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Associations of metabolic heterogeneity of obesity with frailty progression: Results from two prospective cohorts

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Abstract

Background Previous studies indicated that obesity would accelerate frailty progression. However, obesity is heterogeneous by different metabolic status. The associations of metabolic heterogeneity of obesity with frailty progression remain unclear.

Methods A total of 6730 participants from the China Health and Retirement Longitudinal Study (CHARLS) and 4713 from the English Longitudinal Study of Ageing (ELSA) were included at baseline. Metabolic heterogeneity of obesity was evaluated based on four obesity and metabolic phenotypes as metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight/obesity (MHOO), and metabolically unhealthy overweight/obesity (MUOO). Frailty status was assessed by the frailty index (FI) ranging from 0 to 100 and frailty was defined as FI $\geq$ 25. Linear mixed-effect models were used to analyse the associations of metabolic heterogeneity of obesity with frailty progression.

Results In the CHARLS, MUOO and MUNW presented the accelerated FI progression with additional annual increases of 0.284 (95% CI: 0.155 to 0.413, $P < 0.001$) and 0.169 (95% CI: 0.035 to 0.303, $P = 0.013$) as compared with MHNW. MHOO presented no accelerated FI progression (β: -0.011, 95% CI: −0.196 to 0.173, $P = 0.904$) as compared with MHNW. In the ELSA, the accelerated FI progression was marginally significant for MUOO (β: 0.103, 95% CI: −0.005 to 0.210, $P = 0.061$) and MUNW (β: 0.157, 95% CI: −0.011 to 0.324, $P = 0.066$), but not for MHOO (β: -0.047, 95% CI: −0.157 to 0.062, $P = 0.396$) in comparison with MHNW. The associations of MUOO and MUNW with the accelerated FI progression were stronger after excluding the baseline frail participants in both cohorts. The metabolic status changed over time. When compared with stable MHNW, participants who changed from MHNW to MUNW presented the accelerated FI progression with additional annual increases of 0.356 (95% CI: 0.113 to 0.599, $P = 0.004$) and 0.255 (95% CI: 0.033 to 0.477, $P = 0.024$) in the CHARLS and ELSA, respectively. The accelerated FI progression was also found in MHOO participants who transitioned to MUOO (CHARLS, β: 0.358, 95% CI: 0.053 to 0.663, $P = 0.022$; ELSA, β: 0.210, 95% CI: 0.049 to 0.370, $P = 0.011$).

Conclusions Metabolically unhealthy overweight/obesity and normal weight, but not metabolically healthy overweight/obesity, accelerated frailty progression as compared with metabolically healthy normal weight. Regardless of obesity status, transitions from healthy metabolic status to unhealthy metabolic status accelerated frailty progression as compared with stable metabolically healthy normal weight. Our findings highlight the important role of metabolic status in frailty progression and recommend the stratified management of obesity based on metabolic status.

Keywords Frailty; Obesity; Metabolic status; Heterogeneity; Transition

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Introduction

Frailty, characterized by functional declines in multiple physiological systems and increased vulnerability to stressors, is becoming an emerging global health burden.[1–3] A common instrument to measure frailty is the frailty index (FI), which is calculated as the accumulation of multiple age-related health deficits.[3,4] Previous studies found that higher FI increased risks of adverse health outcomes, such as falls, disability, cardiovascular disease, and all-cause mortality.[5–7] However, recent evidence showed that frailty was a dynamic process and could be reversed after effective interventions.[3,8] Therefore, identifying the risk factors of frailty is of great importance, which provides the opportunity to implement the targeted intervention and prevention at a specific time window.

Obesity is a worldwide epidemic and highly prevalent in the middle-aged and older adults.[9,10] Previous studies indicated that obesity was associated with the accelerated frailty progression.[11–13] However, these studies did not take into account the metabolic heterogeneity of obesity. Despite varying around the world, epidemiological surveys showed that about one-third of overweight and obese individuals were metabolically healthy.[14,15] These individuals were classified as metabolically healthy overweight/obesity (MHOO), whereas the others as metabolically unhealthy overweight/obesity (MUOO). This heterogeneity was also observed in individuals with normal weight, which were classified as metabolically healthy normal weight (MHNW) and metabolically unhealthy normal weight (MUNW).[16] Whether the different obesity and metabolic phenotypes have different effects on frailty progression is still unclear. Furthermore, the metabolic status is not stable and changes over time.[17,18] The effects of metabolic status transitions on frailty progression also remain to be elucidated.

To address these knowledge gaps, we used data of two prospective cohorts as China Health and Retirement Longitudinal Study (CHARLS) and English Longitudinal Study of Ageing (ELSA). We aimed to investigate the associations of metabolic heterogeneity of obesity and metabolic status transitions with frailty progression. We hypothesized that MUOO and MUNW, but not MHOO, would accelerate frailty progression as compared with MHNW. Transitions from healthy metabolic status to unhealthy metabolic status (e.g., MHNW to MUNW and MHOO to MUOO) would accelerate frailty progression as compared with stable MHNW.

Methods

Study design and population

This study used data of two prospective cohorts (CHARLS and ELSA), which were conducted in China and United Kingdom, respectively. Detailed study designs of these two cohorts were described in Supplemental Methods. For CHARLS, we used data from wave 1 (2011–2012) to wave 4 (2018) with wave 1 as the baseline. For ELSA, we used data from wave 2 (2004–2005) to wave 7 (2014–2015) with wave 2 as the baseline. The CHARLS and ELSA were approved by the ethics committees of Peking University and London Multi-Centre Research according to the 1964 Declaration of Helsinki, respectively. The informed consent was obtained from each participant in these two cohorts.

Figure 1 shows the selection process of the study population. Participants were recruited if they were aged ≥50 years and attended the blood test or nurse visit at baseline. Participants were excluded if they had no valid data of body mass index (BMI) or BMI < 18.5 kg/m^2 or failed to identify the metabolic status or with missing data >10% items of FI at baseline. Furthermore, participants without the reassessment of FI (loss to follow-up) were excluded. Based on the inclusion and exclusion criteria, 6730 participants from the CHARLS and 4713 participants from the ELSA were included at baseline. Among the baseline eligible participants, 4553 from the CHARLS and 2893 from the ELSA could identify obesity and metabolic status at the second resurvey (wave 3 in the CHARLS and wave 4 in the ELSA). These 7446 participants were included in the transition analyses.

Definitions of obesity and metabolic status

Obesity status was assessed by BMI based on country-specific criteria.[18,19] In the CHARLS, participants were categorized into three groups as normal weight ($18.5 \leq$ BMI < 24.0 kg/m^2), overweight ($24.0 \leq$ BMI < 28.0 kg/m^2), and obesity (BMI ≥ 28.0 kg/m^2). In the ELSA, normal weight, overweight, and obesity were defined as $18.5 \leq$ BMI < 25.0 kg/m^2, $25.0 \leq$ BMI < 30.0 kg/m^2, and BMI ≥ 30.0 kg/m^2, respectively. Metabolic status was assessed based on four metabolic components.[20–22] Participants who met two or more of the following four criteria were classified as metabolically unhealthy: (1) elevated blood pressure, systolic blood pressure (SBP) $\geq$ 130 mmHg or diastolic blood pressure

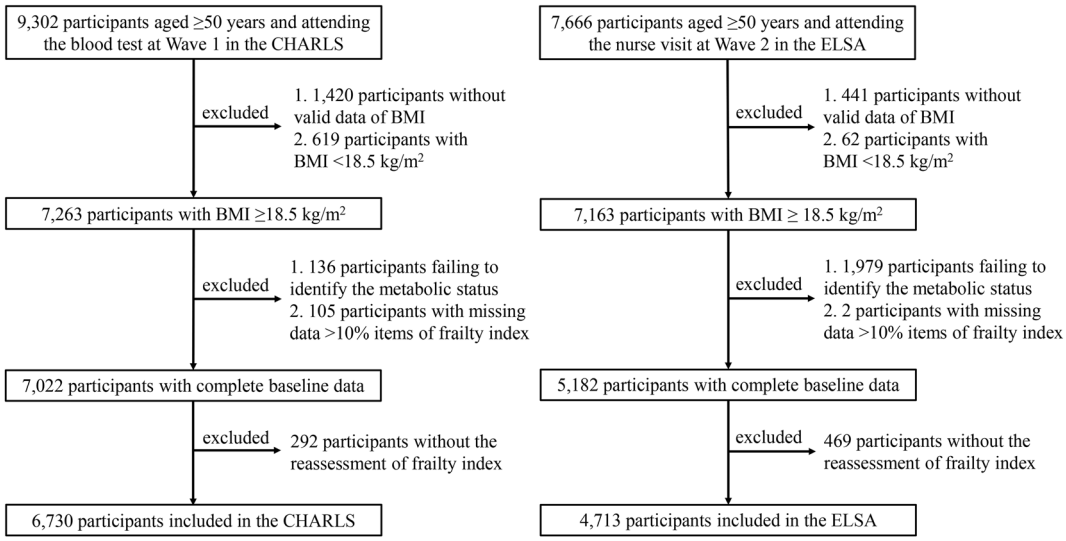

Figure 1 Selection process of the study population at baseline. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; BMI, body mass index.

(DBP) ≥ 85 mmHg or use of antihypertensive drugs; (2) impaired glycemic control, fasting blood glucose (FBG) ≥ 5.6 mmol/L or glycated haemoglobin (HbA_{1c}) ≥ 6.0% or use of antidiabetic drugs; (3) elevated triglyceride (TG), TG ≥ 1.7 mmol/L or use of lipid-lowering drugs; (4) reduced high-density lipoprotein cholesterol (HDL-C), HDL-C < 1.03 mmol/L for men or <1.29 mmol/L for women or use of lipid-lowering drugs. Combined with obesity and metabolic status, participants were divided into four BMI-metabolic phenotypes as MHNW, MUNW, MHOO, and MUOO to evaluate the metabolic heterogeneity of obesity. Four BMI-metabolic phenotypes were identified both at baseline and the second resurvey. Transitions of metabolic status were evaluated based on the changes of BMI-metabolic phenotypes from baseline to the second resurvey (four-year interval).

Assessment of frailty

Frailty was evaluated by the FI, which was calculated as the accumulation of age-related health deficits. We constructed the FI following standard procedures as described previously.[4,23] After screening the data of CHARLS and ELSA, 32 items were selected to construct the FI, including variables of comorbidity, physical function, disability, depression, and cognition (Table S1). Each item was dichotomized into 0 or 1 according to the specific cut-off value except for item 32. The value of 0 indicated the absence of the deficit, and 1 indicated the presence. Item 32 was a continuous variable that ranged from 0 to 1, and a higher value indicated worse cognition. Because the missing rate across 32 items was relatively low (<5%), we imputed the missing data using the median of the corresponding item to maximize the sample size.[24,25] For each participant, the 32-FI was calculated as the sum of present health deficits divided by 32 and multiplied by 100. Therefore, the 32-FI was a continuous variable ranging from 0 to 100, and a higher value indicated a higher degree of frailty. As suggested by previous studies, frailty was defined as the 32-FI ≥ 25.[3,26] The 32-FI was calculated in each wave of the CHARLS and ELSA, respectively. Frailty progression was evaluated by the repeated measurements of FI.

Covariates

The covariates in this study included age, sex, education level, marital status, smoking status, and drinking status. For the consistency of covariate classification between CHARLS and ELSA, education level was divided into two categories as high school or above and below high school. Marital status was classified as married or partnered and other marital status (unmarried, separated, divorced, or widowed). Smoking status was divided into three categories as current smokers, former smokers, and never smokers. Drinking status was assessed based on the frequency of drinking in the last 12 months, and was categorized as ≥1 time per month, <1 time per month, and never drinkers.

Statistical analyses

For descriptive statistics, continuous variables were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]). Categorical variables were presented as number (percentage). Comparisons of the

baseline characteristics were performed with one-way ANOVA or Kruskal–Wallis rank sum tests for continuous variables and Chi-square tests for categorical variables.

To analyse the associations of BMI-metabolic phenotypes with frailty progression, linear mixed-effect models were used to calculate the regression coefficients (β) and 95% confidence intervals (95% CI) with MHNW as the reference. In the linear mixed-effect models, all available repeated measurements of FI (including baseline FI) were included as the outcome variables (Y). BMI-metabolic phenotypes, time (follow-up years since baseline), interaction of BMI-metabolic phenotypes and time, and covariates were included as the exposure variables (X) for fixed effects. The regression coefficients of BMI-metabolic phenotypes indicated the differences in baseline FI as compared with the reference. The regression coefficient of time indicated the overall FI change rate during follow-up (annual FI change). The regression coefficients of interaction terms (BMI-metabolic phenotypes and time) indicated the differences in FI change rates during follow-up (additional annual FI changes) as compared with the reference. Covariates included age, sex, education level, marital status, smoking status, and drinking status. In addition, both the intercept and slope were included as random effects to account for inter-individual differences at baseline and different rates of FI changes during follow-up, respectively. Using similar methods, we also analysed the associations of metabolic status transitions with frailty progression with stable MHNW as the reference.

Several sensitivity analyses were performed: (1) using metabolic syndrome (MetS) criteria[27] to define the metabolic status; (2) additionally adjusting for the C-reactive protein (CRP); (3) using the 30-FI after removing self-reported hypertension and diabetes from the 32-FI to avoid the possible overlap of metabolic status criteria with these two items; (4) using WHO criteria[28] to define the obesity status in the CHARLS, which was consistent with the ELSA. All statistical analyses were performed by R software (Version 4.0.2). All P values were two-sided, and the statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics of the study population

A total of 11 443 eligible participants were included at baseline, including 6730 from the CHARLS (mean [SD] age: 61.6 [7.8] years, female: 52.0%) and 4713 from the ELSA (mean [SD] age: 65.6 [8.9] years, female: 54.9%). The median follow-up periods were 6.9 and 9.7 years in the CHARLS and ELSA, respectively. Table 1 presents the baseline characteristics of the study population by BMI-metabolic phenotypes. In both cohorts, MUOO had the highest means of BMI, WC, SBP,

Table 1 Baseline characteristics of the study population by BMI-metabolic phenotypes

Variables	CHARLS (n = 6730)				ELSA (n = 4713)			
	MHNW	MUNW	MHOO	MUOO	MHNW	MUNW	MHOO	MUOO
Number	1923	1971	668	2168	911	356	1593	1853
Female, *n* (%)	783 (40.7)	1007 (51.1)	384 (57.5)	1327 (61.2)	577 (63.3)	194 (54.5)	891 (55.9)	924 (49.9)
Age, mean (SD), years	61.3 (7.7)	63.3 (8.2)	59.6 (7.0)	61.0 (7.3)	65.0 (8.9)	68.0 (9.5)	64.6 (8.8)	66.2 (8.7)
High school or above, *n* (%)	158 (8.2)	141 (7.2)	77 (11.5)	216 (10.0)	552 (60.6)	191 (53.7)	915 (57.4)	908 (49.0)
Married or partnered, *n* (%)	1690 (87.9)	1595 (80.9)	608 (91.0)	1928 (88.9)	618 (67.8)	234 (65.7)	1201 (75.4)	1329 (71.7)
Current smoker, *n* (%)	778 (40.5)	660 (33.5)	157 (23.5)	463 (21.4)	130 (14.3)	77 (21.6)	131 (8.2)	225 (12.1)
Drink ≥ once a month, *n* (%)	610 (31.7)	503 (25.5)	163 (24.4)	422 (19.5)	742 (81.4)	249 (69.9)	1314 (82.5)	1368 (73.8)
BMI, mean (SD), kg/m^2	21.2 (1.5)	21.7 (1.5)	26.3 (2.7)	27.4 (3.2)	22.7 (1.6)	23.3 (1.4)	28.8 (3.3)	30.6 (4.3)
WC, mean (SD), cm	78.9 (9.2)	81.4 (9.5)	89.6 (11.9)	93.8 (11.6)	82.3 (7.9)	85.7 (7.8)	96.8 (10.1)	102.7 (11.0)
SBP, mean (SD), mmHg	122.0 (18.3)	137.6 (21.9)	125.9 (18.5)	140.1 (21.5)	128.3 (18.5)	139.2 (18.0)	131.6 (17.5)	140.2 (17.4)
DBP, mean (SD), mmHg	70.9 (10.9)	77.2 (11.9)	74.3 (11.3)	80.5 (11.8)	72.2 (10.0)	74.2 (11.1)	75.3 (10.2)	77.3 (11.4)
HbA_{1c}, mean (SD), %	5.11 (0.55)	5.33 (0.93)	5.15 (0.5)	5.51 (1.01)	5.36 (0.38)	5.71 (0.83)	5.40 (0.32)	5.87 (0.95)
FBG, mean (SD), mmol/L	5.49 (1.04)	6.69 (2.55)	5.54 (1.15)	6.79 (2.34)	4.78 (0.45)	5.19 (1.01)	4.82 (0.45)	5.36 (1.25)
TG, mean (SD), mmol/L	0.98 (0.36)	1.70 (1.32)	1.08 (0.35)	2.04 (1.51)	1.14 (0.48)	2.19 (0.96)	1.39 (0.71)	2.38 (1.26)
HDL-C, mean (SD), mmol/L	1.53 (0.37)	1.26 (0.39)	1.42 (0.30)	1.11 (0.31)	1.77 (0.41)	1.48 (0.37)	1.61 (0.34)	1.35 (0.33)
32-FI, median (IQR)	8.4 (4.7–17.4)	11.3 (5.1–20.8)	10.8 (4.7–19.7)	12.1 (6.7–21.2)	7.0 (3.8–11.4)	8.0 (4.4–16.8)	7.4 (3.9–16.4)	13.1 (6.9–22.7)
Frailty, *n* (%)	238 (12.4)	370 (18.8)	89 (13.3)	436 (20.1)	64 (7.0)	56 (15.7)	186 (11.7)	386 (20.8)

Comparisons of the baseline characteristics across four BMI-metabolic phenotypes are performed with one-way ANOVA or Kruskal–Wallis rank sum tests for continuous variables and χ^2 tests for categorical variables. All variables are significantly different ($P < 0.001$) across four BMI-metabolic phenotypes in the CHARLS and ELSA.
CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight/obesity; MUOO, metabolically unhealthy overweight/obesity; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, glycated haemoglobin; FBG, fasting blood glucose; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FI, frailty index.

DBP, HbA_{1c}, FPG, TG, and the lowest mean of HDL-C among four BMI-metabolic phenotypes. MUNW had higher means of SBP, HbA_{1c}, FPG, TG, and a lower mean of HDL-C than MHOO, whereas MHOO had higher means of BMI and WC than MUNW. For frailty, MUOO showed the highest median of FI and the highest percentage of frailty, then followed by MUNW and MHOO, whereas MHNW showed the lowest FI and frailty percentage. The pairwise comparisons of the baseline characteristics among four BMI-metabolic phenotypes are summarized in Tables S2 and S3.

Associations of BMI-metabolic phenotypes with frailty at baseline

After controlling for the covariates, Table 2 shows the associations of BMI-metabolic phenotypes with FI at baseline. In the CHARLS, when compared with MHNW, MUOO had significantly higher FI (β: 2.76, 95% CI: 2.05 to 3.46, $P < 0.001$), then followed by MUNW (β: 1.47, 95% CI: 0.76 to 2.19, $P < 0.001$) and MHOO (β: 1.01, 95% CI: 0.02 to 2.01, $P = 0.047$). Similar results were also observed in the ELSA with significantly higher FI in MUOO (β: 5.62, 95% CI: 4.75 to 6.48, $P < 0.001$), MHOO (β: 2.33, 95% CI: 1.45 to 3.21, $P < 0.001$), and MUNW (β: 1.72, 95% CI: 0.39 to 3.05, $P = 0.011$) as compared with MHNW.

Associations of BMI-metabolic phenotypes with frailty progression

Table 3 shows the associations of BMI-metabolic phenotypes with the FI progression among all participants. In the CHARLS, MUOO and MUNW presented the accelerated progression of FI in comparison with MHNW with additional annual increases of 0.284 (95% CI: 0.155 to 0.413, $P < 0.001$) and 0.169 (95% CI: 0.035 to 0.303, $P = 0.013$), respectively. No accelerated FI progression was found in MHOO (β: -0.011, 95% CI: −0.196 to 0.173, $P = 0.904$) as compared with MHNW. In the ELSA, the accelerated FI progression was marginally significant for MUOO (β: 0.103, 95% CI: −0.005 to 0.210, $P = 0.061$) and MUNW (β: 0.157, 95% CI: −0.011 to 0.324, $P = 0.066$), but not for MHOO (β: -0.047, 95% CI: −0.157 to 0.062, $P = 0.396$) as compared with MHNW. After excluding participants with frailty at baseline, the associations of MUOO and MUNW with the accelerated FI progression were stronger (Table 4). MUOO and MUNW presented additional annual increases of 0.370 (95% CI: 0.236 to 0.503, $P < 0.001$) and 0.272 (95% CI: 0.135 to 0.410, $P < 0.001$) as compared with MHNW in the CHARLS, whereas those were 0.208 (95% CI: 0.098 to 0.318, $P < 0.001$) and 0.215 (95% CI: 0.044 to 0.386, $P = 0.014$) in the ELSA. However, MHOO still presented no accelerated FI progression in both cohorts among the baseline non-frail participants as compared with MHNW. Figures 2 and 3 show the predicted FI

Table 2 Associations of BMI-metabolic phenotypes with the baseline FI

BMI-metabolic phenotypes	CHARLS		ELSA	
	β (95% CI)	*P* value	β (95% CI)	*P* value
MHNW	[Reference]	—	[Reference]	—
MUNW	1.472 (0.758 to 2.186)	<0.001	1.716 (0.387 to 3.046)	0.011
MHOO	1.014 (0.015 to 2.013)	0.047	2.327 (1.446 to 3.209)	<0.001
MUOO	2.757 (2.053 to 3.460)	<0.001	5.616 (4.751 to 6.482)	<0.001

The β and *P* values are adjusted for age, sex, education level, marital status, smoking status, and drinking status.
BMI, body mass index; FI, frailty index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight/obesity; MUOO, metabolically unhealthy overweight/obesity.

Table 3 Associations of BMI-metabolic phenotypes with the FI progression among all participants

BMI-metabolic phenotypes	CHARLS		ELSA	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Time, years	1.066 (0.971 to 1.161)	<0.001	0.667 (0.579 to 0.754)	<0.001
MHNW × Time	[Reference]	—	[Reference]	—
MUNW × Time	0.169 (0.035 to 0.303)	0.013	0.157 (−0.011 to 0.324)	0.066
MHOO × Time	−0.011 (−0.196 to 0.173)	0.904	−0.047 (−0.157 to 0.062)	0.396
MUOO × Time	0.284 (0.155 to 0.413)	<0.001	0.103 (−0.005 to 0.210)	0.061

The β and *P* values are adjusted for age, sex, education level, marital status, smoking status, and drinking status.
BMI, body mass index; FI, frailty index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight/obesity; MUOO, metabolically unhealthy overweight/obesity.

Table 4 Associations of BMI-metabolic phenotypes with the FI progression among non-frail participants

BMI-metabolic phenotypes	CHARLS		ELSA	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Time, years	1.132 (1.036 to 1.227)	<0.001	0.669 (0.582 to 0.756)	<0.001
MHNW × Time	[Reference]	—	[Reference]	—
MUNW × Time	0.272 (0.135 to 0.410)	<0.001	0.215 (0.044 to 0.386)	0.014
MHOO × Time	0.006 (−0.181 to 0.193)	0.947	−0.020 (−0.130 to 0.090)	0.721
MUOO × Time	0.370 (0.236 to 0.503)	<0.001	0.208 (0.098 to 0.318)	<0.001

The β and *P* values are adjusted for age, sex, education level, marital status, smoking status, and drinking status.
BMI, body mass index; FI, frailty index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight/obesity; MUOO, metabolically unhealthy overweight/obesity.

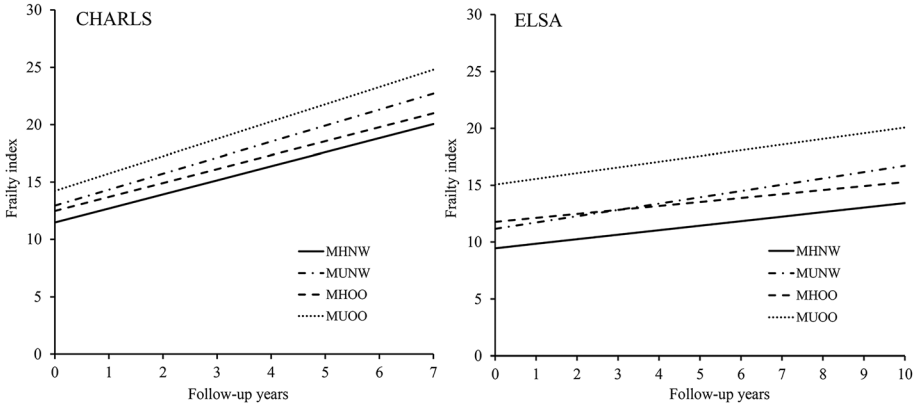

Figure 2 Predicted FI trajectories by four BMI-metabolic phenotypes among all participants. The intercept of each line represents the baseline FI. The slope of each line represents the annual FI increase. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; FI, frailty index; BMI, body mass index; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight/obesity; MUOO, metabolically unhealthy overweight/obesity.

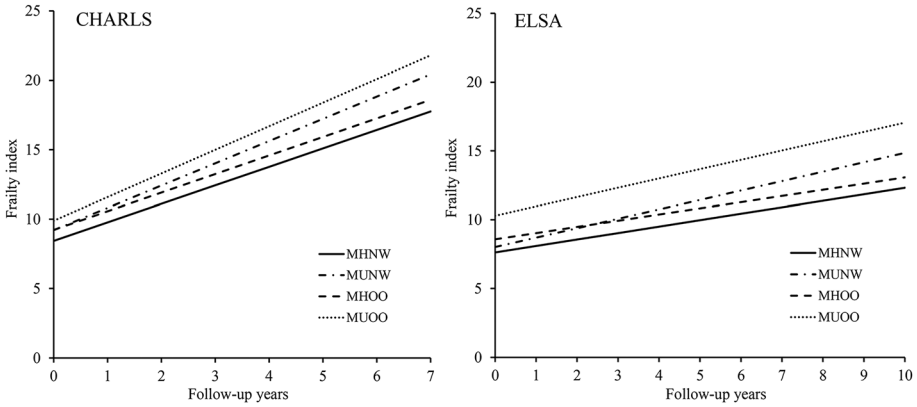

Figure 3 Predicted FI trajectories by four BMI-metabolic phenotypes among non-frail participants. The intercept of each line represents the baseline FI. The slope of each line represents the annual FI increase. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; FI, frailty index; BMI, body mass index; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight/obesity; MUOO, metabolically unhealthy overweight/obesity.

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trajectories by four BMI-metabolic phenotypes among all participants and non-frail participants, respectively.

Associations of metabolic status transitions with frailty progression

The metabolic status changed over time (Table S4). For example, 43.8% and 41.6% of MHOO transitioned to MUOO in the CHARLS and ELSA after 4 years of follow-up. Table 5 shows the associations of metabolic status transitions with the FI progression. When compared with stable MHNW, participants who changed from MHNW to MUNW presented the accelerated FI progression with additional annual increases of 0.356 (95% CI: 0.113 to 0.599, P = 0.004) and 0.255 (95% CI: 0.033 to 0.477, P = 0.024) in the CHARLS and ELSA, respectively. The accelerated FI progression was also found in MHOO participants who transitioned to MUOO (CHARLS, β: 0.358, 95% CI: 0.053 to 0.663, P = 0.022; ELSA, β: 0.210, 95% CI: 0.049 to 0.370, P = 0.011), but not for stable MHOO in comparison with stable MHNW. In addition, stable MUNW and MUOO presented the accelerated progression of FI, whereas participants who changed from MUNW to MHNW and MUOO to MHOO presented neither accelerated FI increase nor decrease in comparison to stable MHNW. For the intergroup comparisons (Table S5), when compared with the stable counterparts, metabolically healthy participants who transitioned to unhealthy metabolic status (MHNW to MUNW and MHOO to MUOO) presented the accelerated progression of FI. In contrast, metabolically unhealthy participants who transitioned to healthy metabolic status (MUNW to MHNW and MUOO to MHOO) presented the attenuated progression of FI.

Sensitivity analyses

Tables S6–S17 show the results of sensitivity analyses including using MetS criteria to define the metabolic status, additionally adjusting for the CRP, and using the 30-FI by removing the self-reported hypertension and diabetes. Consistent with the main analyses, similar results were found in these sensitivity analyses. At baseline, MUNW, MHOO, and MUOO still had higher FI than MHNW. During follow-up, MUOO and MUNW also presented the accelerated FI progression in comparison with MHNW, whereas no accelerated FI progression was found in MHOO. In the transition analyses, the accelerated FI progression was still found in participants who changed from MHNW to MUNW, MHOO to MUOO, and participants with stable MUNW, stable MUOO in comparison with stable MHNW. In addition, consistent results were also observed when using WHO criteria to define the obesity status in the CHARLS (Tables S18–S21).

Discussion

In this study with two prospective cohorts, we examined the associations of metabolic heterogeneity of obesity with frailty progression. When compared with MHNW, MUOO and MUNW presented higher FI at baseline and accelerated progression of FI during follow-up. MHOO only presented higher FI at baseline, but no accelerated progression of FI during follow-up in comparison with MHNW. In addition, the metabolic status changed over time. Transitions from MHNW to MUNW and MHOO to MUOO presented the accelerated progression of FI during follow-up in comparison with stable MHNW.

To our knowledge, this study is the first to investigate the associations of metabolic heterogeneity of obesity with frailty progression. Previous studies have indicated that obesity is associated with the accelerated frailty progression.[11–13] However, obesity is heterogeneous by different metabolic status. Several meta-analyses showed that obesity combined with unhealthy metabolic status presented higher risks of multiple age-related diseases, such as type 2 diabetes, cardiovascular

Table 5 Associations of metabolic status transitions with the FI progression

BMI-metabolic phenotype transitions	CHARLS		ELSA	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Time, years	0.906 (0.762 to 1.049)	<0.001	0.413 (0.292 to 0.533)	<0.001
Stable MHNW × Time	[Reference]	—	[Reference]	—
MHNW to MUNW × Time	0.356 (0.113 to 0.599)	0.004	0.255 (0.033 to 0.477)	0.024
Stable MUNW × Time	0.307 (0.106 to 0.509)	0.003	0.299 (0.055 to 0.544)	0.017
MUNW to MHNW × Time	0.022 (−0.237 to 0.280)	0.869	0.078 (−0.258 to 0.414)	0.650
Stable MHOO × Time	0.063 (−0.258 to 0.385)	0.700	0.061 (−0.093 to 0.216)	0.435
MHOO to MUOO × Time	0.358 (0.053 to 0.663)	0.022	0.210 (0.049 to 0.370)	0.011
Stable MUOO × Time	0.431 (0.250 to 0.611)	<0.001	0.251 (0.110 to 0.392)	<0.001
MUOO to MHOO × Time	−0.058 (−0.381 to 0.265)	0.723	0.046 (−0.165 to 0.257)	0.666

The β and *P* values are adjusted for age, sex, education level, marital status, smoking status, and drinking status.
BMI, body mass index; FI, frailty index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight/obesity; MUOO, metabolically unhealthy overweight/obesity.

diseases, and cancers.[29–31] In our results, we found that MUOO presented the accelerated FI progression as compared with MHNW, but that was not found in MHOO. This finding suggested that MUOO might be a worse phenotype of obesity for frailty progression. Furthermore, the accelerated FI progression was also observed in MUNW as compared with MHNW, which indicated the adverse effects of unhealthy metabolic status on frailty progression. To avoid reverse causality, we also excluded the baseline frail participants and found stronger associations of MUOO and MUNW with the accelerated FI progression.

The metabolic status changes over time.[17,18] A single evaluation of metabolic status at baseline might be insufficient to reflect the effects on frailty progression. Therefore, our study also investigated the transitions of metabolic status. We found that participants who transitioned from MHNW to MUNW and MHOO to MUOO presented the accelerated FI progression in comparison with stable MHNW. This finding further indicated the associations of unhealthy metabolic status with the accelerated frailty progression. Maintaining the metabolic health would be important for preventing frailty progression. This finding also suggested that MHOO might not be a benign condition for frailty progression due to the high likelihood of transition towards MUOO (43.8% in the CHARLS and 41.6% in the ELSA). In contrast, the attenuated FI progression was observed in participants who transitioned from MUNW to MHNW and MUOO to MHOO as compared with stable MUNW and stable MUOO, respectively. This finding suggested the benefits of reversing unhealthy metabolic status for delaying frailty progression.

Obesity and frailty share the similar pathophysiological mechanisms, such as systemic inflammation, insulin resistance (IR), and redox imbalance.[3,32] Previous studies found that MUOO had higher levels of systemic inflammation than MHOO.[33,34] The high levels of systemic inflammation would cause immunosenescence, which impaired the functions of immune cells and induced apoptosis.[35,36] However, our results were not changed after additionally adjusting for the CRP, suggesting the systemic inflammation could not completely explain the difference in frailty progression between MUOO and MHOO. In addition, metabolically unhealthy individuals had higher levels of IR than those with healthy metabolic status.[33,34] The increased IR would accelerate age-related skeletal muscle loss and replace it with adipose tissue (sarcopenia), leading to declines in both muscle mass and strength.[37,38] This view was also supported by the finding that higher skeletal muscle mass and quality were observed in individuals with healthy metabolic status.[39] Therefore, another plausible explanation could be raised that MUOO had higher levels of IR than MHOO, which was more likely to cause sarcopenia, then led to frailty.

Our findings have some clinical and public health implications. First, stratified management of obesity by different metabolic status is necessary for frailty. Individuals with MUOO should be considered as the primary target to prevent frailty progression. Health professionals should evaluate their frailty status regularly and carry out stringent clinical treatments as early as possible. Meanwhile, healthy lifestyle interventions are needed to improve the obesity and metabolic status. For MHOO, maintaining metabolic health is crucial for preventing frailty progression. However, obesity is the main driver for unhealthy metabolic status. Therefore, maintenance of metabolic health combined with control for weight would be the best strategy for MHOO. For MUNW, these individuals were often paid less attention in the health management because of their seemingly normal weight, then delaying interventions. Therefore, distinguishing MUNW from normal weight individuals is important for the prevention of frailty progression.

This study had several strengths. We included two prospective cohorts from different ethnicities with large sample sizes. For the exposure, we considered BMI-metabolic phenotypes both at baseline and their transitions during follow-up. For the outcome, multiple repeated measurements of FI and the use of linear mixed-effect models enabled the comprehensive assessment of frailty progression. Meanwhile, diverse sensitivity analyses ensured the robustness of our results.

This study also had some limitations. First, the definition of metabolic status had no uniform criteria, which might affect the comparability of our results. For this issue, we used the most common definition with four metabolic components from MetS criteria (excluding WC).[27] Meanwhile, we used MetS criteria to define the metabolic status in sensitivity analyses and found consistent results. Second, despite CHARLS and ELSA were sister cohorts with similar designs, heterogeneity still existed between these two cohorts. However, our results were consistent in the CHARLS and ELSA, indicating the generalizability of our findings. Third, the selection bias might occur because 292 (4.2%) participants from the CHARLS and 469 (9.1%) participants from the ELSA were excluded due to loss to follow-up. We compared the baseline characteristics (Table S22) and found that included participants were healthier than excluded participants. However, the rates of loss to follow-up were relatively low, suggesting the potential bias was small. Similarly, the selection bias might occur in the transition analyses (Table S23). Finally, although we had adjusted for multiple covariates, other residual confounding or unmeasured variables might remain, such as diet and genetic susceptibility.

Conclusions

In summary, metabolically unhealthy overweight/obesity and normal weight, but not metabolically healthy over-

weight/obesity, accelerated frailty progression as compared with metabolically healthy normal weight. Regardless of obesity status, transitions from healthy metabolic status to unhealthy metabolic status accelerated frailty progression as compared with stable metabolically healthy normal weight. Our findings highlight the important role of metabolic status in frailty progression and recommend the stratified management of obesity based on metabolic status.

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Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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