLS and ELSA cohorts. The selection of these covariates was based on their statistical significance in the univariate linear regression (**Supplemental Table 2**) and univariate Cox regression analyses (**Supplemental Table 3**). Consequently, the fully adjusted models included sociodemographic characteristics, lifestyle behaviors, and clinical parameters. Sociodemographic variables consisted of age, sex, education (below high school, high school, and college or above), and marital status, which was dichotomized into married or partnered vs other statuses (separated, divorced, never married, or widowed). Lifestyle factors included smoking status and drinking status, defined as current versus noncurrent, and physical activity levels classified as inactive, light, moderate, and vigorous. Anthropometric and clinical parameters included body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Statistical analysis

The descriptive characteristics of the study population were stratified by CTI tertiles. Continuous variables are expressed as the means (standard deviations [SDs]) and were compared using one-way analysis of variance, while categorical variables were presented as frequencies (percentages) and compared using the chi-square test. To examine the cross-sectional association between the CTI and baseline frailty, multivariable linear regression models were constructed. For the longitudinal analysis of the risk of incident frailty, multivariable Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals. To further explore the shape of the dose–response relationships and test for potential nonlinearity, restricted cubic spline (RCS) functions were integrated into both the multivariable linear regression models (for baseline FI) and the Cox proportional hazards models (for incident frailty). We specified 5 knots located at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the CTI distribution. Tests for nonlinearity were conducted by examining the statistical significance of the nonlinear coefficients using the Wald test.

To analyze the longitudinal trajectories of the FI over the follow-up period, linear mixed-effects models were employed. In these models, the outcome variable comprised all available repeated measurements of the FI, including the baseline assessment. The time metric was

defined as the actual duration from baseline to each specific FI measurement point. The regression coefficients for the CTI represented the average change in the FI over the follow-up period associated with either a one-unit increase in the continuous CTI score or relative to the lowest tertile (T1). To account for interindividual heterogeneity, both random intercepts and random slopes were included to model variations in baseline frailty levels and rates of progression, respectively. The covariance structure for the random effects was modeled using Cholesky factorization.

Missing data for covariates, with rates detailed in **Supplemental Table 4**, were addressed using multiple imputation by chained equations. For the purpose of analysis, diabetes was defined as a self-reported physician diagnosis, the use of any glucose-lowering medication, an FBG level ≥ 7.0 mmol/L, or a glycated hemoglobin (HbA1c) level ≥ 6.5% at baseline. Furthermore, subgroup analyses were conducted and visualized using forest plots to explore potential effect modifiers. These analyses were stratified by sex (male vs female), age (< 65 vs ≥ 65 years), obesity status (non-obese vs obese, defined as BMI ≥ 28 kg/m^2), baseline frailty status (non-frail vs frail, defined as baseline FI ≥ 25), and diabetes status (non-diabetic vs diabetic). All the statistical analyses were two-sided, and statistical significance was defined as $P < 0.05$.

Sensitivity analysis

To evaluate the robustness of our results, several sensitivity analyses were performed. First, we utilized a modified 30-item FI, derived by removing the diabetes item from the original 31-item scale, to circumvent potential collinearity and mathematical circularity caused by the overlap between the CTI and diabetes status. Second, to minimize the potential for reverse causality, we conducted a lag analysis by excluding frailty events and FI assessments that occurred within the first two years of the follow-up period.

Results

Baseline characteristics

The baseline characteristics of the study participants, stratified by CTI tertiles, are presented in Table 1. The final analytical sample comprised 6,524 participants from the CHARLS cohort and 3,026 from the ELSA cohort. In the CHARLS cohort, participants in the highest CTI tertile (T3) compared with those in the lowest tertile (T1) were significantly older and comprised a lower proportion of males. Significant differences were observed in educational attainment, drinking status, and physical activity levels across the groups. Metabolically, participants at T3 presented a worse clinical profile, characterized by a higher BMI, elevated levels of LDL-C and HbA1c, an increased incidence of diabetes, and lower HDL-C concentrations. Furthermore, baseline health status deteriorated markedly with increasing CTI levels, as evidenced by significantly higher FI scores and a greater prevalence of frailty in the T3 group than in the T1 group ($P < 0.001$). Similarly, in the ELSA cohort, elevated CTI were significantly associated with older age and higher BMI. Consistent with the findings in CHARLS, participants in the highest tertile demonstrated pronounced metabolic dysregulation, including higher LDL-C, HbA1c, and diabetes incidence, alongside lower HDL-C levels. Behavioral factors, including smoking status, drinking habits, and physical activity, differed significantly across CTI tertiles, with the T3 group showing higher rates of current smoking and physical inactivity. Mirroring the CHARLS results, a graded increase in both the FI and the prevalence of frailty was observed across ascending CTI tertiles ($P < 0.001$).

Table 1
Baseline characteristics of participants

Variables	CHARLS				ELSA			
	T1	T2	T3	P	T1	T2	T3	P
N	2175	2174	2175		1009	1008	1009	
Age, years	59.8 ± 9.5	60.8 ± 9.1	60.9 ± 9.2	< 0.001	62.6 ± 7.1	63.7 ± 7.3	64.3 ± 7.4	< 0.001
Male	912 (41.9)	844 (38.8)	791 (36.4)	< 0.001	440 (43.6)	462 (45.8)	487 (48.3)	0.110
Married or partnered	1900 (87.4)	1858 (85.5)	1874 (86.2)	0.185	779 (77.2)	754 (74.8)	747 (74)	0.226
Education				0.027				0.463
Below high school	2037 (93.7)	2031 (93.4)	2001 (92.0)		434 (43)	431 (42.8)	425 (42.1)	
High school	98 (4.5)	106 (4.9)	109 (5.0)		155 (15.4)	133 (13.2)	133 (13.2)	
College or above	40 (1.8)	37 (1.7)	65 (3.0)		420 (41.6)	444 (44)	451 (44.7)	
Current smokers	774 (35.6)	755 (34.7)	727 (33.4)	0.320	95 (9.4)	138 (13.7)	186 (18.4)	< 0.001
Current drinkers	670 (30.8)	589 (27.1)	544 (25.0)	< 0.001	835 (82.8)	799 (79.3)	758 (75.1)	< 0.001
Physical activity				< 0.001				< 0.001
Inactive	222 (10.2)	217 (10)	306 (14.1)		9 (0.9)	19 (1.9)	23 (2.3)	
Light	443 (20.4)	468 (21.5)	646 (29.7)		34 (3.4)	58 (5.8)	103 (10.2)	
Moderate	617 (28.4)	709 (32.6)	668 (30.7)		389 (38.6)	470 (46.6)	503 (49.9)	
Vigorous	893 (41.1)	780 (35.9)	555 (25.5)		577 (57.2)	461 (45.7)	380 (37.7)	
BMI, kg/m^2	22.4 ± 3.8	23.6 ± 4.0	25.2 ± 4.2	< 0.001	25.3 ± 3.4	28.0 ± 4.4	29.9 ± 4.9	< 0.001
HDL-C, mmol/L	1.5 ± 0.4	1.3 ± 0.4	1.1 ± 0.3	< 0.001	1.7 ± 0.4	1.5 ± 0.4	1.4 ± 0.3	< 0.001
LDL-C, mmol/L	2.9 ± 0.8	3.1 ± 0.9	3.0 ± 1.1	< 0.001	3.6 ± 0.9	3.8 ± 1.0	3.8 ± 1.0	< 0.001
HbA1c, %	5.1 ± 0.5	5.2 ± 0.5	5.6 ± 1.2	< 0.001	5.3 ± 0.3	5.4 ± 0.4	5.7 ± 0.7	< 0.001
Diabetes	151 (6.9)	281 (12.9)	778 (35.8)	< 0.001	16 (1.6)	29 (2.9)	110 (10.9)	< 0.001
FI	18.3 ± 9.3	19.2 ± 9.9	20.6 ± 11.3	< 0.001	6.5 ± 8.3	8.3 ± 8.9	11.2 ± 11.1	< 0.001
Frailty	417 (19.2)	507 (23.3)	602 (27.7)	< 0.001	41 (4.1)	70 (6.9)	127 (12.6)	< 0.001

T1 was the lowest tertile, T2 was the middle tertile, and T3 was the highest tertile. In the CHARLS, T1 of CTI ≤ 8.40, 8.40 < T2 < 9.08, T3 of CTI ≥ 9.08. In the ELSA, T1 of CTI ≤ 8.54, 8.54 < T2 < 9.25, T3 of CTI ≥ 9.25. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging; CTI, C-reactive protein-triglyceride-glucose index; T, tertile; N, Number; SD, standard deviation; FI, frailty index; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HbA1c, Hemoglobin A1c. Data presented as mean ± SD for continuous variables, and frequency (percentage) for categorical variables.

Association between CTI and FI in baseline

The associations of the CTI with the baseline FI are summarized in Table 2. Compared with T1, T3 had significantly greater FI (CHARLS: β = 2.14, 95% CI 1.47–2.80, P < 0.001; ELSA: β = 1.92, 95% CI 1.04–2.80, P < 0.001), followed by T2 (CHARLS: β = 0.87, 95% CI 0.28–1.55, P = 0.004; ELSA: β = 0.35, 95% CI -0.45–1.14, P = 0.395). The trend tests revealed increasing trends in baseline FI with increasing CTI in both cohorts (both P for trend < 0.001). Continuous CTI was also associated with baseline FI for a significant increase per 1-unit increase in CTI (CHARLS: β = 1.31, 95% CI 0.98–1.63, P < 0.001; ELSA: β = 1.16, 95% CI 0.67–1.65, P < 0.001). Furthermore, RCS analyses visually confirmed these associations, demonstrating a linear positive dose–response relationship between the CTI and baseline FI in both cohorts (Fig. 2). Subgroup analyses (Fig. 3) indicated that the positive association between the CTI and baseline FI was robust across subgroups stratified by sex, age, baseline frailty and obesity. However, a significant interaction was observed for diabetes status (CHARLS: *P* for interaction = 0.009; ELSA: *P* for interaction = 0.048). Specifically, the deleterious effect of elevated CTI on frailty was more significant in non-diabetic participants than in those with diabetes.

Table 2
Association between CTI and FI in baseline.

Variables	CHARLS					ELSA				
CTI Tertiles	Total	Univariate Model β (95% CI)	P	Fully-adjusted Model β (95% CI)	P	Total	Univariate Model β (95% CI)	P	Fully-adjusted Model β (95% CI)	P
T1	2175	[Reference]		[Reference]		1009	[Reference]		[Reference]	
T2	2174	0.86 (0.25 ~ 1.46)	0.005	0.87 (0.28 ~ 1.55)	0.004	1008	1.79 (0.96 ~ 2.62)	< 0.001	0.35 (-0.45 ~ 1.14)	0.395
T3	2175	2.26 (1.65 ~ 2.87)	< 0.001	2.14 (1.47 ~ 2.80)	< 0.001	1009	4.71 (3.88 ~ 5.54)	< 0.001	1.92 (1.04 ~ 2.80)	< 0.001
P for Trend			< 0.001		< 0.001			< 0.001		< 0.001
CTI per 1-unit	6524	1.24 (0.95 ~ 1.52)	< 0.001	1.31 (0.98 ~ 1.63)	< 0.001	3026	2.68 (2.24 ~ 3.13)	< 0.001	1.16 (0.67 ~ 1.65)	< 0.001

Multivariable linear regression models were performed to examine the cross-sectional association between CTI and baseline FI. Fully-adjusted Model: age, sex, education, marital status, smoking status, drinking status, physical activity, BMI, HDL-C, LDL-C. T1 was the lowest tertile, T2 was the middle tertile, and T3 was the highest tertile. In the CHARLS, T1 of CTI ≤ 8.40, 8.40 < T2 < 9.08, T3 of CTI ≥ 9.08. In the ELSA, T1 of CTI ≤ 8.54, 8.54 < T2 < 9.25, T3 of CTI ≥ 9.25. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging. CTI, C-reactive protein-triglyceride-glucose index; β, coefficient; T, tertile; CI, confidence intervals; FI, frailty index; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Association between CTI and the incidence of frailty

The associations of the CTI with incident frailty are shown in Table 3. According to the fully adjusted Cox regression models, participants in the highest CTI tertile (T3) had a significantly increased risk of developing frailty compared with those in the lowest tertile (T1) (CHARLS: HR = 1.16, 95% CI 1.02–1.31, P = 0.027; ELSA: HR = 1.27, 95% CI 1.06–1.51, P = 0.008). Significant dose—response relationships were observed, with increasing trends of frailty risk across CTI tertiles in both cohorts (P for trend = 0.027 in CHARLS; P for trend = 0.008 in ELSA). Furthermore, when analyzed as a continuous variable, each 1-unit increase in the CTI was associated with a greater risk of incident frailty (CHARLS: HR = 1.15, 95% CI 1.08–1.23, P < 0.001; ELSA: HR = 1.14, 95% CI 1.04–1.26, P = 0.007). Consistent with these findings, RCS analyses visually demonstrated a linear positive dose—response relationship between the CTI and the risk of incident frailty in both cohorts (Fig. 4). Subgroup analyses (Fig. 5) indicated that the positive association between the CTI and the risk of incident frailty was robust across subgroups stratified by sex, age, obesity, baseline frailty and diabetes status.

Table 3
Association between CTI and the incidence of frailty.

Variables	CHARLS					ELSA				
CTI Tertiles	Cases/Total	Univariate Model HR (95% CI)	P	Fully-adjusted Model HR (95% CI)	P	Cases/Total	Univariate Model HR (95% CI)	P	Fully-adjusted Model HR (95% CI)	P
T1	634/1758	[Reference]		[Reference]		285/968	[Reference]		[Reference]	
T2	628/1667	1.06 (0.95 ~ 1.18)	0.302	1.06 (0.95 ~ 1.19)	0.318	358/938	1.47 (1.26 ~ 1.72)	< 0.001	1.12 (0.95 ~ 1.33)	0.165
T3	617/1573	1.13 (1.01 ~ 1.26)	0.030	1.16 (1.02 ~ 1.31)	0.027	409/882	2.09 (1.79 ~ 2.43)	< 0.001	1.27 (1.06 ~ 1.51)	0.008
P for Trend			0.030		0.027			< 0.001		0.008
CTI per 1-unit	1879/4998	1.11 (1.06 ~ 1.17)	< 0.001	1.15 (1.08 ~ 1.23)	< 0.001	1052/2778	1.51 (1.39 ~ 1.63)	< 0.001	1.14 (1.04 ~ 1.26)	0.007

Multivariable Cox proportional hazards regression models were used to estimate the risk of incident frailty. Fully-adjusted Model: age, sex, education, marital status, smoking status, drinking status, physical activity, BMI, HDL-C, LDL-C. T1 was the lowest tertile, T2 was the middle tertile, and T3 was the highest tertile. In the CHARLS, T1 of CTI ≤ 8.40, 8.40 < T2 < 9.08, T3 of CTI ≥ 9.08. In the ELSA, T1 of CTI ≤ 8.54, 8.54 < T2 < 9.25, T3 of CTI ≥ 9.25. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging. HR, hazard ratio; T, tertile; CI, confidence intervals; CTI, C-reactive protein-triglyceride-glucose index; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Association between CTI and the progress speed of FI

The associations of the CTI with the progression speed of FI are summarized in Table 4. Linear mixed-effects models revealed that T3 of the CTI was associated with a significantly faster increase in FI over the follow-up period in both cohorts (CHARLS: β = 0.281, 95% CI 0.150–0.413, $P < 0.001$; ELSA: β = 0.319, 95% CI 0.233–0.405, $P < 0.001$). For T2, a significant acceleration in frailty progression was observed in ELSA (β = 0.186, 95% CI 0.101–0.271, $P < 0.001$), whereas the association in CHARLS did not reach statistical significance (β = 0.120, 95% CI -0.011–0.250, $P = 0.072$). The trend tests indicated significant increasing trends in frailty progression speed with increasing CTI levels in both populations (both P for trend < 0.001). Consistently, a continuous CTI score was positively associated with the rate of FI increase (CHARLS: β = 0.140, 95% CI 0.075–0.206, $P < 0.001$; ELSA: β = 0.160, 95% CI 0.117–0.203, $P < 0.001$). These longitudinal patterns are visualized in Fig. 6, which plots the predicted trajectories of the FI over time stratified by CTI tertiles. In both cohorts, the trajectories for the highest tertile (T3) exhibited markedly steeper positive slopes compared with the lowest tertile (T1), indicating that elevated CTI levels were associated with a faster rate of deficit accumulation and accelerated health deterioration throughout the follow-up period. Subgroup analyses (Fig. 7) indicated that the positive association between the CTI and the rate of FI increase was generally robust across subgroups defined by age, obesity, baseline frailty and diabetes status. However, a significant interaction was observed for sex in the CHARLS cohort (P for interaction = 0.039). Specifically, the accelerating effect of the CTI on frailty progression was more significant and pronounced in female participants than in males.

Table 4
Association between CTI and the progress speed of FI.

Variables	CHARLS					ELSA				
CTI Tertiles	Total	Univariate Model β (95% CI)	P	Fully-adjusted Model β (95% CI)	P	Total	Univariate Model β (95% CI)	P	Fully-adjusted Model β (95% CI)	P
T1	2175	[Reference]		[Reference]		1009	[Reference]		[Reference]	
T2	2174	0.121 (-0.010, 0.252)	0.069	0.120 (-0.011, 0.250)	0.072	1008	0.191 (0.106, 0.276)	< 0.001	0.186 (0.101, 0.271)	< 0.001
T3	2175	0.284 (0.152, 0.416)	< 0.001	0.281 (0.150, 0.413)	< 0.001	1009	0.324 (0.238, 0.411)	< 0.001	0.319 (0.233, 0.405)	< 0.001
P for Trend			< 0.001		< 0.001			< 0.001		< 0.001
CTI per 1-unit	6524	0.142 (0.076, 0.208)	< 0.001	0.140 (0.075, 0.206)	< 0.001	3026	0.163 (0.120, 0.206)	< 0.001	0.160 (0.117, 0.203)	< 0.001

Linear mixed-effects models were employed to analyze the longitudinal trajectories of the FI over the follow-up period. Fully-adjusted Model: age, sex, education, marital status, smoking status, drinking status, physical activity, BMI, HDL-C, LDL-C. T1 was the lowest tertile, T2 was the middle tertile, and T3 was the highest tertile. In the CHARLS, T1 of CTI ≤ 8.40, 8.40 < T2 < 9.08, T3 of CTI ≥ 9.08. In the ELSA, T1 of CTI ≤ 8.54, 8.54 < T2 < 9.25, T3 of CTI ≥ 9.25. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging. CTI, C-reactive protein-triglyceride-glucose index; β, coefficient; T, tertile; CI, confidence intervals; FI, frailty index; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Statistical analysis

To evaluate the robustness of our findings, two sets of sensitivity analyses were performed. First, we repeated the analyses using a modified 30-item FI that excluded the diabetes item to mitigate potential circularity and collinearity with the CTI. The cross-sectional positive associations between the CTI and the modified baseline FI remained consistent with the primary results in both cohorts (**Supplemental Table 5**). Regarding the risk of incident frailty, while the associations for categorical CTI tertiles were attenuated, the continuous CTI score (per unit increase) remained significantly associated with an increased risk of frailty in the CHARLS cohort (HR = 1.09, 95% CI 1.03–1.16, *P* = 0.005) and showed a borderline significant trend in the ELSA cohort (HR = 1.10, 95% CI 0.99–1.21, *P* = 0.062) (**Supplemental Table 6**). Importantly, the longitudinal analyses for frailty progression remained highly robust; elevated CTI levels were significantly associated with a faster rate of increase in the modified FI over time in both populations (**Supplemental Table 7**). These accelerated frailty trajectories were visually confirmed in **Supplemental Fig. 1**.

Second, to address potential reverse causality, a lag analysis was conducted by excluding frailty events and FI measurements occurring within the first two years of follow-up. In these analyses, the continuous CTI remained a significant predictor of incident frailty in both the CHARLS (HR = 1.13, 95% CI 1.04–1.22, *P* = 0.004) and ELSA (HR = 1.13, 95% CI 1.01–1.26, *P* = 0.034) cohorts, with the highest tertile (T3) in ELSA also showing a significantly elevated risk compared with T1 (HR = 1.22, 95% CI 1.01–1.49, *P* = 0.044) (**Supplemental Table 8**). Furthermore, linear mixed-effects models consistently demonstrated that higher CTI scores were associated with a significantly steeper slope of frailty progression in both cohorts (**Supplemental Table 9**). **Supplemental Fig. 2** further illustrates these divergent longitudinal patterns, showing that participants with higher baseline CTI levels experienced more rapid health deterioration even after early follow-up data were excluded.

Discussion

In the present study, we utilized data from two large-scale, nationwide prospective cohorts to investigate the longitudinal association between the CTI and the dynamic evolution of frailty. To our knowledge, this is the first study to elucidate the impact of this composite inflammatory and metabolic marker on frailty trajectories across different populations. Our findings demonstrate that elevated CTI levels are consistently associated with greater baseline FI, an increased risk of incident frailty, and a faster rate of frailty progression in both Chinese and English older adults.

A striking observation from our descriptive analysis is the significant disparity in the baseline health status between the two cohorts. The baseline prevalence of frailty and the mean FI scores were notably higher in the CHARLS cohort than in the ELSA cohort. Despite substantial disparities in initial frailty burdens, the longitudinal trajectories associated with elevated CTI exhibited remarkable parallelism

across these diverse cohorts. This consistency suggests that the deleterious effect of inflammatory and metabolic dysregulation on physiological reserve is a fundamental biological process that transcends ethnic and socioeconomic boundaries, thereby reinforcing the robustness and external validity of our conclusions. The observed disparity in baseline frailty burdens between the two cohorts may be largely explained by the differing prevalence and management of chronic metabolic diseases, particularly type 2 diabetes. As a composite index incorporating glucose and lipid parameters, the CTI is intrinsically linked to diabetic status. Our data revealed that the prevalence of diabetes in the CHARLS cohort was substantially greater than that in the ELSA cohort. This aligns with national epidemiological data indicating a rapid rise in diabetes prevalence in China, which has now surpassed global averages [20]. Furthermore, unlike the healthcare environment in the UK, the management of diabetes in China, especially in rural areas covered by CHARLS, faces unique challenges. Studies have shown that rates of diabetes awareness, treatment, and control are suboptimal in rural Chinese populations, with medication adherence being significantly lower than that in developed countries [21]. Poor glycemic control and nonadherence to medication accelerate the accumulation of deficits, such as neuropathy and macrovascular complications, thereby driving the higher baseline FI observed in the Chinese cohort[22, 23]. The fact that the CTI effectively predicts frailty progression even in this high-risk population highlights its sensitivity as a surveillance tool.

Notably, the interaction between the CTI and diabetes status exhibited distinct patterns across different analytical dimensions. While a significant interaction was observed in the cross-sectional analysis—where the association was attenuated in participants with diabetes—this heterogeneity dissipated in the longitudinal analyses, where the CTI consistently predicted frailty progression regardless of diabetes status. This discrepancy may be attributed to the distinction between the "physiological state" and "accumulative process." In the cross-sectional analysis, the association in patients with type 2 diabetes may be attenuated by the 'saturation effect' of deficit accumulation or the pleiotropic anti-inflammatory properties of metabolic pharmacotherapies, such as metformin and statins [24, 25]. However, longitudinal models capture the dynamic velocity of health deterioration. Over a follow-up period of nearly a decade, the chronic toxicity caused by metabolic and inflammatory dysregulation likely outweighs the transient protective effects of medication or baseline ceilings. This suggests that while diabetes status may modify the *static* correlation at a single time point, elevated CTI serves as a universal driver of *accelerated* aging trajectories over the long term. Furthermore, our linear mixed-effects models identified a cohort-specific interaction in the CHARLS, where the accelerating effect of the CTI on frailty progression was significantly more pronounced in women than in men. This sex disparity was not observed in the ELSA cohort. This phenomenon in the Chinese population may result from the intersection of biological and socioeconomic vulnerabilities. Biologically, the loss of the anti-inflammatory protection of estrogen in postmenopausal women renders them more susceptible to the metabolic derangements captured by the CTI [26]. Sociologically, older women in the CHARLS cohort, particularly those from rural areas, historically faced lower socioeconomic status and limited access to healthcare [27]. This "double jeopardy" of biological susceptibility and resource deprivation may explain why Chinese women exhibit a steeper trajectory of frailty in response to composite metabolic and inflammatory stress.

Several pathophysiological mechanisms may underlie the association between the CTI and frailty progression, with skeletal muscle deterioration representing a central pathway linking these metabolic derangements to physical decline. First, the CTI captures chronic low-grade inflammation, a hallmark of "inflammaging" [28]. Persistently elevated CRP levels reflect the upregulation of proinflammatory cytokines, which induce anabolic resistance and trigger proteolysis via the ubiquitin—proteasome pathway, directly driving muscle catabolism and sarcopenia [29, 30]. Second, the TyG component serves as a surrogate for the IR. As the principal tissue for insulin-mediated glucose disposal, skeletal muscle is profoundly vulnerable to this defect. IR impairs metabolic flexibility and mitochondrial oxidative capacity, resulting in reduced energy production and clinically manifesting muscle weakness [31–34]. Concurrently, the hypertriglyceridemia inherent to a high CTI fosters intramyocellular lipid accumulation. This intramyocellular lipid accumulation generates toxic lipid intermediates, such as ceramides, that structurally disrupt muscle architecture and further inhibit insulin signaling [35]. In addition to somatic mechanisms, the neuroimmunological pathway involving depression may also mediate this association. Elevated inflammatory cytokines and metabolic disturbances are well-established drivers of depressive symptoms [36]. Reciprocally, depression precipitates deleterious behavioral adaptations—including physical inactivity, nutritional inadequacy, and social withdrawal—thereby engendering a vicious cycle that exacerbates physiological depletion and accelerates frailty progression [37–39]. Thus, the CTI may reflect a broader systemic vulnerability that encompasses both physical and mental domains. Finally, the synergistic interaction between inflammation and glucolipotoxicity induces endothelial dysfunction and oxidative stress, compromising microvascular perfusion to critical organ systems [40–42]. This systemic physiological dysregulation ultimately depletes the body's homeostatic reserves, manifesting clinically as the accelerated progression of frailty.

Our study has notable strengths. This is the first longitudinal analysis linking the CTI to dynamic frailty trajectories using linear mixed-effects models. The use of two large, ethnically diverse cohorts (CHARLS and ELSA) enhances the generalizability and robustness of our findings. Finally, rigorous sensitivity analyses, including the use of a modified FI and lag analysis, confirmed the results' stability against potential circularity and reverse causality. However, some limitations also exist. First, the observational design precludes causal inference.

Second, single-baseline CTI measurements do not capture longitudinal fluctuations in biomarkers. Third, potential selection bias arose from the exclusion of participants with missing data or those lost to follow-up. Finally, residual confounding from unmeasured factors, such as genetics or detailed dietary patterns, cannot be entirely ruled out.

Conclusion

Our study provides the first longitudinal evidence that the CTI is a robust and independent predictor of frailty progression among older adults in both China and the UK. Despite notable disparities in baseline frailty burdens and the prevalence of chronic metabolic diseases between the two cohorts, the acceleration of health deterioration driven by elevated CTI levels was remarkably consistent. These findings suggest that the composite burden of metabolic and inflammatory dysregulation is a fundamental biological driver of physiological decline that transcends regional and socioeconomic boundaries. Consequently, the CTI holds significant promise as a simple, cost-effective surveillance tool. Monitoring CTI trajectories may facilitate the early identification of high-risk individuals and guide targeted interventions to mitigate composite metabolic and inflammatory stress, ultimately delaying the onset of frailty and promoting healthy aging.

Abbreviations

Frailty index (FI)

Insulin resistance (IR)

C-reactive protein (CRP)

Triglyceride-glucose (TyG)

C-reactive protein-triglyceride-glucose (CTI) index

Cardiovascular disease (CVD)

China Health and Retirement Longitudinal Study (CHARLS)

English Longitudinal Study of Aging (ELSA)

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

Fasting plasma glucose (FPG)

Triglyceride (TG)

Center for Epidemiologic Studies Depression Scale (CES-D)

Body mass index (BMI)

High-density lipoprotein cholesterol (HDL-C)

Low-density lipoprotein cholesterol (LDL-C).

Standard deviations [SD

Restricted cubic spline (RCS)

Declarations

Author Contributions:

Conceptualization: Zhen-Yu Liu; Xiao-Qun Wang; Rui-Yan Zhang;

Study design, data analysis, and data interpretation: Zhen-Yu Liu; Zhi-Ran Yue

Writing - original draft preparation: Zhen-Yu Liu; Zhi-Ran Yue

Writing - review and editing: Xiao-Qun Wang; Rui-Yan Zhang

Supervision: Xiao-Qun Wang; Rui-Yan Zhang

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Ethics approval and consent to participate

Ethical approval for the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Aging (ELSA) were obtained from the Peking University Ethics Committee and the London Multi-Centre Research Ethics Committee, respectively. Informed written consent was obtained from all participants involved in the studies.

Consent for publication

The authors declare that they have approved this study.

Availability of data and material

The CHARLS data are available upon request (https://charls.pku.edu.cn/). The ELSA data are available upon request (https://www.elsa-project.ac.uk/).

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Figures

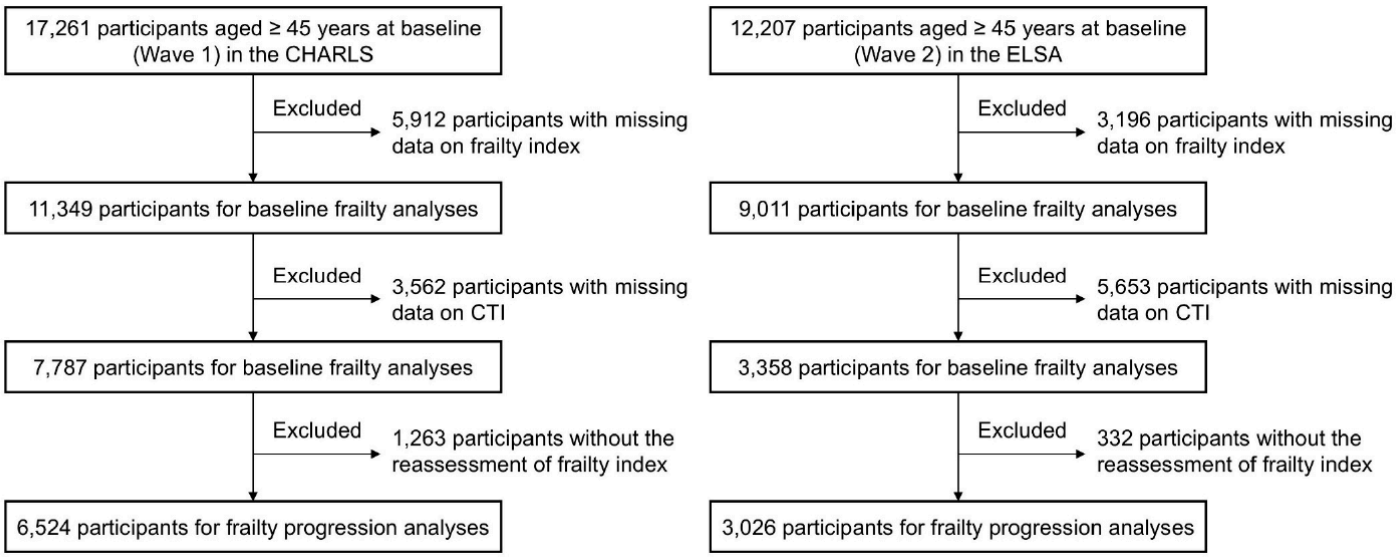


Figure 1

Flowchart of study participant selection. The diagram illustrates the screening process, exclusion criteria, and final analytical sample sizes for the baseline and longitudinal analyses in the CHARLS and ELSA cohorts. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging; CTI, C-reactive protein-triglyceride-glucose index.

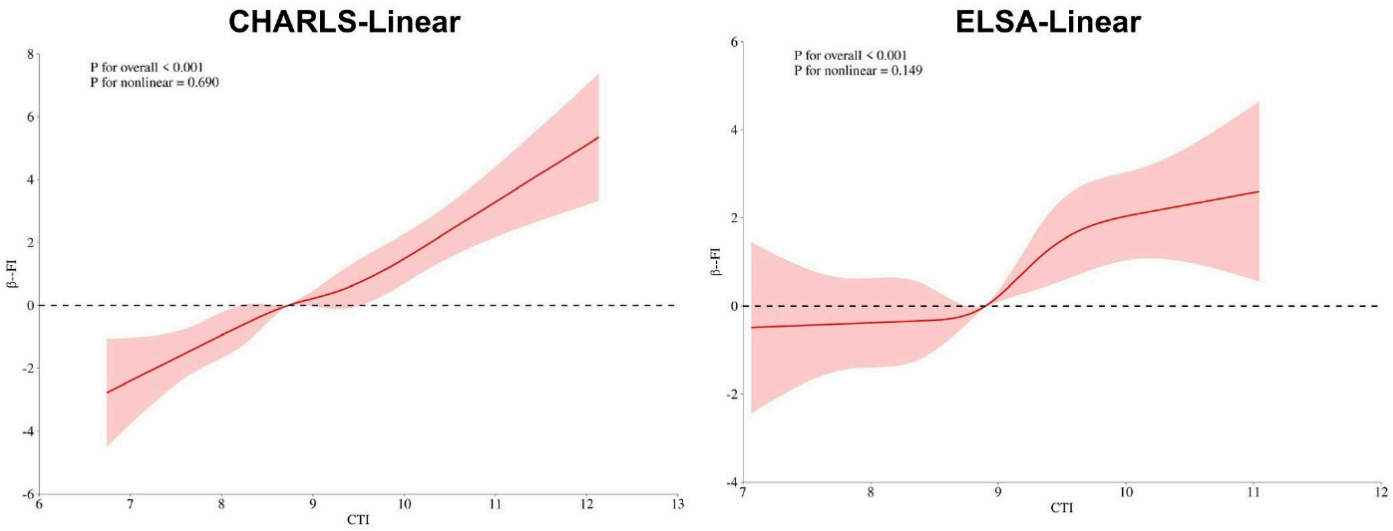


Figure 2

Dose—response relationship between the CTI and baseline FI. Restricted cubic spline (RCS) analyses visualizing the nonlinear association between continuous CTI scores and baseline FI in the CHARLS and ELSA cohorts. The solid red line represents the estimated β coefficient, and the shaded red area indicates the 95% CI. All covariates were adjusted for in the fully adjusted model. CTI, C-reactive protein-triglyceride-glucose index; CI, confidence interval; FI, Frailty Index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging.

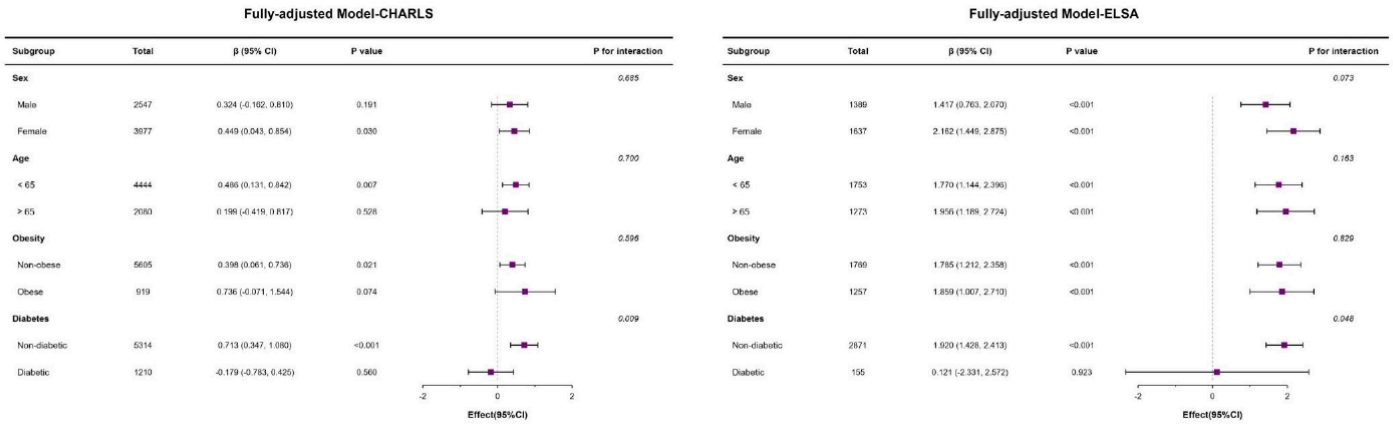


Figure 3

Subgroup analyses of the association between the CTI and baseline FI. Forest plots displaying the β coefficients and 95% CIs for the association between the CTI (per 1-unit increase) and baseline FI stratified by sex, age, obesity, and diabetes status. P for interaction values are provided for each stratification. Abbreviations: CTI, C-reactive protein-triglyceride-glucose index; CI, confidence interval; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging.

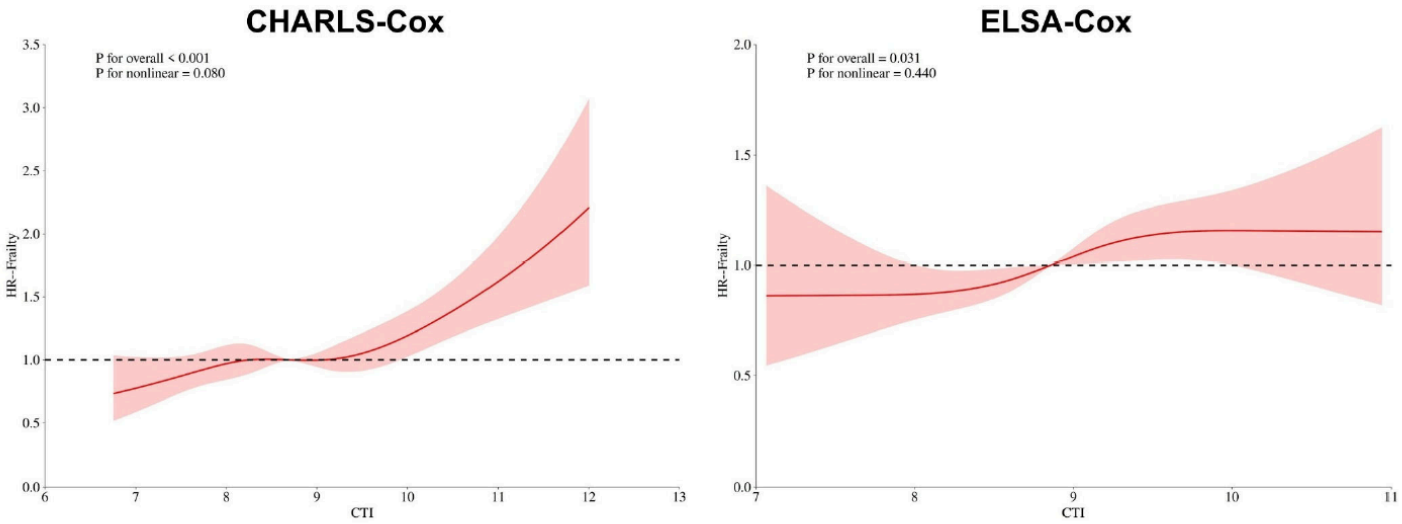


Figure 4

Dose—response relationship between the CTI and the risk of incident frailty. Restricted cubic spline (RCS) analyses visualizing the nonlinear association between continuous CTI scores and the HR for incident frailty in the CHARLS and ELSA cohorts. The solid red line represents the estimated HR, and the shaded red area indicates the 95% CI. The dashed line represents the reference hazard ratio of 1.0. All covariates were adjusted for in the fully adjusted model. CTI, C-reactive protein-triglyceride-glucose index; CI, confidence interval; HR, hazard ratio; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging.

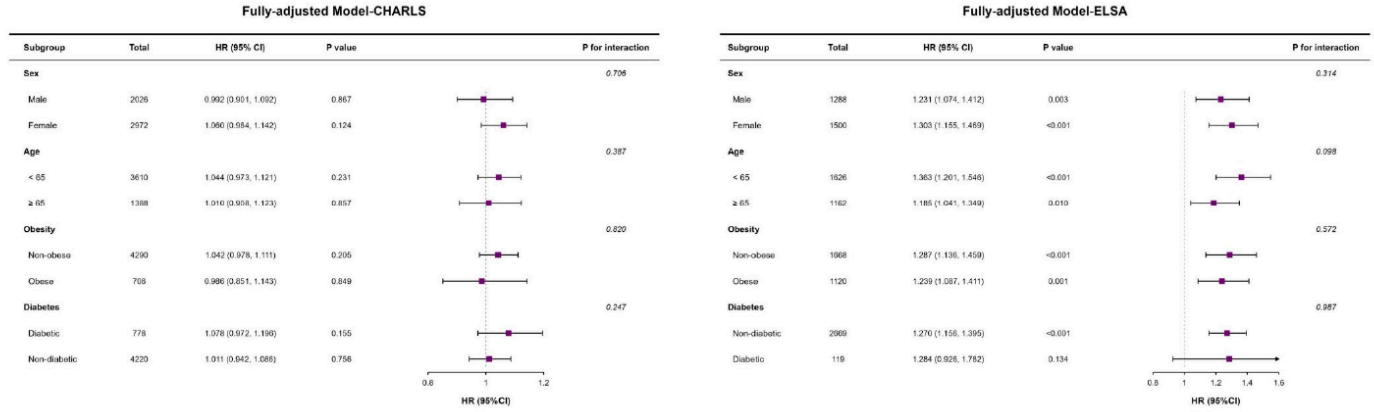


Figure 5

Subgroup analyses of the association between the CTI and the risk of incident frailty. Forest plots displaying the HR and 95% CI for the association between the CTI (per unit increase) and incident frailty stratified by sex, age, obesity, and diabetes status. P for interactions are provided for each stratification. CTI, C-reactive protein-triglyceride-glucose index; HR, hazard ratio; CI, confidence interval; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging.

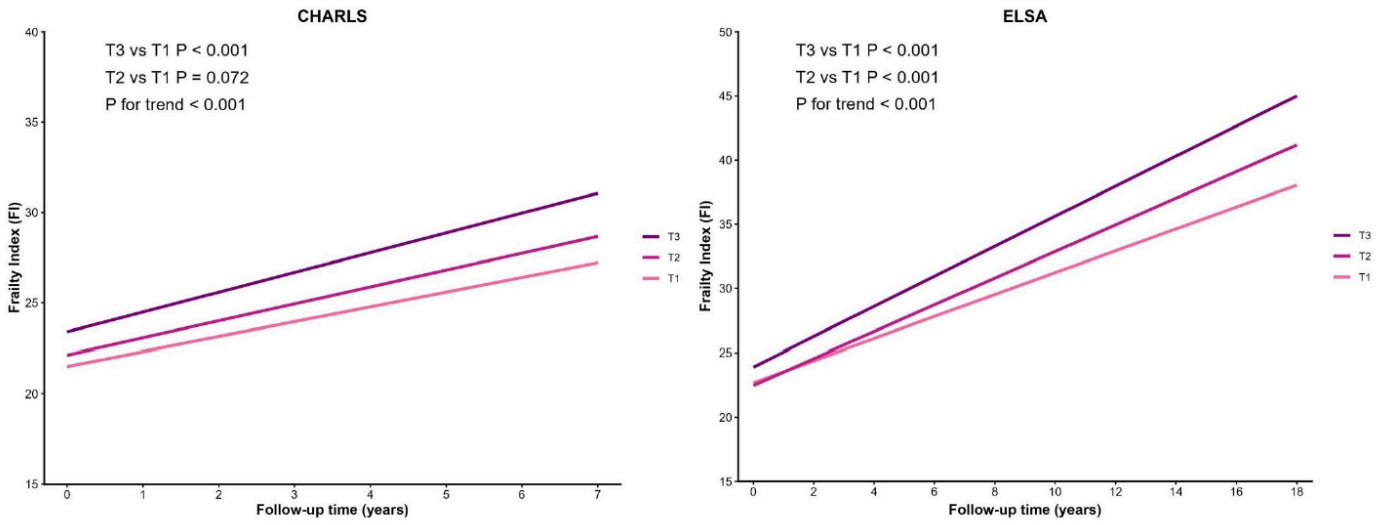


Figure 6

Longitudinal trajectories of FI by CTI tertiles. Predicted trajectories of frailty progression over the follow-up period stratified by CTI tertiles (T1, T2, T3) using linear mixed-effects models. The slopes represent the rate of FI increase over time (in years). T1 represents the lowest tertile (reference), T2 represents the middle tertile, and T3 represents the highest tertile. CTI, C-reactive protein-triglyceride-glucose index; FI, Frailty index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging.

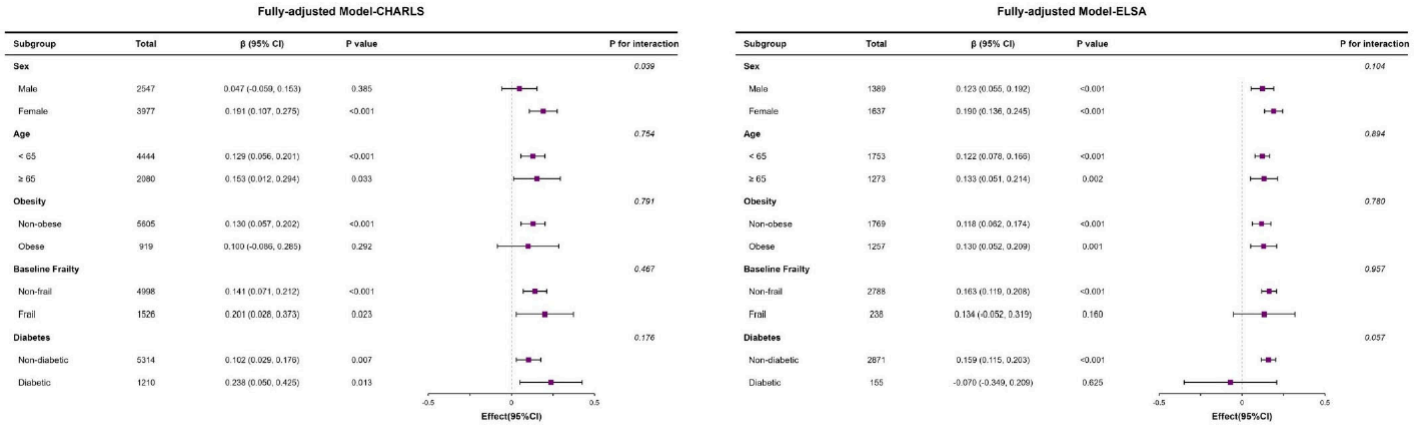


Figure 7

Subgroup analyses of the association between the CTI and the progression speed of FI. Forest plots displaying the β coefficients and 95% CIs for the associations between the CTI (per 1-unit increase) and the rate of FI increase (P for interaction) stratified by sex, age, obesity, baseline frailty, and diabetes status. P for interactions are provided for each stratification. CTI, C-reactive protein-triglyceride-glucose index; CI, confidence interval; FI, frailty index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Aging.

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