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Association of metabolic syndrome severity with frailty progression among Chinese middle and old-aged adults: a longitudinal study

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Abstract

Background The binary diagnosis of Metabolic Syndrome(MetS) fails to accurately evaluate its severity, and the association between MetS severity and frailty progression remains inadequately elucidated. This study aims to clarify the relationship between the severity of MetS and the progression of frailty among the middle-aged and elderly population in China.

Method Participants from the 2011–2018 China Health and Retirement Longitudinal Study(CHARLS) were included for a longitudinal analysis. The study employs a frailty index(FI) based on 32 health deficits to diagnose frailty and to assess FI trajectories. An age-sex-ethnicity-specific MetS scoring model (MetS score) was used to assess metabolic syndrome severity in Chinese adults. The Cumulative MetS score from 2012 to 2015 was calculated using the formula: (MetS score in wave 1 + MetS score in wave 3) / 2 × time(2015 - 2012). The association between MetS score, Cumulative MetS score, and the risk and trajectory of frailty were evaluated using Cox regression/logistic regression, and linear mixed models. Restricted Cubic Splines(RCS) models were utilized to detect potential non-linear associations.

Results A higher MetS score was significantly associated with an increased risk of frailty(HR per 1 SD increase = 1.205; 95%CI: 1.14 to 1.273) and an accelerated FI trajectory(β per 1 SD increase = 0.113 per year; 95%CI: 0.075 to 0.15 per year). Evaluating changes in MetS score using a Cumulative MetS score indicated that each 1 SD increase in the Cumulative MetS score increased the risk of frailty by 22.2%(OR = 1.222; 95%CI: 1.133 to 1.319) and accelerated the rate of increase in FI(β = 0.098 per year; 95%CI: 0.058 to 0.138 per year). RCS model results demonstrated a dose-response curve relationship between MetS score and Cumulative MetS score with frailty risk. Stratified analysis showed

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consistency across subgroups. The interaction results indicate that in males and individuals under aged 60, MetS score may accelerate the increase in FI, a finding consistent across both models.

Conclusions Our findings underscore the positive correlation between the severity of MetS and frailty progression in the middle-aged and elderly, highlighting the urgent need for early identification of MetS and targeted interventions to reduce the risk of frailty.

Keywords Metabolic syndrome severity, Frailty, Longitudinal study, Trajectory analysis, CHARLS

Introduction

In confronting the challenges of global aging, frailty has garnered increasing attention due to its impact on the global burden of disease [1, 2]. Frailty, a comprehensive concept that encompasses Cumulative deficiencies in physical and cognitive-psychological functions as well as a decline in resilience, is a dynamic process closely associated with aging and influenced by multidimensional physical and socio-psychological factors [3, 4]. Numerous studies have indicated that frailty is related to adverse outcomes such as decreased quality of life [5], falls [6], chronic diseases [7–9], hospitalization [10], and mortality [1, 11, 12]. Investigating the development trends and long-term patterns of frailty is crucial for the early identification of adjustable risk factors and the formulation of effective prevention strategies.

Metabolic syndrome(MetS), represents a cluster of metabolic disorders including hypertension, hyperglycemia, dyslipidemia, and abdominal obesity, closely linked to cardiovascular diseases and related mortality [13–16]. MetS and frailty are common comorbidities in the elderly, with cohort studies from community-dwelling older adults revealing a link between MetS and an increased risk of incidental frailty [17–19]. Specific characteristics of MetS, such as insulin resistance and obesity, may accelerate the decline in muscle function and physical capability, thereby promoting the development of frailty [20, 21]. Previous studies, primarily cross-sectional in design, focused on the static state of MetS and did not adequately consider the dynamic changes in metabolism or the developmental trajectory of frailty [22]. Additionally, the binary classification of MetS failed to accurately reflect the severity of metabolic disturbances and overlooked differences in race, sex, and age, leading to inadequate capture of the subtle variations in the progression of MetS. To address these issues, Yang et al. developed an age-sex-race-specific MetS scoring system(MetS score) for the Chinese population [23]. This system quantifies the severity of MetS by reweighting five common metabolic disorder factors—triglycerides(TG), high-density lipoprotein cholesterol(HDL-C), fasting blood glucose(FBG), waist circumference(WC), and mean arterial pressure(MAP)—and has been validated in three large population samples for its effectiveness in predicting adverse outcomes associated with MetS. This approach provides a valuable tool for comprehensively assessing and monitoring the severity and developmental trends of MetS in the Chinese population.

This study aims to deepen the understanding of the interaction between MetS and frailty by prospectively investigating the relationship between continuous MetS score and long-term frailty trajectories, considering the impact of changes in MetS score on frailty trajectories. Data were sourced from the China Health and Retirement Longitudinal Study(CHARLS), a nationally representative prospective cohort study in China. We hypothesize that an increase in MetS score is associated with an accelerated development trajectory of long-term frailty.

Methods

Study population

This study utilized data from CHARLS, a nationally representative longitudinal survey targeting residents of China aged 45 and above. For a detailed description of the methodologies employed, refer to Supplemental Methods [24]. Our analysis included data from wave 1(2011–2012), wave 2(2013–2014), wave 3(2015–2016), and wave 4(2018), with wave 1 serving as the baseline. Further insights into the research design can be found in Fig. 1. The analysis excluded participants who were under 45 years of age at baseline, those missing baseline MetS score or Frailty index(FI) data, as well as individuals who were lost to follow-up or diagnosed as frailty at baseline. Consequently, a total of 6220 participants were included in the analysis. Among those meeting baseline criteria, 7915 participants(including participants with baseline frailty), 3632(excluding participants with baseline frailty), and 4599(including participants with baseline frailty) had complete MetS score by wave 3 and were included in further transitional analyses.

Frailty evaluation

Following the previous description, FI was constructed to quantify the accumulation of age-related health deficits using data from the CHARLS database [25]. 32 variables covering physical functioning, cognitive psychology, and disease conditions were selected. Cognitive scores were treated as continuous variables with values ranging from 0 to 1, while the remaining variables were

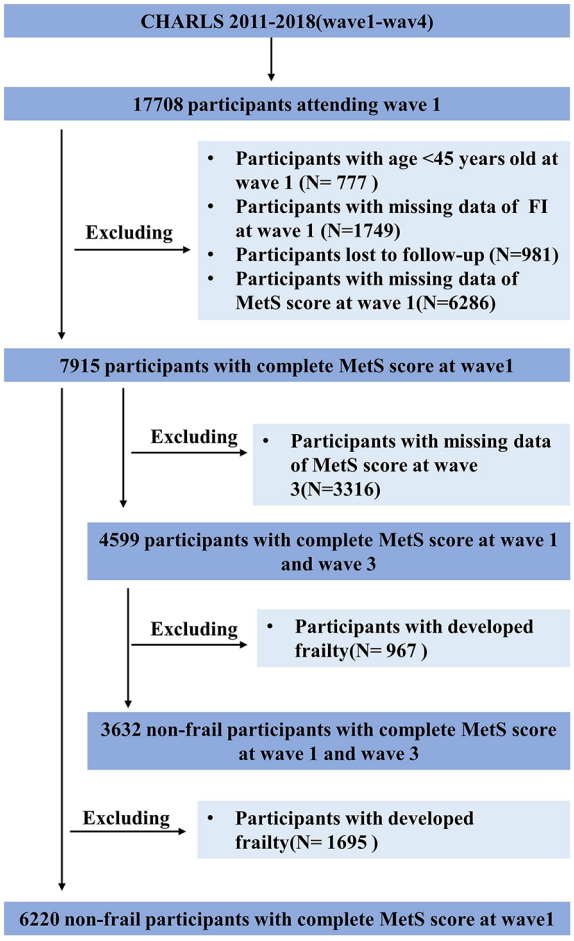

Fig. 1 Flowchart of the population included in our final analysis

transformed into binary variables(0 or 1) based on specific cutoff values. Here, 0 indicates the absence of health deficits, and 1 indicates their presence. The FI was calculated by summing all health deficits, dividing by 32, and then multiplying by 100. Thus, FI values range from 0 to 100, with higher values indicating greater frailty. Following previous research, frailty was defined as FI≥25 [1]. To maximize the sample size, samples with less than 10% missing data for the 32 variables were retained, and multiple imputation methods were used to estimate missing values. Detailed variables and methods can be found in Supplementary Methods and Table 1.

Assessment of MetS score and the change in MetS score

In line with the age-sex-ethnicity-specific MetS score model developed by Yang et al. for Chinese adults, we structured MetS score following standard procedures [26]. Detailed methodologies are available in Supplementary Table S2. Consistent with prior studies, we assessed the change in MetS Score by calculating the Cumulative MetS score between 2012 and 2015 [27, 28]. The formula used for calculation is (MetS score in wave 1 + MetS score in wave 3) / 2 × time(2015 − 2012). Additionally, we employed an unsupervised machine learning technique, namely K-means clustering using Euclidean distance, to categorize the MetS score from 2012 to 2015 and evaluate changes [29]. The K-means algorithm partitions the dataset into K clusters by minimizing the within-cluster sum of squares. The optimal cluster number K was determined to be 4 using the elbow method.

Covariates

This study incorporates several covariates, including age(measured in years), gender, education, residence, living alone, marital status, current smoking, alcohol consumption, physical activity, household income, and health insurance. Education level is categorized into two groups: below high school and high school or above. Residence is distinguished between rural and urban settings. Marital status is divided into married or partnered(in a stable partnership) and other statuses, which include divorced, separated, widowed, or single. Alcohol consumption is defined as drinking at least once per week. Individuals engaging in moderate to vigorous physical activities at least once a week are considered to have a physically active lifestyle. Household income is classified into three tiers based on the total income of the previous year: low, middle, and high income. Finally, health insurance is segmented into three categories: uninsured, public insurance, and private insurance.

Statistical analysis

In the descriptive statistics section, continuous variables were reported as means(standard deviation[SD]) or medians(interquartile range[IQR]), while categorical variables were presented as counts(percentages). Baseline characteristics between groups were compared using one-way ANOVA or the Kruskal-Wallis test for continuous variables, and the Chi-square test for categorical variables. Continuous MetS score were performed using baseline mean and SD for z-score transformation for further analysis.

To assess the relationship between the MetS score and the incidence of frailty during the follow-up period, proportional Cox regression models were used, with follow-up time as the time scale, to calculate hazard ratios(HRs) and their 95% confidence intervals(CIs). The index date was defined as the baseline assessment wave(wave 1) when the MetS score was first measured. The time at which frailty occurred was recorded as the time at the beginning of the first follow-up wave when the participant was identified as frail. Frailty was assessed at each follow-up wave(wave 2, wave 3, and wave 4). The censoring date was defined as the wave of the last follow-up assessment for participants who did not develop frailty, or the date of death if it occurred before the development

Table 1 Baseline characteristics of the study population by quartiles of baseline MetS score

Characteristic	Quartiles of baseline MetS score					*p*-value
	Overall	Q1	Q2	Q3	Q4	
N	6220	1562	1582	1527	1549	
Age, mean(SD), year	58.08 (8.91)	58.38 (9.04)	57.68 (9.01)	58.03 (9.02)	58.21 (8.55)	0.047
Age, n(%)						0.022
<60	3761 (60.5)	947 (60.6)	1001 (63.3)	916 (60.0)	897 (57.9)	
≥60	2459 (39.5)	615 (39.4)	581 (36.7)	611 (40.0)	652 (42.1)	
Female, n(%)	3114 (50.1)	501 (32.1)	790 (49.9)	819 (53.6)	1004 (64.8)	< 0.001
Residence, n(%)						< 0.001
Urban	2310 (37.1)	438 (28.0)	529 (33.4)	615 (40.3)	728 (47.0)	
Rural	3910 (62.9)	1124 (72.0)	1053 (66.6)	912 (59.7)	821 (53.0)	
Educational level, n(%)						0.8
Below high school	5527 (88.9)	1389 (88.9)	1415 (89.4)	1353 (88.6)	1370 (88.4)	
High school or above	693 (11.1)	173 (11.1)	167 (10.6)	174 (11.4)	179 (11.6)	
Marital status, n(%)						0.7
Married or partnered	5570 (89.5)	1392 (89.1)	1416 (89.5)	1364 (89.3)	1398 (90.3)	
Other	650 (10.5)	170 (10.9)	166 (10.5)	163 (10.7)	151 (9.7)	
Physically active, n(%)	4273 (68.7)	1180 (75.5)	1117 (70.6)	1017 (66.6)	959 (61.9)	< 0.001
Health insurance, n(%)						0.6
Uninsured	327 (5.3)	79 (5.1)	79 (5.0)	87 (5.7)	82 (5.3)	
Public	5846 (94.0)	1474 (94.4)	1494 (94.4)	1428 (93.5)	1450 (93.6)	
Private	47 (0.8)	9 (0.6)	9 (0.6)	12 (0.8)	17 (1.1)	
Alcohol consumption, n(%)	1088 (17.5)	443 (28.4)	261 (16.5)	212 (13.9)	172 (11.1)	< 0.001
Current smoking, n(%)	2018 (32.4)	730 (46.7)	517 (32.7)	431 (28.2)	340 (21.9)	< 0.001
Household income, n(%)						0.002
Low	1904 (30.6)	490 (31.4)	493 (31.2)	480 (31.4)	441 (28.5)	
Middle	2118 (34.1)	556 (35.6)	566 (35.8)	503 (32.9)	493 (31.8)	
High	2198 (35.3)	516 (33.0)	523 (33.1)	544 (35.6)	615 (39.7)	
Living alone, n(%)	267 (4.3)	81 (5.2)	64 (4.0)	60 (3.9)	62 (4.0)	0.3
MetS score, mean(SD)	0.16 (0.86)	− 0.86 (0.38)	− 0.15 (0.15)	0.38 (0.17)	1.30 (0.54)	
MetS, n (%)	1570 (25.2)	23 (1.5)	70 (4.4)	322 (21.1)	1155 (74.6)	< 0.001
Frailty index, median (IQR)	13.39 (9.60, 17.19)	11.50 (8.37, 16.74)	11.72 (8.48, 17.08)	13.62 (10.27, 17.30)	14.06 (10.71, 17.86)	< 0.001

Categorical variables were shown as n(percent, %). Continuous variables were shown as mean(standard deviation, SD) or median(Interquartile range, IQR): P values for differences between groups were derived using a Kruskal-Wallis rank sum test or Pearson's Chi-squared test. This Other marital status refers to divorced, separated, widowed, or never married statuses

MetS score, metabolic syndrome score. *SD* standard deviation, *IQR* inter-quartile range

of frailty. The time of frailty occurrence was recorded as the first follow-up wave in which the participant was identified as frail. We incorporated an interaction term between follow-up time and exposure in the model to test for any violations of the proportional hazards assumption [30]. The results showed that the interaction term was not statistically significant, indicating that there was no significant deviation from the proportional hazards assumption. The association between Cumulative MetS score and the incidence of frailty was analyzed using logistic regression to estimate odds ratios(ORs) and their 95%CIs. Non-linear relationships were estimated using restricted cubic splines(RCS) models. The relationship between the MetS score and FI trajectories was examined using linear mixed models, considering individual variability as a random effect. Specifically, to accommodate the baseline differences and changes over time at the individual level, both random intercepts and random slopes were included in the model. An unstructured covariance structure was assumed to model the covariance between random effects, allowing for a flexible representation of within-participant correlations in the repeated measures. All available repeated measures of FI(including baseline FI) were included as outcomes, with MetS score, time(follow-up time), their interaction term(MetS score × time), and covariates as fixed effects. Here, the MetS score refers to the baseline measurement of MetS score(wave 1), and the regression coefficient of the interaction term indicates an association between changes in MetS score and the annual rate of change in FI. Additionally, this analysis was repeated for different classes of MetS score changes Cumulative MetS score and Change in the MetS score). Baseline characteristics were used as modifiers in stratified interaction analyses

to evaluate potential differences in the effects of the MetS score across subgroups, with both Cox regression and mixed linear models being repeated.

In sensitivity analyses, the primary analysis was replicated with: (1) The application of inverse probability weighting to address potential selection bias, where individuals' analysis weights were recalculated as the reciprocal of their probability of being included in the analysis, and the Absolute standardized mean difference was used to assess differences between included and excluded participants; (2) Beyond linear mixed models, Group-Based Trajectory Modeling(GBTM) was used to define FI trajectories and logistic regression was employed to estimate the association between MetS score and FI progression, along with ORs and 95%CIs; (3) the K-means method was reapplied to reassess the transition of MetS score about frailty progression; (4) The longitudinal association between MetS score and FI trajectories was repeated among participants including participants with baseline frailty, considering $P<0.05$ as statistically significant. All statistical analyses were performed using R version 4.2.2 and SAS version 9.4.

Result

Baseline characteristics

A total of 6220 participants were included in the final analysis, with a mean age(SD) of 58.08(9.91) years, and 3,114(50.1%) were female. Table 1 presents the baseline characteristics of the study population according to quartiles of baseline MetS score. The results indicate that participants with higher baseline MetS score were more likely to be female, urban residents, physically inactive, less likely to smoke and alcohol consumption, have higher household income, and exhibit higher FI. The baseline characteristics of the transition analysis are also detailed in supplemental Tables S3, S4, S5.

Association of MetS score with frailty progression

As demonstrated in Table 2, Cox regression analysis revealed a positive correlation between the MetS score and the risk of frailty across all models. After adjusting for all covariates, each 1 SD increase in MetS score was associated with a 20.5% increase in the risk of frailty(HR = 1.205; 95%CI: 1.14 to 1.273). When the continuous MetS score was categorized into quartiles, the risk associated with the highest quartile(Q4) was 46.6% higher than that in the lowest quartile(Q1) (HR = 1.466; 95%CI: 1.228 to 1.676), with a significant linear trend observed in the test for trend(P for trend < 0.001). Further examination using RCS for potential non-linear relationships indicated an almost linear relationship between the continuous MetS score and frailty risk(P for non-linear = 0.184, Fig. 2A).

Table 3 presents the association between MetS and FI trajectory as defined by a linear mixed model. The results showed that, after adjustment for all variables, each 1 SD increase in the MetS score was associated with a faster increase in FI(β = 0.113 per year; 95%CI: 0.075 to 0.15 per year). Upon categorizing the Continuous MetS score into quartiles, the increase in FI associated with Q4 compared to Q1 was 0.275 per year(95%CI: 0.185 to 0.368 per year), with the linear trend P-value < 0.001.

Association of change in MetS score with frailty progression

We developed a Cumulative MetS score to investigate the impact of changes in MetS score on the progression to frailty. As illustrated in Table 4, within a fully adjusted logistic regression model, each 1 SD increment in the Cumulative MetS score was significantly associated with an increased risk of frailty(OR = 1.222,95%CI: 1.133 to 1.319). Transitioning the Cumulative MetS score into quartiles revealed that, compared to Q1, Q4 faced a markedly elevated frailty risk(OR = 1.648, 95%CI: 1.332 to 2.041), with a significant linear trend observed in the test for trend(P for trend < 0.001). Analysis utilizing the RCS model suggested a nearly linear relationship between the Cumulative MetS score and frailty risk(P for non-linear = 0.245, Fig. 1B).

Table 2 Associations of MetS score with frailty

	Crude model		Model 1		Model 2	
	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value
MetS score, per SD	1.231 (1.169,1.296)	< 0.001	1.167 (1.106,1.231)	< 0.001	1.205 (1.14,1.273)	< 0.001
MetS score quartiles						
Q1	Ref.		Ref.		Ref.	
Q2	1.148 (1.009,1.316)	0.042	1.079 (0.947,1.238)	0.246	1.074 (0.933,1.227)	0.3
Q3	1.307 (1.178,1.533)	< 0.001	1.196 (1.046,1.369)	0.002	1.223 (1.067,1.401)	0.001
Q4	1.597 (1.382,1.788)	< 0.001	1.381 (1.21,1.576)	< 0.001	1.466 (1.228,1.676)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	

Crude model: non-adjusted (univariate analysis); Model1:Sex and Age were adjusted; Model2: Model1 plus residence, marital status, alcohol consumption, physically active, health insurance, current smoking, household income, living alone, and educational level were adjusted. HR was calculated using the Cox regression model, which estimated the associations between the MetS score and the risk of frailty

Ref Reference; *MetS score* metabolic syndrome score, *CI* confidence interval, *HR* Hazard Ratio

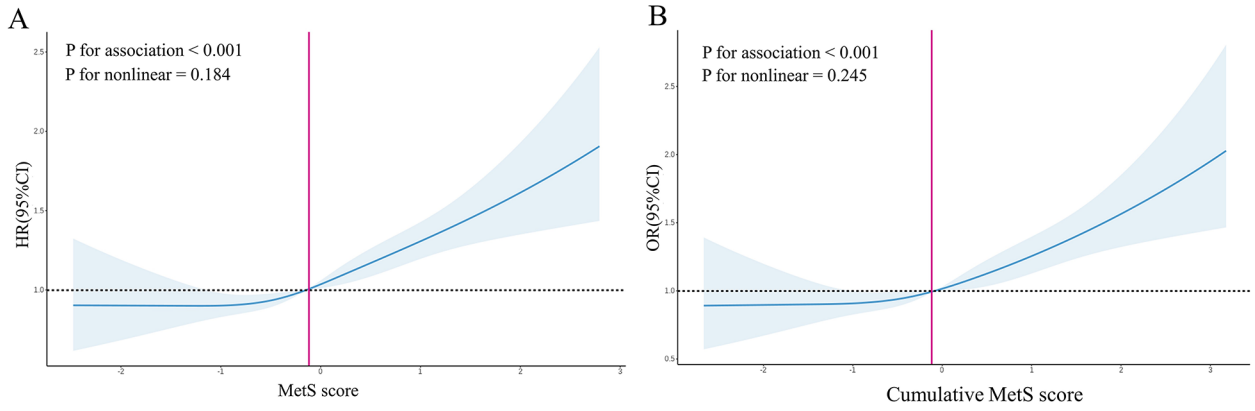

Fig. 2 Analysis of restricted cubic spline regression. Adjusted restricted cubic spline models were controlled for variables including covariates including sex, age, residence, marital status, alcohol consumption, physically active, health insurance, current smoking, household income, living alone, and educational level. Solid lines indicate HR or OR, and shadow shapes indicate 95% CIs. *Ref* Reference *MetS score* metabolic syndrome score; *FI* frailty index score, *CI* confidence interval *OR* odds ratio, *HR* Hazard Ratio

Table 3 Longitudinal association between different classes of MetS score and rate of change in FI

Characteristic	β(95% CI)	*p*-value
MetS score, per SD	0.113 (0.075,0.15)	< 0.001
MetS score, quartiles		
Q1	Ref.	Ref.
Q2	0.082 (– 0.009,0.172)	0.071
Q3	0.146 (0.055,0.237)	0.002
Q4	0.275 (0.185,0.368)	< 0.001
P for trend	< 0.001	
Cumulative MetS score, per SD	0.098 (0.058,0.138)	< 0.001
Cumulative MetS score, quartiles		
Q1	Ref.	Ref.
Q2	0.093 (– 0.021,0.208)	0.108
Q3	0.163 (0.049,0.277)	0.005
Q4	0.284 (0.171,0.398)	< 0.001
P for trend	< 0.001	
Change in the MetS score		
Class1	Ref.	Ref.
Class2	0.112 (0.002,0.223)	0.046
Class3	0.203 (0.088,0.318)	0.001
Class4	0.28 (0.133,0.427)	< 0.001
P for trend	< 0.001	

Change in MetS score from 2012 to 2015 was analyzed and classified into 4 classes using K-means clustering. β Coefficient was estimated using linear mixed models, with the positive value representing accelerated frailty. Adjusted covariates include sex, age, residence, marital status, alcohol consumption, physically active, health insurance, current smoking, household income, living alone, and educational level

Ref Reference, MetS score, metabolic syndrome score, *FI* frailty index score, *SD* standard deviation, *CI* confidence interval, *OR* odds ratio

Further insights from linear mixed model analysis underscored the relationship between Cumulative MetS score and FI trajectory as defined within this analytical model. As shown in Table 3, after adjusting for all covariates, each 1 SD increase in Cumulative MetS score significantly accelerated the rate of increase in FI(β = 0.098 per year; 95%CI:0.058 to 0.138 per year). Specifically, when the Cumulative MetS score was categorized into quartiles for analysis, the rate of increase in the FI for Q4 compared to Q1was β = 0.284 per year, with a 95% CI of 0.171 to 0.398 per year.

Stratified and interaction analyses

The stratified analysis revealed that the association between the MetS score and the risk and frailty progression was broadly consistent across different stratification factors(Fig. 3). In two distinct models, we observed that age and gender could modify the relationship between the MetS score and frailty progression(P for interaction < 0.05). Furthermore, within the stratified analyses of the linear mixed models, we also identified interactions between being physically active(P for interaction = 0.003) and living alone(P for interaction = 0.001) with the association between the MetS score and FI trajectories.

Sensitivity analysis

Sensitivity analyses were largely robust. After reweighting participant characteristics using the inverse probability-weighted method to minimize biases, differences between included and excluded participants were reduced compared to the original unweighted sample, indicating that our primary findings were not influenced by baseline participant characteristics(Supplemental Fig. S1, Supplemental Tables S6, S7). Additionally, the GBTM method consistently identified three frailty trajectories across different populations: accelerated frailty, moderate frailty, and stable frailty(Fig. 4A–B). Both binary logistic regression and multivariable logistic regression models demonstrated a positive correlation between accelerated FI increase trajectory and MetS score and Cumulative MetS score(Supplemental Tables S8, S9). The K-means method identified four trajectories: class 1(persistently low MetS

Table 4 Associations of different classes of change in MetS score with Frailty

	Crude model		Model 1		Model 2	
	OR(95% CI)	*p*-value	OR(95% CI)	*p*-value	OR(95% CI)	*p*-value
Cumulative MetS score, per SD	1.046 (1.031,1.062)	< 0.001	1.175 (1.093,1.264)	< 0.001	1.222 (1.133,1.319)	< 0.001
Cumulative MetS score quartiles						
Q1	Ref.		Ref.		Ref.	
Q2	1.138 (0.929,1.396)	0.213	1.085 (0.88,1.337)	0.445	1.091 (0.883,1.35)	0.42
Q3	1.268 (1.037,1.552)	0.021	1.136 (0.922,1.399)	0.231	1.189 (0.961,1.472)	0.111
Q4	1.724 (1.416,2.102)	< 0.001	1.512 (1.231,1.858)	< 0.001	1.648 (1.332,2.041)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	
Change in the MetS score						
Class1	Ref.		Ref.		Ref.	
Class2	1.147 (0.942,1.398)	0.174	1.068 (0.873,1.31)	0.523	1.067 (0.868,1.313)	0.542
Class3	1.36 (1.111,1.669)	0.003	1.18 (0.956,1.459)	0.125	1.253 (1.009,1.559)	0.042
Class4	1.894 (1.474,2.435)	< 0.001	1.644 (1.268,2.133)	< 0.001	1.842 (1.408,2.412)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	

Change in MetS score from 2012 to 2015 was analyzed and classified into 4 classes using K-means clustering. Crude model: non-adjusted (univariate analysis); Model 1:Sex and Age were adjusted.Model 2: Model 1 plus residence, marital status, alcohol consumption, physical activity, health insurance, current smoking, household income, living alone, and educational level were adjusted. ORs were calculated using a binary logistic regression model, which estimated the associations between MetS score and the risk of frailty

Ref Reference, *MetS score* metabolic syndrome score, *CI* confidence interval, *OR* odds ratio

score), class 2(moderately increasing MetS score), class 3(stable high MetS score), and class 4(initially highest but slowly decreasing MetS score). Consistent with the primary analysis, compared to class 1, class 4 was associated with the highest risk of frailty(Table 4) and the fastest rate of change in FI(Table 3). Similar results were obtained when the primary analysis was repeated with complete data, including participants who were frail at baseline(Supplemental Table S10).

Discussion

In conclusion, our study demonstrates a significant association between MetS score and the progression of frailty in a large prospective cohort. Both higher baseline MetS score and changes in MetS score over time were associated with an elevated risk of frailty and a faster increase in FI. This relationship persisted after adjusting for various covariates, suggesting that MetS is an independent predictor of frailty progression. Notably, RCS models revealed a dose-response relationship between MetS score, Cumulative MetS score, and the risk of frailty. Moreover, stratified and interaction analyses indicate that the impact of MetS on frailty risk is consistent across different population subgroups, although modified by factors such as age, gender, physical activity, and living situation. Sensitivity analyses employing different methodological approaches, including inverse probability weighting, GBTM, and K-means clustering, corroborated the robustness of our primary findings, highlighting the potential of MetS as a target for interventions aimed at preventing or delaying the progression of frailty. These findings underscore the importance of monitoring and managing MetS components as part of comprehensive strategies to mitigate frailty risk among aging populations.

Multiple studies have explored the relationship between the binary classification of MetS and frailty [18, 31, 32]. Prospective cohort studies from communities in Australia and the United States have found associations between MetS and stages of frailty, ranging from pre-frailty to full frailty [33]. Similarly, an Irish Longitudinal Study on Ageing indicated that MetS significantly increased the risk of frailty [34], a finding supported by several meta-analyses that generally suggest a positive correlation between MetS and frailty [31]. Nonetheless, the binary diagnostic model of MetS, based on "presence or absence" criteria, fails to accurately reflect the actual severity of metabolic disturbances and overlooks the impact of demographic differences. A study utilizing nationally representative data from the United States developed a MetS severity scoring system for adolescents and adults, validated against the risk of cardiovascular diseases and diabetes during follow-up [35]. However, due to differences in genetic backgrounds, lifestyles, prevalence of MetS, and heterogeneity in the outcomes of its components, there is a significant variation in the composition and weighting of MetS scoring models across populations. Therefore, developing assessment tools specific to certain populations becomes particularly important. For instance, a prospective study tailored to the Chinese population suggested that HDL-C, TG, and WC are more accurate indicators of insulin resistance than blood pressure and blood glucose, offering better predictive value for metabolic disorders [36]. In response to this need, Yang et al. developed an age-sex-race-specific MetS severity scoring system tailored to the Chinese

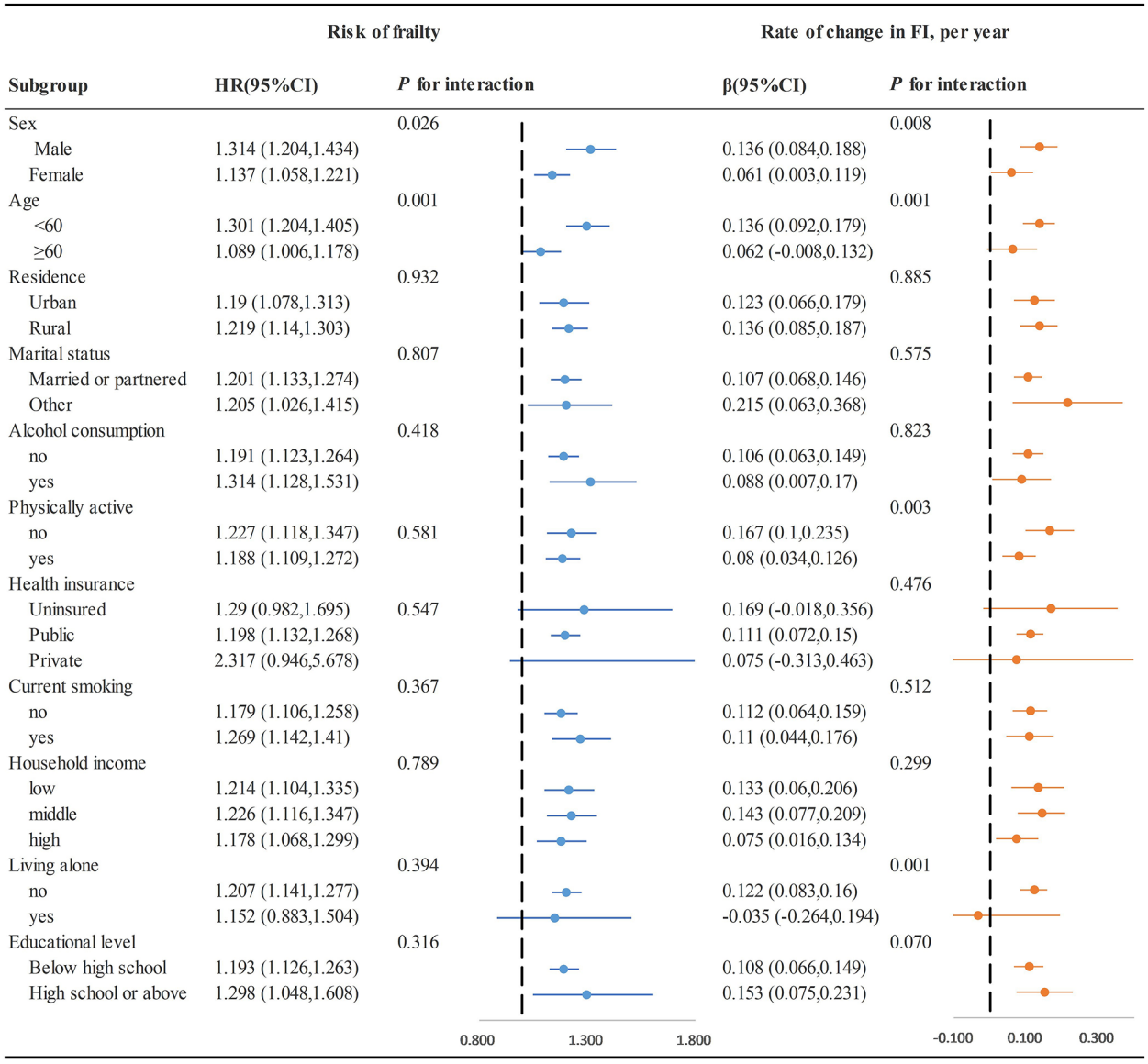

Fig. 3 Association of MetS score and the risk of frailty and FI trajectory stratified by participant characteristics. β Coefficient was estimated using linear mixed models, with the positive value representing accelerated frailty. Adjusted covariates include sex, age, residence, marital status, alcohol consumption, physically active, health insurance, current smoking, household income, living alone, and educational level. *FI* frailty index score, *HR* Hazard Ratio

population. This innovative system takes into account the diversity of metabolic disorder factors and the impact of demographic characteristics, offering an effective tool for accurately assessing and monitoring the severity and progression of MetS in the Chinese population. This research fills a gap in existing studies and provides new insights for the personalized diagnosis and treatment of MetS.

Our research underscores the significance of the positive correlation between the severity of MetS and the development of frailty. Although the specific mechanisms of interaction between MetS and frailty are not fully understood, possible explanations include factors such as insulin resistance [37] and chronic inflammation [38]. A prospective cohort study from a community found a significant association between insulin resistance, assessed using HOMA-IR, and the risk of frailty in the elderly [39]. Insulin resistance may contribute to skeletal muscle metabolic imbalance and aging, including a reduction in muscle mass and strength, by impairing insulin-dependent glucose handling capacity and reducing blood flow to the muscle microvasculature system, thereby accelerating the onset of frailty [40, 41]. The study also discovered that inflammatory markers in individuals with MetS, including C-reactive protein, interleukins, and tumor necrosis factors, were elevated, which is associated with frailty [32]. The systemic low-grade inflammation triggered by metabolic dysregulation could also lead

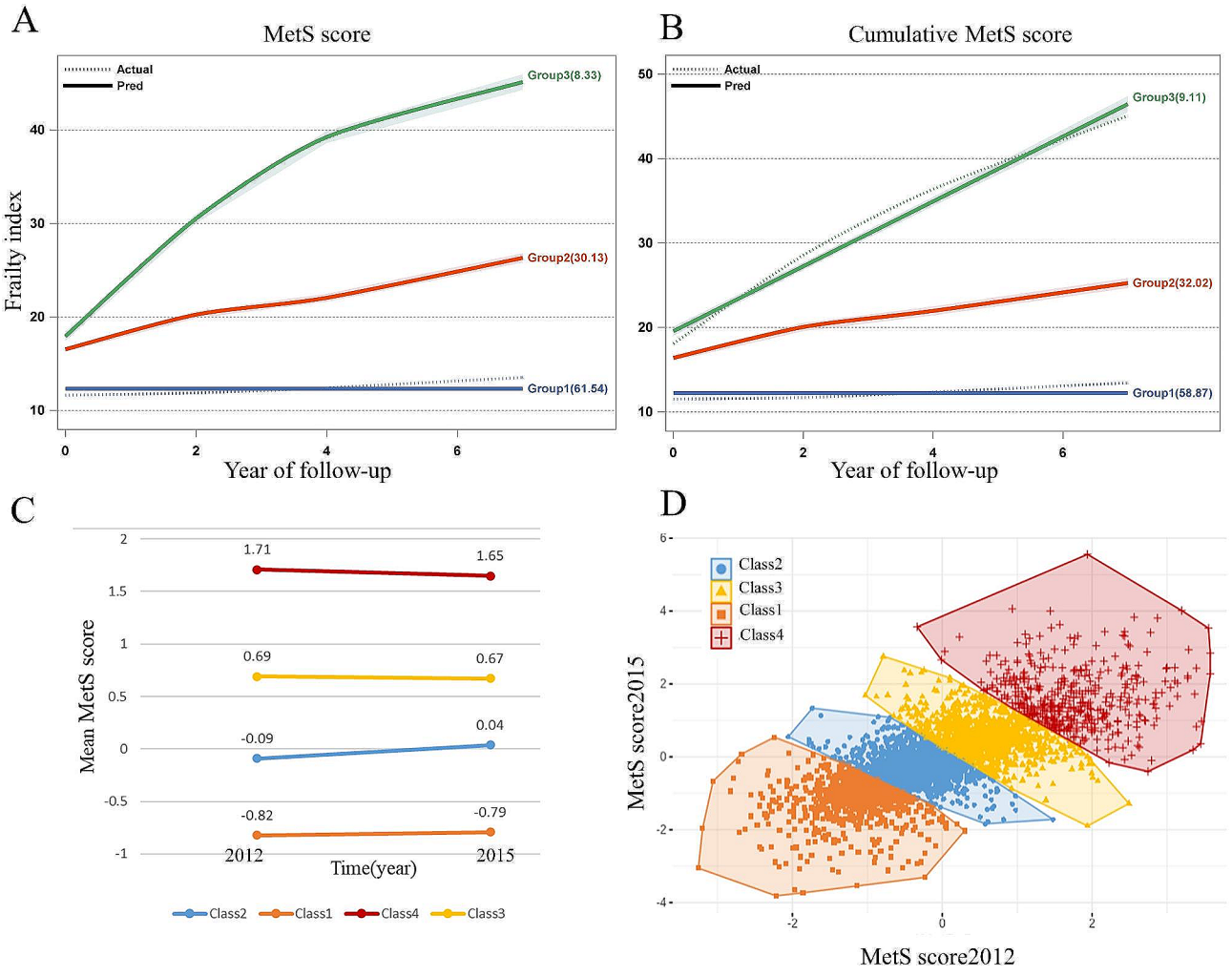

Fig. 4 Sensitivity analysis. **A.** The GBTM method redefinesthe FI trajectory in 6220 non-frail participants with complete MetS score at wave 1. **B.** The GBTM method redefines the FI trajectory in 3632 non-frail participants with complete MetS scores at wave 1 and wave 3. **C.** The changes in MetS score from 2012 to 2015 were visualized by k-means clustering analysis. **D.** Change in mean MetS score between 2012 and 2015 for the four classes based on k-means clustering. *FI* frailty index score, *HR* Hazard Ratio

to multi-organ dysfunction and frailty manifestations such as muscle weakness and physical function decline, through various mechanisms including oxidative stress and endothelial dysfunction [42]. Moreover, stratified analysis results indicate that among participants without frailty at baseline, men, younger individuals, and those physically inactive exhibited a closer relationship between the severity of MetS and the development of frailty. This may explain the variability in sensitivity to metabolic disorders among different populations: men are more prone to abdominal obesity, which is strongly associated with cardiovascular diseases and metabolic issues; younger and male populations, due to an active metabolic state, may show early signs of metabolic stress such as mild insulin resistance and elevated blood pressure earlier. Physical exercise might effectively mitigate the adverse effects of metabolic dysregulation on frailty progression [4]. Our research results indicate that living alone might impact the relationship between MetS score and depression. However, given the small proportion of participants living alone in our sample, there is a potential reduction in statistical power to detect significant associations, or it may result in biased estimates. Therefore, it is essential to conduct further studies with a larger proportion of individuals living alone to validate and elucidate these findings. Further analysis of the Cumulative MetS score and its dynamic changes over the follow-up period revealed a dose-response relationship between the Cumulative MetS score and the risk of frailty in our RCS model. Classifications identified through K-means clustering analysis showed that a persistently high MetS score was most significantly associated with the development of frailty, despite variations, overall based on the level of metabolic dysregulation at baseline. This emphasizes the

importance of early identification and intervention for frailty.

Our study presents several significant strengths. Firstly, our sample is nationally representative and derived from a long-term, prospective cohort study. Secondly, during the follow-up period, not only were data on frailty risk collected but the FI was measured multiple times, employing various methods to define frailty trajectories in the middle-aged and elderly population in China. Additionally, we utilized a newly developed MetS score with age-gender-race specificity to quantify the severity of MetS, making it more suitable for the Chinese population, particularly considering the impacts of age, gender, and ethnicity, and offering advantages such as being non-invasive, easily accessible, and cost-effective. We also calculated the transitions of MetS score, deepening our understanding of the relationship between changes in MetS severity and the progression of frailty. The diversity of sensitivity analyses enhanced the robustness of our results. However, our study is not without limitations. Due to restrictions in the database, only two sets of complete metabolic data were collected, and the follow-up period was relatively short, which may not fully capture the impact of MetS score transitions on frailty. In future research, we will conduct longer follow-up periods to further validate our findings and provide deeper insights into the long-term relationship between MetS severity and frailty progression. The reliance on self-reported questionnaires for FI data subjects our findings to information bias. Additionally, the observational design and the dropout rate during follow-up inevitably introduce selection bias. We cannot rule out the potential impacts of unmeasured or residual confounding factors. For example, chronic diseases such as cardiovascular disease, diabetes, and chronic inflammatory conditions, as well as acute health events occurring during the follow-up period, such as infections or injuries, and medication use, may affect baseline MetS score and frailty progression. These factors might not have been fully adjusted for, thereby introducing residual confounding. It is important to note that chronic diseases are also components of the frailty score, complicating the interpretation of our findings. To address residual confounding in future research, it is necessary to conduct more detailed health assessments, including comprehensive medical histories and diagnostic evaluations. Extending the follow-up period and conducting repeated measurements of both MetS components and frailty indicators will help capture temporal changes and transient health events, thus reducing residual confounding. Furthermore, our study involves only Chinese participants and uses formulas developed for a specific population, hence the results may not be generalizable to other countries.

Conclusion

This study shows that MetS score and their changes are linked to frailty progression in Chinese middle-aged and older adults. These findings underscore the clinical importance of tracking MetS score to identify individuals at high frailty risk early, guiding preventive and management strategies

Abbreviations

CHARLS	China health and retirement longitudinal study
MetS	Metabolic syndrome
MetS score	Metabolic syndrome score
FI	Frailty Index
TG	Triglycerides
WC	Waist circumference
HDL-C	High-density lipoprotein cholesterol
FBG	Fasting blood glucose
MAP	Mean arterial pressure
HRs	Hazard ratios
IQR	Interquartile range
SD	Standard deviation
ORs	Odds ratios
CIs	Confidence intervals
Ref.	Reference
RCS	Restricted cubic splines
GBTM	Group-based trajectory modeling

Supplementary Information

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Supplementary Material 1

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Author contributions

The study was conceived and designed by CJ, FL, and PZ. The data was acquired, analyzed, and interpreted by PZ, MJ-L, CJ, FL, and. The initial draft of the manuscript was prepared by PZ and JX-C, while CJ and FL provided critical revisions. All authors have given their final approval and have agreed to take responsibility for the integrity and accuracy of the work.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

As this study was derived from a public database, no additional ethics approval was required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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