

Original Article

Metabolic Syndrome and Its Components Are Associated with Frailty: A Nationwide Population-Based Study in Taiwan

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ABSTRACT

Background/Purpose: The study aimed to explore association between frailty and metabolic syndrome and its components across different groups.

Methods: The cross-sectional study comprised of 1,006 community-living middle and old-age Taiwanese. Metabolic syndrome defined by using National Cholesterol Education Programme Adult Treatment Panel III guidelines. A frailty index of 35 items derived basing on the standard principles of frailty index development. As opposed to the usual method, frailty index (FI) ≤ 0.08 denoted non-frail; FI ≥ 0.25 indicated frail; the rest were pre-frail. Multivariable logistic regression analysis was employed to investigate associations between frailty and metabolic syndrome.

Results: Of all, 130 individuals (12.9%) were frail and 366 subjects (36.4%), who met criteria of metabolic syndrome, were older and higher BMI, but similar in education years and proportion of smoking and drinking. Both prevalence of frailty (p for trend < 0.001) and metabolic syndrome (p for trend 0.005) increased along with aging. Median of FI and percentage of frailty increased along with accumulating counts of metabolic risk factors ($p < 0.001$ for both). Those with metabolic syndrome were strongly associated with frailty status and presenting a dose-dependent effect than their counterparts (OR: 2.4, 95% CI: 1.5-3.8 for prefrail; OR: 3.2, 95%CI: 1.7-6.0 for frail). These associations were stronger in female than male and in older than younger adults.

Conclusion: The study demonstrated associations between frailty and metabolic syndrome and its individual components except low HDL-C, especially in females and older adults.

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Frailty, frailty index, metabolic syndrome, sex-specific analysis.

1. INTRODUCTION

Metabolic syndrome is a cluster of risk factors that

gathering together raises risk of cardio-metabolic diseases such as stroke, myocardial infarction or diabetes.¹ Those posing three or more out of five

components met criteria of metabolic syndrome, which included central obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), high blood pressure or treated for previous hypertension, and impaired fasting glucose or treated for previous diabetes.² Frailty is a concept of increasing vulnerability stem from accumulated multi-system deficits and disrupted homeostasis, and emerging poor health outcomes while threaten by stressors.³ There are two mainstream to describe frailty. One adopted a phenotypic approach and the other used a mathematic method constructed by fraction of accumulated defects counts.^{4,5}

Both metabolic syndrome and frailty are common in the older people and increasing prevalence as aging.^{6,7} Frailty index (FI), based on accumulating physiological deficits, represented a biological rather than chronological and could be a better predictor for biological age than DNA methylation age could.⁸ Epidemiological evidences supported predictive ability of FI on adverse health outcomes such as hospitalization, institutionalization and mortality.^{9,10} Metabolic syndrome has been showed great impacts on cardiovascular health and associated mortality.^{11,12} A study of 1,499 participants aged 60 years and over followed up at a period of 3.5 years affirmed increasing insulin resistance associated with incident frailty.¹³ A cross-sectional study of 3,141 older adults showed positive associations between two major physiological features of metabolic syndrome- insulin-resistance and chronic inflammatory- and incident frailty.¹⁴ A study of 927 Taiwanese showed a positive relationship between relative handgrip strength and cardio-metabolic risk as well as metabolic syndrome, while handgrip strength could be core component of frailty.¹⁵ A secondary analysis of data from the Beijing Longitudinal Study of Ageing showed clustering of metabolic syndrome and frailty in relation to mortality,¹⁶ which deserved further investigation their reciprocal associations for health promotion purpose.

It is well-known that females live a longer life expectancy than males but experienced more disability, which resulting in female encounter both more frail with regard to poor health conditions and less frail relating to lower mortality risk. A paradox of female-male health outcomes was consistent across populations, which may result in substantially influences on frailty research, especially frailty measured by FI.¹⁷ A secondary data analysis from US National Health and Nutrition Examination Survey tried to investigate paradoxical differences of the association between young and older adults,¹⁸ however, little to known whether presented differences across sex, educational levels and other vulnerable groups. The study aimed to explore the association between FI and metabolic syndrome as well as in different subgroups by using a nation-wide representative population-based cohort.

2. METHODS

2.1. Participants and Study Design

The Social Environment and Biomarkers of Aging Study (SEBAS), a national representative population-based cohort, obtained study sample by using a multistage proportional-to-size sampling strategies to produce a national representative sample of the middle and old-aged Taiwanese. SEBAS aimed to explore the relationship between biopsychosocial characteristics and aging throughout incorporating biological markers and physical examinations. Details of study design, sampling strategies and cohort profile have been reported previously.¹⁹ Briefly, 1,284 of 1,659 participants invited for SEBAS in 2006 received an in-person home interview by well-trained research nurses after they were fully consented. Among them, 1,036 participants attended nearby hospitals for complete physical assessments and overnight fasting blood sampling.³⁰ The participants with incompleteness of biochemistry data were excluded for analysis, which left data of 1,006 participants for analysis. The observational design and reporting format of this study followed STROBE guidelines.²⁰ The Joint Institutional Review Board of Taiwan approved the study protocol and signed informed consent were obtained from all participants. The design and procedures of the study were performed in accordance with the principles of the Declaration of Helsinki.

2.2. Anthropometric and Biochemistry Data

Anthropometric measurements of body height, weight and abdominal circumference were done by standard procedure. Body mass index (BMI) was calculated as body weight in kilograms divided by body height in meter square. All serum biomarkers were collected from overnight fasting participants. Serum levels of fasting glucose, total cholesterol, triglyceride, and HDL-C were measured using commercial kits (Beckman Coulter Synchron LX20 Inc., Fullerton, CA, USA), which had sensitivity of 3 mg/dl, 5 mg/dl, 10 mg/dl, and 5 mg/dl and respective inter-assay coefficients of variance of 1.7%, 1.4%, 1.6% and 3.1%.

Research nurses took blood pressure by an automatic monitor (Omron[®] Model HEM-7011) three times successively with at least one-minute interval between each reading. The average of the three blood pressure measurements were used for analysis.

2.3. Definition of Metabolic Syndrome

Metabolic syndrome defined by using National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guidelines.² Those with any three or more of following measurements met the criteria of metabolic syndrome: 1). waist circumference

greater than 80 cm for women and 90 cm for men; 2). triglyceride level of 150 mg/dl or greater; 3). HDL-C of less than 40 mg/dl for men or less than 50 mg/dl for women; 4). systolic blood pressure of 130 mmHg or greater or diastolic blood pressure of 85 mmHg or greater; and 5). fasting glucose of 100 mg/dl or greater.

2.4. Status of Frailty and Other Covariates

Based on the standard procedures of frailty index (FI) development,⁵ a frailty index of 35 items was created in previous SEBAS cohort and affirmed its association with mortality.¹⁰ As opposed to the usual method, FI ≤ 0.08 denoted non-frail; FI ≥ 0.25 indicated frail; and the rest were pre-frail.²¹ Other covariates such as age, sex, education years, smoke and drink were adjusted in the analytical models due to the potential influences on frailty and metabolic syndrome. Smoke was defined as any tobacco consumption in the past six months.

2.5. Statistical Analysis

The continuous variables were expressed as mean \pm standard deviation, and categorized variables was expressed as number (%). Student t was used to compare numerical differences between groups with or without metabolic syndrome, and Chi square or Fisher Exact test were used for comparison of categorical variables when appropriate. Multivariable logistic regression was used to examine the association between frailty status and metabolic syndrome as well as individual components of metabolic syndrome. Subgroup analysis was conducted at various potential confounders, when crude logistic regression was employed for exploring relation between frailty and metabolic syndrome among age (<65 vs. ≥ 65 year), sex (male vs. female), education years (≤ 6 vs. > 6 years), smoke (yes vs. no), drink (yes vs. no) and BMI (<24.7 vs. ≥ 24.7 kg/m²). A p-value (2-tailed) less than 0.05 was considered statistically significant. All analyses were carried out with the SAS statistical package, version 9.4 (SAS Institute, Inc., Cary, NC).

3. RESULTS

Of all, 130 individuals (12.9%) were frail and 366 subjects (36.4%), who met criteria of metabolic syndrome, were older and higher BMI, but similar in education years and proportion of smoking and drinking (Table 1). Both prevalence of frailty (p for trend <0.001) and metabolic syndrome (p

for trend 0.005) increased along with aging (Figure 1A). Median of FI and percentage of frailty increased along with accumulating counts of metabolic risk factors (p <0.001 for both) (Figure 1B). Those with metabolic syndrome was strongly associated with frailty status and presenting a dose-dependent effect than their counterparts. Of five components constituting metabolic syndromes, all except low HDL-C were associated with frail status (Table 2).

Crude logistic regression analysis showed association

Table 1. Clinical characteristics of all participants.

	All	No Metabolic Syndrome	Metabolic Syndrome	p
n	1,006	640	366	
Age (years)	65.8 \pm 9.5	65.3 \pm 9.3	66.7 \pm 9.8	0.021
Education (years)	7.2 \pm 4.9	7.4 \pm 4.9	6.9 \pm 4.9	0.089
Smoke	195 (19.4)	118 (18.4)	77 (21.0)	0.315
Drink	282 (28.0)	183 (28.6)	99 (27.0)	0.600
Body mass index (kg/m ²)	24.7 \pm 3.4	23.6 \pm 3.1	26.6 \pm 3.1	<0.001

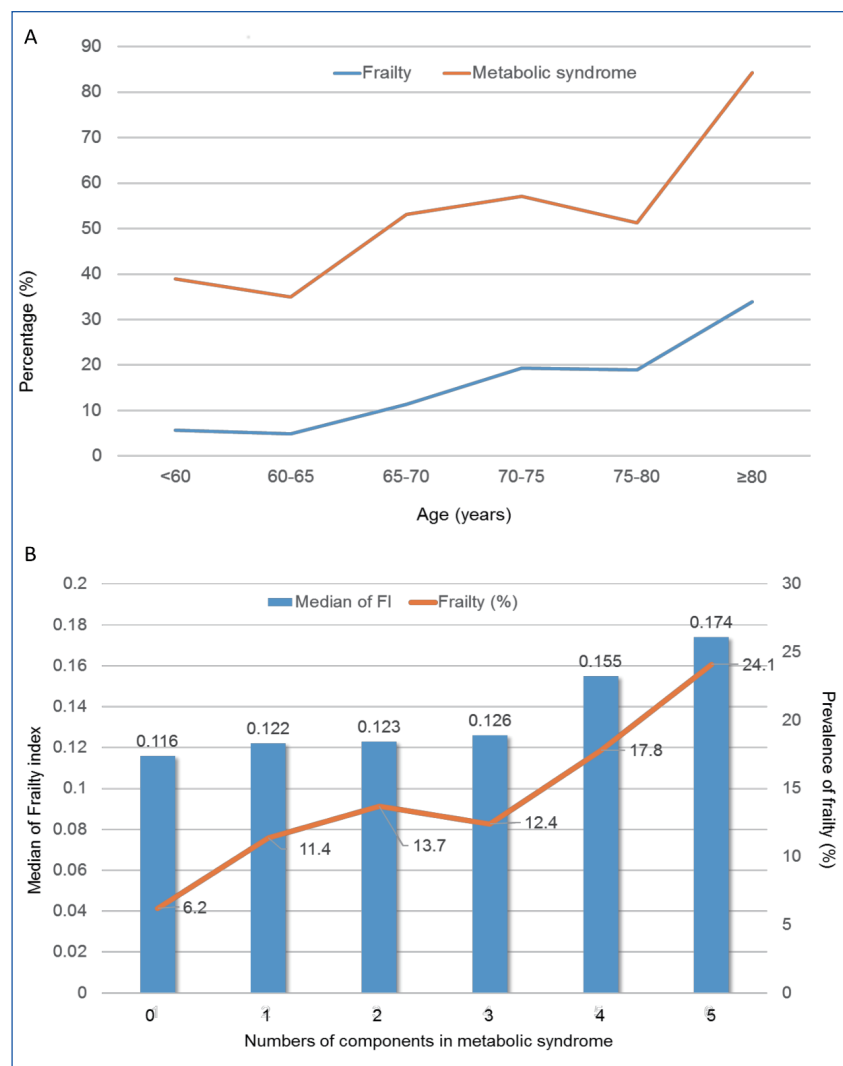
Numerical variable expressed as mean plus/minus standard deviation. Categorical variable expressed as number (percentage).

Table 2. Logistic regression analysis to explore association between frailty status and metabolic syndrome and its components.

	n/Total	Model I OR (95% CI), p	Model II OR (95% CI), p
Metabolic syndrome			
Robust	33/158	1	1
Prefrail	274/718	2.3 (1.5-3.4), <0.001	2.4 (1.5-3.8), <0.001
Frail	59/130	2.9 (1.6-5.0), <0.001	3.2 (1.7-6.0), <0.001
Individual Components			
High blood pressure			
Robust	52/158	1	1
Prefrail	348/718	1.7 (1.2-2.5), 0.003	1.8 (1.2-2.6), 0.004
Frail	80/130	2.8 (1.6-4.7), <0.001	2.8 (1.6-4.9), <0.001
Abdominal obesity			
Robust	48/158	1	1
Prefrail	312/718	1.5 (1.1-2.3), 0.025	1.8 (1.0-3.1), 0.051
Frail	74/130	2.1 (1.2-3.6), 0.006	3.8 (1.7-8.6), 0.001
Impaired glucose			
Robust	55/158	1	1
Prefrail	347/718	1.7 (1.2-2.5), 0.004	1.7 (1.2-2.5), 0.004
Frail	68/130	2.1 (1.2-3.5), 0.006	2.0 (1.2-3.5), 0.009
High triglyceride			
Robust	32/158	1	1
Prefrail	194/718	1.7 (1.1-2.6), 0.018	1.7 (1.1-2.6), 0.026
Frail	41/130	2.7 (1.5-4.8), 0.001	2.6 (1.4-4.8), 0.002
Low high density cholesterol			
Robust	61/158	1	1
Prefrail	311/718	1.2 (0.8-1.7), 0.366	1.1 (0.8-1.7), 0.492
Frail	60/130	1.2 (0.7-2.0), 0.512	1.1 (0.7-1.9), 0.670

OR: odds ratio; CI: confidence interval; Model I: adjusted for age, sex and education; Model II: adjusted for model I plus smoke, drink, body mass index.

Figure 1. Association between frailty and metabolic syndrome by (A) age (B) numbers of metabolic risk factors.



between metabolic syndrome and frailty was stronger in female than male, in older than younger adults, in nonsmokers or nondrinkers than their counterparts, and in lower than higher BMI (Figure 2). Full-adjusted logistic regression showed similar sex-, and age-, specific differences, and not conducted in smoking or drinking groups due to limited numbers of events (data not shown).

4. DISCUSSION

The study showed FI was significant associated with metabolic syndrome by using a nation-wide representative population-based cohort. Moreover, that association was stronger in female than male and in older than younger adults. Of five components constituting metabolic syndromes, FI were significant associated with all individual components except HDL-C. Previous study failed to demonstrate correlations between FI and each components of metabolic syndrome, except a weak correlation for waist circumference.¹⁸ The present study used categorical variable adjusted for relevant confounders

showed positive association between FI and all components except low HDL-C of metabolic syndrome. In addition, items of frailty index created in this analysis did not include components of metabolic syndrome, which might reduce bias introduction, and would be strength of this study.

Diabetes has been proven a risk factor of frailty,²² and findings from the study suggested that high blood pressure, hypertriglyceridemia, abdomen obesity and impaired fasting glucose all contributed to burden of frailty. Interesting, FI or prevalence of frailty increased dramatically when numbers of metabolic components reached four. It reflected nature of FI that sharing the numbers of deficits as important as contexture of deficits themselves. From viewpoint of health promotion intervention, reducing some of these risk factors might attenuate burden of FI.

Sex-difference is one of important issue in the field of frailty research.¹⁷ These differences may be more important for Asian due to unique picture of sarcopenia presenting in both sex when considering different body compositions from Caucasians.²³ The study was the first to look at the sex-specific relationship between FI and metabolic syndrome for Asian. Compared to male, female have higher percentage of adiposity associated with prevalence of metabolic syndrome.²⁴ The stronger association between frailty and metabolic syndrome in female remained significant after adjusting body shape as BMI. Putative mechanism between frailty and metabolic syndrome may be attributable to a cross talk between adipose tissue and skeletal muscle based on fundamental features of insulin resistance and chronic inflammatory.^{25,26} Metabolic syndrome may accelerated skeletal muscle aging as altering glucose-insulin dynamics and disturbing mitochondria function or energy flow.²⁷ Eventually, reducing protein synthesis and glucose uptake and replacing muscle with intramuscular adipose and fibrous tissue resulted into muscle wasting, which is at central position of frailty.^{25,27,28} Based on this biological plausibility, high adiposity in female associated with high prevalence of metabolic syndrome and its stronger association with frailty.

Odds ratio of being frailty among those with metabolic syndrome was higher less educational level group, which was in line with previous study.¹⁸ Low education attainment linked to higher risk of obesity,²⁹ which may

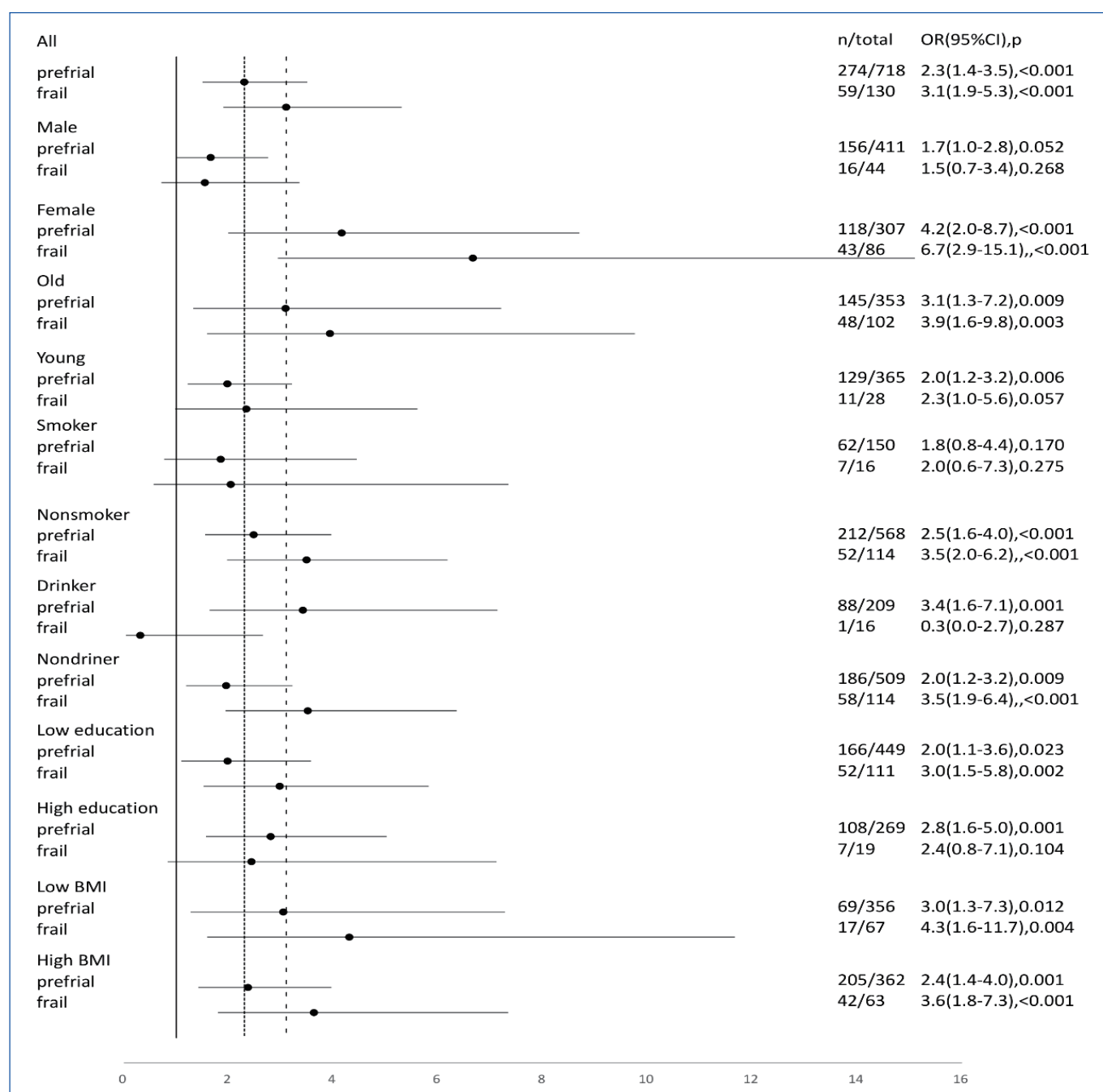
contribute to metabolic syndrome.³⁰ A study of 3,893 participants from the US National Health and Nutrition Examination Survey from 1988 to 1994 showed that significant association between homeostasis model assessment-estimated insulin resistance and frailty was found in the elderly group but not seen in the middle age group.³¹ That finding supports results from our study that stronger association between frailty and metabolic syndrome in the elderly than middle age groups.

There are some limitations in the study. First, temporal and causal relationship between frailty and metabolic syndrome could not be inferred due to inherent limitation of cross-sectional study. Second,

the lack of measurements for body composition in this study may hinder the investigation for influence of interplay between muscle, adiposity and bone on association between frailty and metabolic syndrome, although body mass index was used for adjustment as body shape. Nevertheless, it was hard to conduct precise measurements for body composition in such a national cohort. Lastly, some potential confounders such as diet pattern, protein uptake and daily energy intake and expenditures were not available for the analysis in this study.

In conclusion, this current study demonstrated associations between frailty and metabolic syndrome

Figure 2. Forest plot for exploring association between metabolic syndrome and frailty status across age, sex, education, smoke, drink, and body mass index.



and its individual components except low HDL-C. Furthermore, that association was stronger in female than male and in older than younger adults.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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