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Effect of overweight/obesity and metabolic syndrome on frailty in middle-aged and older Japanese adults

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Abstract

Background: The potential for developing frailty exists in middle-aged and older adults. While obesity and metabolic syndrome (MetS) increase the risk of frailty in older adults, this relationship remains unclear in middle-aged adults, who are prone to developing lifestyle-related diseases.

Objective: To examine the effect of overweight/obesity and MetS on frailty development in middle-aged and older Japanese adults using real-world data.

Methods: This nationwide cohort study used exhaustive health insurance claims data of 3,958,708 Japanese people from 2015 to 2019 provided by the Japan Health Insurance Association. Participants aged ≥35 and < 70 years who received health checkups in 2015 were included. Multivariate logistic regression was used to assess the effect of body mass index (BMI) and MetS or MetS components (i.e., diabetes, hypertension, and dyslipidemia) in 2015 on frailty risk assessed using the hospital frailty risk score in 2019. Additionally, a subgroup analysis was performed to examine the interaction effects of MetS components and 4-year weight change (%) on frailty risk among participants who were overweight and obese (BMI ≥25 kg/m^2).

Results: In 2019, 7204 (0.2%) and 253,671 (6.4%) participants were at high and intermediate frailty risks, respectively. Obesity and MetS were independently associated with intermediate/high frailty risk (odds ratio (OR) 1.36, $p < 0.05$; OR 1.23, $p < 0.05$, respectively) and high frailty risk (OR 1.80, $p < 0.05$; OR 1.37, $p < 0.05$, respectively) in all participants. Although all MetS components were frailty risk factors, these effects diminished with age in both sexes. Subgroup analysis of patients with diabetes revealed that 5%–10% weight loss was associated with reduced frailty risk in both sexes.

Conclusions: Obesity, MetS, and MetS components were independent frailty risk factors in middle-aged and older Japanese adults. Weight loss of up to 10% over 4 years prevented frailty in patients with diabetes who were overweight and obese.

KEYWORDS
frailty, metabolic syndrome, obesity, overweight

1 | INTRODUCTION

Frailty is a common clinical syndrome in older adults and a state of increased vulnerability to poor resolution of homeostasis after a stressful event, increasing the risk of worsening disability, hospitalization, and mortality.[1] Japan is the oldest country in the world, and the proportion of older adults aged ≥65 years was reportedly 29.1% in 2022. The prevalence of pre-frailty and frailty among Japanese older adults aged ≥65 was estimated to be 48.1% and 7.4%, respectively[2]; a recent microsimulation modeling study in Japan showed that the expected need for health care and formal long-term care is anticipated to reach costs of US$125 billion for dementia and $97 billion for frailty per annum in 2043.[3] Moreover, the prevalence of frailty among community-dwelling adults aged ≥50 was estimated at 24% in 62 countries worldwide,[4] and this proportion is expected to increase further with increasing life expectancy. Therefore, preventing the development of frailty is a global health and economic challenge. Although most previous studies have focused on frailty in older adults, Hanlon et al.[5] surveyed the prevalence of frailty in middle-aged and older adults (37–73 years), demonstrating that more than 30% of adults had pre-frailty conditions, which is defined as an intermediate stage between non-frailty and frailty. Therefore, early intervention in middle-aged adults may be necessary for preventing frailty in the senile state.

Being underweight or malnourished is a major risk factor for frailty[6] and unintentional weight loss is one of the components of the well-known frailty phenotype defined by Fried et al.[7] However, in a recent meta-analysis focused on Western population, Jiang et al.[8] showed that obesity is associated with an increased risk of disability in basic activities of daily living (ADLs) or instrumental activities of daily living (IADLs). Watanabe et al.[9] also demonstrated a U-shaped relationship between body mass index (BMI) and the prevalence of frailty, indicating that both obesity and underweight are associated with frailty and disability in IADLs among Japanese older adults. Obesity promotes low-level inflammation, leading to insulin resistance and muscle catabolism, resulting in sarcopenia characterized by decreased muscle mass.[10] Sarcopenic obesity contributes to the risk of frailty and disability in ADLs and IADLs.[11] Moreover, recent meta-analyses have clarified that metabolic syndrome (MetS) is significantly associated with frailty.[12,13] MetS correlates with frailty among young and middle-aged adults (20–65 years) but not older adults (>65 years).[14] Thus, interventions for obesity and MetS in middle-aged individuals might prevent the development of frailty.

However, previous studies that examined the association between obesity and frailty had some shortcomings.[15] First, these studies did not consider the coexistence of diabetes, hypertension, and dyslipidemia; thus, the frailty risk of uncomplicated obesity might be overestimated. Second, only a few longitudinal studies have evaluated the relationship between BMI and/or MetS and frailty in middle-aged populations. Third, it is unclear whether weight reduction in patients with obesity and MetS components decreases or increases the risk of frailty. These points are essential for developing a treatment plan for middle-aged and older adults with obesity at risk of MetS and frailty.

In Japan, The Ministry of Health, Labour, and Welfare introduced Specific Health Checkups, an annual nationwide checkup, to identify individuals at risk of MetS in 2008.[16] These nationwide inspection results have been integrated with data of medical claims, and have become available for analysis. Meanwhile, Gilbert et al.[17] recently developed the hospital frailty risk score based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) diagnostic codes. This algorithm, also applicable to the Japanese claims data, has been reported to be valid in predicting mortality and long-term care unit use among community living older Japanese people.[18] Using this frailty risk score, this study aimed to examine the effect of overweight/obesity and MetS on frailty development in middle-aged and older adults in a nationwide longitudinal cohort data. In addition, as a subgroup analysis, the dose-response relationship between the severity of MetS components and frailty was examined, as well as the interaction between weight changes and MetS components in people with overweight/obesity.

2 | METHODS

2.1 | Study design, participants, and inclusion criteria

A large cohort study was conducted using exhaustive health insurance claims data from 2015 to 2019 provided by the Japan Health Insurance Association, comprising approximately 40 million people aged 0–74. The primary inclusion criteria were: (1) participants aged ≥35 and < 70 years in 2015; (2) subscribers from 1 April 2015, to 31 March 2020; (3) claims data that could be obtained from 2015 to 2019; and (4) those who received health checkups in 2015. Of the 4,385,445 adults who met the primary inclusion criteria, the following were excluded from the present analysis: (1) patients given a treatment or disease code related to pregnancy and childbirth between 2015 and 2019 (n = 29,220), (2) those who have had more than an intermediate risk of frailty in 2015 (n = 193,850), and (3) those with missing health checkup data (n = 203,667). Finally, 260,875 participants with new intermediate/high frailty risk and 3,697,833 participants with low frailty risk after 2015 were analyzed. A flow diagram of the study population selection is shown in Figure 1.

Anonymized data were used in this study. This study was approved by the Ethics Committee of Keio University (approval number [no.]:

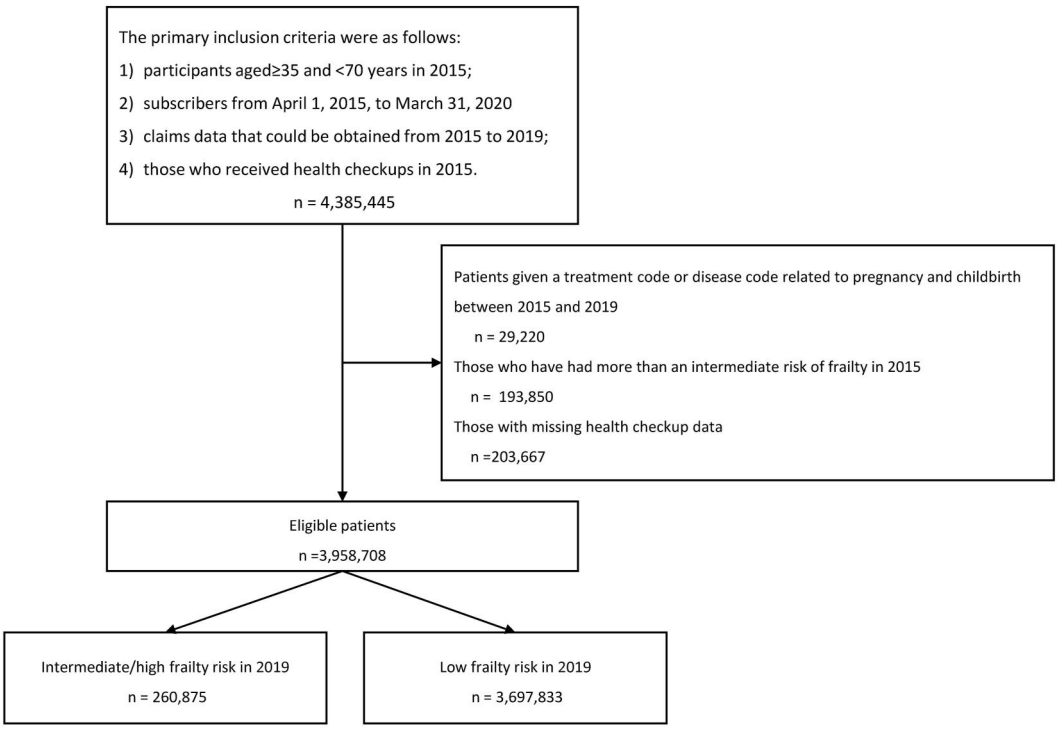

FIGURE 1 Study population selection.

2020-05), Tokyo Medical and Dental University (approval no.: M2020-385), and Tokyo Medical University (approval no.: T2021-0052) and was exempted from the need to obtain informed consent from participants owing to the use of deidentified data.

2.2 | Outcome and exposures

The outcome was defined as the frailty risk evaluated in 2019. Frailty conditions were assessed using the hospital frailty risk score, which evaluated frailty risk by the total number of points awarded for each of the 109 ICD-10 codes.[17] This score did not include diabetes, hypertension, and dyslipidemia and was expected to be able to evaluate frailty independently of MetS. The participants' frailty risks were categorized as low (score <5), intermediate (score 5–15), or high (score >15).

The exposures included BMI, MetS, coexistence of MetS components (i.e., diabetes, hypertension, and dyslipidemia), and weight change (%) from 2015 to 2019. Body mass index (kg/m^2) was classified into seven categories as follows: <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0, where overweight and obesity were defined as BMI of 25.0–29.9 kg/m^2 and BMI ≥30.0 kg/m^2, respectively. Metabolic syndrome was defined according to the Japanese criteria[19] as having a waist circumference of ≥85 cm in men and ≥90 cm in women and meeting two or more of the following criteria[1]: systolic blood pressure ,SBP ≥130 mmHg and/or diastolic blood pressure ,DBP ≥85 mmHg or antihypertensive medication use[2]; fasting serum triglyceride (TG) level ≥150 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) level <40 mg/dL or lipid-lowering medication use; and[3] fasting glucose level ≥110 mg/dL or antidiabetic medication use.

The prevalence of diabetes was defined as a fasting blood glucose level of ≥126 mg/dL or taking antidiabetic medication from the questionnaire. For those who had missing fasting blood glucose data, the data were replaced with the estimated values from the following formula obtained from the 2015 data among participants without diabetic medication.

Estimated fasting blood glucose (mg/dL) = 23.38 × HbA1c (%) −34.31.

The prevalence of hypertension and dyslipidemia was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg or taking antihypertensive medication, and HDL-C level <40 mg/dL and/or TG level ≥150 mg/dL in fasting conditions or taking lipid lowering medication, respectively.

Sex, age, smoking status, residential area, occupation, and comorbidity status were used as potential confounders. As with MetS being potential confounder for the association of obesity and frailty, several other comorbidities might affect the effect of underweight on frailty risk. Of the ICD-10 diagnosis codes not included in the hospital frailty risk score, the following covariate diseases that were frequent in this population and might affect weight change were adopted: respiratory tuberculosis (A16), chronic hepatitis/cirrhosis/liver failure/liver cancer (C22, K72, K74), malignancy (C16, C18, C20, C34, C50, C53, C54, C56, C61, C25, C67, C73, C77, C78, C79, C85), schizophrenia (F20), heart failure (I50), chronic obstructive pulmonary disease (J42, J43, J44), interstitial pneumonia (J84), and connective tissue disease (M06, M32, M35).

2.3 | Statistical analysis

Demographics were presented as numbers and frequency distributions for categorical variables, if appropriate. Multivariate binomial logistic regression was used to assess the effect of BMI and MetS or MetS components on frailty risk according to sex and age group. Odds ratio (OR) (ORs) for two frailty risk categories, high (score ≥15) or intermediate/high (≥5) versus low-risk category (score <5), were examined. If high frailty risk was used as the dependent variable, individuals with intermediate frailty risk (frailty risk score 5–15) were excluded from the analysis. In addition, the dose relationship between the BMI and frailty risk, adjusted for the presence of MetS, was examined using a restricted cubic spline model based on six knots at points 18.5, 20.0, 22.5, 25.0, 27.5, and 30.0. Odds ratio and 95% confidence intervals (CIs) for frailty risk were calculated for each BMI value with respect to the reference BMI value of 22.5 kg/m^2. All the multivariate logistic models were adjusted for age, residential area, occupation, smoking status, and other comorbidities.

Two subgroup analyses were conducted using a multivariate binomial logistic regression model. In the first subgroup analysis, the dose-response relationships between each MetS component and frailty risk were examined among patients who did not take any medication for diabetes, hypertension, and dyslipidemia. The fasting blood glucose levels were classified into four categories; blood pressure was categorized into five by combining systolic and DBP; dyslipidemia was classified into three categories using HDL-C and TG levels. Although dyslipidemia in the MetS is defined by HDL-C and TG levels, the current questionnaire for lipid medication use in Specific Health Checkups also includes low-density lipoprotein cholesterol (LDL-C) lowering medication; thus, LDL-C was added to the analysis and categorized into four groups. In the second subgroup analysis, the impact of weight change (%) from 2015 to 2019 on frailty risk was examined among participants with overweight/obesity in 2015 who received health checkups in 2019; the interaction effects between MetS components and weight change were also evaluated.

All tests were two-sided, using an α level of 0.05 for statistical significance. Multivariable-adjusted ORs and the 95% CIs were calculated using R 4.0.4 statistical software. Multicollinearity for each logistic regression model was checked using the variable inflation factor (car package), with all variable inflation factor values ≤ 2.0. Restricted cubic spline was drawn using the rms package.

3 | RESULTS

Participant characteristics in 2015 are presented in Table 1. The proportion of participants with overweight/obesity (BMI ≥25 kg/m^2) was 28.1%, whereas that of underweight (BMI <18.5 kg/m^2) was 6.9%. Approximately 13.2% of participants had MetS, and males had higher prevalence of MetS and MetS components than females in all age groups. The deterioration of fasting blood sugar levels and blood pressure was observed with age in both sexes. The percentage of poor lipid conditions was almost the same in males in each age group, while older females had worse conditions. In particular, the proportion of women with a higher LDL-C level (≥120 mg/dL) was remarkably higher among females aged ≥50 years. Of the 3,958,708 participants, 7204 (0.2%) were at high frailty risk, and 253,671 (6.4%) were at intermediate frailty risk in 2019.

The prevalence of intermediate/high frailty risk was higher in participants with overweight/obesity (8.0%) than that in underweight (7.4%) participants. Obesity (BMI ≥30 kg/m^2) and MetS were significantly associated with intermediate/high frailty risk (ORs 1.36, 95% CI 1.34–1.39; ORs 1.23, 95% CI 1.21–1.24, respectively) and high frailty risk (OR 1.80, 95% CI 1.62–1.99; OR 1.37, 95% CI 1.28–1.46, respectively) in all participants (Table 2). The results of the multivariate logistic regression analysis that examined the relationship between BMI, MetS components, and frailty risk are presented by sex and age groups in Table 3. Having either underweight or obesity (BMI ≥30.0 kg/m^2) increased frailty risk in both sexes. Although all MetS components were risk factors for frailty, these effects were diminished with age in both sexes. Diabetes and hypertension were associated with frailty risk in males, while the effect of dyslipidemia in females was larger than that in males. When focusing on high risk as the outcome, ORs of high frailty risk for overweight females up to the 60s were higher than those for overweight males, while ORs of underweight females in the 60s were as high as those in males (OR 1.74, 95% CI 1.46–2.17). Figure 2 shows the dose relationship between BMI and frailty risk. There was a U-shaped relationship between BMI and intermediate/high frailty risk, as well as high frailty risk, in both sexes.

Figure 3 shows the dose-response relationship of MetS components and LDL-C on frailty risk in participants without any medications for MetS in 2015 (male, n = 1,925,352; female, n = 1,296,100). In males, higher fasting blood glucose levels and blood pressure increased the risk of frailty; whereas high blood pressure did not show adverse effects on frailty in females. Low HDL-C and high TG levels were significantly associated with frailty risk in both sexes. Low-density lipoprotein cholesterol level <80 mg/dL was a significantly higher risk than LDL-C level 100–120 mg/dL in males but not in females.

Interactions between MetS components and weight change over 4 years for intermediate/high frailty risk among individuals with overweight/obesity are presented in Table 4 (male, n = 763,895; female, n = 256,870). Weight loss of more than 3% was significantly associated with frailty risk in both sexes. In addition, more than 10% weight gain was also associated with increased frailty risk in males (OR 1.20, 95% CI 1.11–1.31) and females (OR 1.22, 95% CI 1.11–1.33). On the contrary, in participants with diabetes, 5–10% weight loss was associated with reduced frailty risk in males (OR 0.87, 95% CI 0.82–0.93) and females (OR 0.83, 95% CI 0.74–0.93). Weight gain of ≥5% in participants with diabetes increased frailty risk in both sexes. As for blood pressure, weight loss of more than 5% in males was significantly associated with frailty risk. Although more than 10% weight loss significantly increased the frailty risk in male participants with dyslipidemia, there was no significant interaction between weight change and dyslipidemia in females.

TABLE 1 Characteristics of participants in 2015.

		Male			Female		
	Total	**35–49 years**	**50–59 years**	**60–69 years**	**35–49 years**	**50–59 years**	**60–69 years**
n	3,958,708	1,455,061	661,256	306,835	823,566	497,148	214,842
BMI (kg/m^2)							
<18.5	271,267 (6.9)	49,726 (3.4)	19,797 (3.0)	9642 (3.1)	113,798 (13.8)	58,570 (11.8)	19,734 (9.2)
18.5–19.9	451,717 (11.4)	112,429 (7.7)	43,510 (6.6)	19,755 (6.4)	163,893 (19.9)	83,248 (16.7)	28,882 (13.4)
20.0–22.4	1,096,394 (27.7)	381,393 (26.2)	161,372 (24.4)	75,836 (24.7)	256,060 (31.1)	155,590 (31.3)	66,143 (30.8)
22.5–24.9	1,028,725 (26.0)	419,818 (28.9)	207,405 (31.4)	104,261 (34.0)	141,625 (17.2)	102,199 (20.6)	53,417 (24.9)
25.0–27.4	609,345 (15.4)	259,575 (17.8)	134,700 (20.4)	64,170 (20.9)	70,744 (8.6)	52,481 (10.6)	27,675 (12.9)
27.5–29.9	285,472 (7.2)	127,862 (8.8)	59,809 (9.0)	23,802 (7.8)	37,196 (4.5)	24,976 (5.0)	11,827 (5.5)
≥30.0	215,788 (5.5)	104,258 (7.2)	34,663 (5.2)	9369 (3.1)	40,250 (4.9)	20,084 (4.0)	7164 (3.3)
Overweight/obesity (BMI≥25 kg/m^2)	1,110,605 (28.1)	491,695 (33.8)	229,172 (34.7)	97,341 (31.7)	141,190 (18.0)	97,541 (19.6)	46,666 (21.7)
MetS	521,640 (13.2)	207,148 (14.2)	161,362 (24.4)	88,482 (28.8)	20,015 (2.4)	25,690 (5.2)	18,943 (8.8)
Weight circumstance							
Male: ≥85, female: ≥90	1,320,293 (33.4)	632,651 (43.5)	330,803 (50.0)	159,829 (52.1)	90,390 (11.0)	69,001 (13.9)	37,619 (17.5)
DM	268,258 (6.8)	74,734 (5.1)	83,977 (12.7)	56,659 (18.5)	14,190 (1.7)	21,117 (4.2)	17,581 (8.2)
Drug use	145,807 (3.7)	35,570 (2.4)	46,469 (7.0)	34,851 (11.4)	6969 (0.8)	11,618 (2.3)	10,330 (4.8)
HT	1,060,212 (26.8)	299,038 (20.6)	283,481 (42.9)	172,683 (56.3)	84,466 (10.3)	128,116 (25.8)	92,428 (43.0)
Drug use	543,328 (13.7)	100,860 (6.9)	156,461 (23.7)	118,142 (38.5)	30,515 (3.7)	73,486 (14.8)	63,864 (29.7)
DL	1,084,280 (27.4)	471,831 (32.4)	257,820 (39.0)	119,369 (38.9)	66,632 (8.1)	96,234 (19.4)	72,394 (33.7)
Drug use	298,899 (7.6)	58,060 (4.0)	76,286 (11.5)	50,151 (16.3)	14,268 (1.7)	50,162 (10.1)	49,972 (23.3)
Smoke	1,262,650 (31.9)	662,114 (45.5)	274,543 (41.5)	98,331 (32.0)	140,729 (17.1)	68,842 (13.8)	18,091 (8.4)
Fasting blood sugar levels (mg/dL)							
<100	2,803,894 (70.8)	1,053,936 (72.4)	360,584 (54.5)	141,047 (46.0)	724,833 (88.0)	381,427 (76.7)	142,067 (66.1)
100–125	956,754 (24.2)	342,790 (23.6)	236,371 (35.7)	124,982 (40.7)	88,486 (10.7)	101,700 (20.5)	62,425 (29.1)
126–155	123,648 (3.1)	32,094 (2.2)	40,658 (6.1)	28,213 (9.2)	5880 (0.7)	9278 (1.9)	7525 (3.5)
156≤	74,412 (1.9)	26,241 (1.8)	23,643 (3.6)	12,593 (4.1)	4367 (0.5)	4743 (1.0)	2825 (1.3)

(Continues)

TABLE 1 (Continued)

	Total	Male			Female		
		35–49 years	50–59 years	60–69 years	35–49 years	50–59 years	60–69 years
Blood pressure (mmHg)							
SBP <120 and DBP <80	1,717,362 (43.4)	613,672 (42.2)	188,239 (28.5)	70,788 (23.1)	533,691 (64.8)	234,794 (47.2)	76,178 (35.5)
SBP: 120–139 or DBP: 80–89	1,538,546 (38.9)	604,665 (41.6)	289,103 (43.7)	139,160 (45.4)	225,962 (27.4)	186,917 (37.6)	92,739 (43.2)
SBP: 140–159 or DBP: 90–99	522,408 (13.2)	171,889 (11.8)	133,943 (20.3)	73,440 (23.9)	48,353 (5.9)	58,593 (11.8)	36,190 (16.8)
SBP: 160–179 or DBP: 100–109	140,841 (3.6)	48,498 (3.3)	39,258 (5.9)	19,241 (6.3)	12,068 (1.5)	13,698 (2.8)	8078 (3.8)
SBP≥180 or DBP≥110	39,551 (1.0)	16,337 (1.1)	10,713 (1.6)	4206 (1.4)	3492 (0.4)	3146 (0.6)	1657 (0.8)
Lipid level							
HDL-C (mg/dL): <40 or TG (mg/dL): 150≤	884,484 (22.3)	441,019 (30.3)	213,743 (32.3)	86,922 (28.3)	55,589 (6.7)	55,586 (11.2)	31,625 (14.7)
HDL-C (mg/dL): 40≤ or TG (mg/dL): <150	3,074,224 (77.7)	1,014,042 (69.7)	447,513 (67.7)	219,913 (71.7)	767,977 (93.3)	441,562 (88.8)	183,217 (85.3)
LDL-C (mg/dL)							
<80	259,890 (6.6)	87,294 (6.0)	42,057 (6.4)	21,625 (7.0)	85,986 (10.4)	16,808 (3.4)	6120 (2.8)
80–99	612,342 (15.5)	206,453 (14.2)	91,406 (13.8)	47,531 (15.5)	188,127 (22.8)	56,022 (11.3)	22,803 (10.6)
100–119	956,701 (24.2)	341,785 (23.5)	153,041 (23.1)	76,110 (24.8)	229,314 (27.8)	109,853 (22.1)	46,598 (21.7)
120≤	2,129,775 (53.8)	819,529 (56.3)	374,752 (56.7)	161,569 (52.7)	320,139 (38.9)	314,465 (63.3)	139,321 (64.8)
Comorbidities (*n*)							
Tuberculosis of lung	15,039 (0.4)	4461 (0.3)	2607 (0.4)	2087 (0.7)	2608 (0.3)	2201 (0.4)	1075 (0.5)
Chronic hepatitis/cirrhosis/liver failure/liver cancer	153,671 (3.9)	53,594 (3.7)	37,063 (5.6)	21,058 (6.9)	17,404 (2.1)	17,342 (3.5)	7210 (3.4)
Malignancy	490,723 (12.4)	105,286 (7.2)	93,737 (14.2)	75,473 (24.6)	111,370 (13.5)	78,681 (15.8)	26,176 (12.2)
Schizophrenia	10,442 (0.3)	4962 (0.3)	1822 (0.3)	426 (0.1)	2264 (0.3)	788 (0.2)	180 (0.1)
Heart failure	104,814 (2.6)	26,699 (1.8)	28,984 (4.4)	23,404 (7.6)	9250 (1.1)	10,481 (2.1)	5996 (2.8)
Chronic obstructive pulmonary disease	27,567 (0.7)	7225 (0.5)	7872 (1.2)	7905 (2.6)	1966 (0.2)	1716 (0.3)	883 (0.4)
Interstitial pneumonia	14,369 (0.4)	2711 (0.2)	2788 (0.4)	2546 (0.8)	2597 (0.3)	2646 (0.5)	1081 (0.5)
Connective tissue disease	83,722 (2.1)	19,262 (1.3)	12,911 (2.0)	7607 (2.5)	19,691 (2.4)	18,370 (3.7)	5881 (2.7)
Intermediate/high frailty risk in 2019	253,671 (6.4)	55,926 (3.8)	44,068 (6.7)	34,714 (11.3)	43,781 (5.3)	42,534 (8.6)	32,648 (15.2)
High frailty risk in 2019	7204 (0.2)	1295 (0.1)	1426 (0.2)	1441 (0.5)	728 (0.1)	931 (0.2)	1383 (0.6)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DL, dyslipidemia; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure.

TABLE 2 Multivariate logistic regression analysis of the association among BMI, MetS, and frailty risk.

Outcome	Variable	Total	Male			Female		
		Adjusted ORs (95% CI)	35–49 years Adjusted ORs (95% CI)	50–59 years Adjusted ORs (95% CI)	60–69 years Adjusted ORs (95% CI)	35–49 years Adjusted ORs (95% CI)	50–59 years Adjusted ORs (95% CI)	60–69 years Adjusted ORs (95% CI)
Intermediate/high risk	BMI							
	<18.5	**1.06 (1.05–1.08)**	**1.11 (1.06–1.17)**	**1.16 (1.09–1.22)**	1.04 (0.97–1.11)	1.02 (0.99–1.06)	**1.06 (1.03–1.10)**	**1.08 (1.03–1.13)**
	18.5–19.9	**0.99 (0.97–0.99)**	0.99 (0.96–1.03)	1.04 (0.99–1.08)	**1.06 (1.01–1.11)**	0.97 (0.94–1.00)	0.97 (0.94–1.01)	0.94 (0.90–0.98)
	20.0–22.4	**0.97 (0.96–0.98)**	0.98 (0.96–1.01)	**0.96 (0.94–0.99)**	**0.97 (0.94–0.99)**	**0.96 (0.93–0.99)**	**0.96 (0.93–0.99)**	0.97 (0.94–1.00)
	22.5–24.9		Ref	Ref	Ref	Ref	Ref	Ref
	25.0–27.4	**1.07 (1.05–1.08)**	**1.07 (1.05–1.10)**	**1.07 (1.04–1.10)**	**1.05 (1.02–1.08)**	**1.06 (1.02–1.10)**	**1.08 (1.04–1.13)**	**1.07 (1.03–1.11)**
	27.5–29.9	**1.15 (1.13–1.17)**	**1.17 (1.14–1.21)**	**1.14 (1.10–1.18)**	**1.14 (1.09–1.19)**	**1.17 (1.12–1.23)**	**1.12 (1.07–1.18)**	**1.08 (1.02–1.14)**
	≥30.0	**1.36 (1.34–1.39)**	**1.43 (1.39–1.48)**	**1.37 (1.32–1.43)**	**1.27 (1.20–1.35)**	**1.31 (1.25–1.37)**	**1.24 (1.18–1.31)**	**1.15 (1.08–1.24)**
	MetS	**1.23 (1.21–1.24)**	**1.29 (1.26–1.33)**	**1.21 (1.18–1.24)**	**1.19 (1.16–1.22)**	**1.31 (1.24–1.39)**	**1.29 (1.23–1.35)**	**1.23 (1.18–1.29)**
High risk	BMI							
	<18.5	**1.39 (1.26–1.54)**	**1.57 (1.18–2.10)**	**1.80 (1.38–2.34)**	**1.56 (1.17–2.08)**	1.17 (0.89–1.52)	1.20 (0.94–1.53)	**1.56 (1.28–1.90)**
	18.5–19.9	1.09 (0.99–1.19)	0.96 (0.75–1.24)	**1.32 (1.06–1.64)**	**1.31 (1.04–1.66)**	0.87 (0.67–1.13)	1.21 (0.97–1.51)	1.07 (0.88–1.30)
	20.0–22.4	1.06 (0.99–1.13)	0.97 (0.83–1.14)	1.00 (0.86–1.17)	**1.21 (1.04–1.41)**	1.09 (0.87–1.36)	1.10 (0.90–1.34)	1.04 (0.89–1.21)
	22.5–24.9		Ref	Ref	Ref	Ref	Ref	Ref
	25.0–27.4	**1.17 (1.09–1.26)**	1.05 (0.88–1.24)	1.05 (0.90–1.23)	**1.26 (1.09–1.46)**	1.05 (0.77–1.43)	**1.42 (1.12–1.80)**	**1.25 (1.05–1.50)**
	27.5–29.9	**1.22 (1.11–1.34)**	1.12 (0.91–1.37)	1.07 (0.87–1.30)	**1.30 (1.06–1.59)**	1.07 (0.73–1.57)	1.36 (0.99–1.87)	**1.34 (1.05–1.71)**
	≥30.0	**1.80 (1.62–1.99)**	**1.73 (1.42–2.11)**	**1.59 (1.29–1.97)**	**1.56 (1.19–2.04)**	**1.92 (1.37–2.68)**	**1.97 (1.42–2.72)**	**1.45 (1.08–1.94)**
	MetS	**1.37 (1.28–1.46)**	**1.53 (1.32–1.78)**	**1.34 (1.17–1.53)**	**1.43 (1.26–1.63)**	**1.85 (1.30–2.64)**	**1.34 (1.02–1.78)**	**1.25 (1.03–1.52)**

Note: Adjusted for age, sex, residential area, occupation, smoking, and comorbidity status in 2015. Bold font indicates statistical significance ($p < 0.05$).

Abbreviations: BMI, body mass index; CI, confidence interval; MetS, metabolic syndrome; Ref, reference.

TABLE 3 Multivariate logistic regression analysis of the association between BMI, MetS components, and frailty risk.

Outcome	Variables	Total	Male			Female		
		Adjusted ORs (95% CI)	35–49 years Adjusted ORs (95% CI)	50–59 years Adjusted ORs (95% CI)	60–69 years Adjusted ORs (95% CI)	35–49 years Adjusted ORs (95% CI)	50–59 years Adjusted ORs (95% CI)	60–69 years Adjusted ORs (95% CI)
Intermediate/high risk	BMI							
	<18.5	**1.13 (1.11–1.15)**	**1.16 (1.11–1.20)**	**1.22 (1.15–1.29)**	**1.08 (1.01–1.15)**	**1.07 (1.03–1.11)**	**1.14 (1.10–1.18)**	**1.16 (1.11–1.22)**
	18.5–19.9	**1.03 (1.01–1.05)**	1.03 (0.99–1.07)	**1.08 (1.03–1.12)**	**1.08 (1.03–1.13)**	1.01 (0.98–1.04)	1.03 (0.99–1.07)	1.00 (0.96–1.04)
	20.0–22.4	0.99 (0.98–1.00)	1.00 (0.98–1.02)	0.98 (0.95–1.00)	**0.96 (0.93–0.99)**	0.99 (0.96–1.04)	1.00 (0.97–1.02)	1.00 (0.97–1.03)
	22.5–24.9		Ref	Ref	Ref	Ref	Ref	Ref
	25.0–27.4	**1.06 (1.04–1.07)**	**1.07 (1.04–1.09)**	**1.06 (1.03–1.09)**	**1.06 (1.02–1.09)**	1.02 (0.98–1.06)	**1.06 (1.03–1.11)**	**1.07 (1.03–1.11)**
	27.5–29.9	**1.12 (1.10–1.14)**	**1.14 (1.11–1.18)**	**1.11 (1.07–1.15)**	**1.14 (1.09–1.19)**	**1.10 (1.05–1.16)**	**1.11 (1.06–1.16)**	**1.10 (1.04–1.16)**
	≥30.0	**1.29 (1.27–1.32)**	**1.32 (1.28–1.36)**	**1.30 (1.25–1.36)**	**1.24 (1.17–1.32)**	**1.20 (1.14–1.25)**	**1.23 (1.17–1.29)**	**1.18 (1.11–1.26)**
	DM	**1.25 (1.24–1.27)**	**1.42 (1.37–1.46)**	**1.25 (1.22–1.29)**	**1.21 (1.18–1.24)**	**1.32 (1.24–1.40)**	**1.21 (1.15–1.26)**	**1.14 (1.09–1.19)**
	HT	**1.25 (1.24–1.26)**	**1.36 (1.33–1.39)**	**1.29 (1.26–1.32)**	**1.20 (1.17–1.23)**	**1.27 (1.23–1.31)**	**1.17 (1.14–1.20)**	**1.17 (1.14–1.20)**
	DL	**1.16 (1.15–1.17)**	**1.11 (1.09–1.13)**	**1.11 (1.09–1.13)**	**1.12 (1.10–1.15)**	**1.29 (1.25–1.33)**	**1.26 (1.23–1.30)**	**1.21 (1.18–1.24)**
High risk	BMI							
	<18.5	**1.58 (1.43–1.75)**	**1.82 (1.36–2.43)**	**2.05 (1.57-2.68)**	**1.61 (1.20–2.14)**	1.29 (0.99–1.69)	**1.39 (1.09–1.79)**	**1.78 (1.46–2.17)**
	18.5–19.9	**1.20 (1.10–1.32)**	1.08 (0.84–1.40)	1.45 (1.17–1.81)	1.30 (1.03–1.64)	0.95 (0.73–1.24)	1.36 (1.09–1.71)	1.18 (0.97–1.43)
	20.0–22.4	**1.11 (1.04–1.19)**	1.04 (0.88–1.22)	1.04 (0.90–1.21)	**1.17 (1.01–1.36)**	1.16 (0.93–1.46)	1.18 (0.97–1.44)	1.10 (0.94–1.28)
	22.5–24.9		Ref	Ref	Ref	Ref	Ref	Ref
	25.0–27.4	**1.14 (1.06–1.23)**	0.98 (0.83–1.16)	1.02 (0.88–1.19)	**1.30 (1.12–1.50)**	0.97 (0.71–1.32)	**1.34 (1.05–1.70)**	**1.23 (1.03–1.47)**
	27.5–29.9	**1.14 (1.04–1.25)**	0.95 (0.77–1.16)	0.98 (0.81–1.19)	**1.32 (1.09–1.61)**	0.95 (0.65–1.39)	1.25 (0.92–1.69)	**1.31 (1.04–1.64)**
	≥30.0	**1.54 (1.40–1.70)**	**1.22 (1.00–1.48)**	**1.35 (1.10–1.66)**	**1.51 (1.16–1.98)**	**1.61 (1.18–2.20)**	**1.71 (1.28–2.30)**	**1.36 (1.03–1.64)**
	DM	**1.64 (1.53–1.75)**	**2.56 (2.19-3.00)**	**1.50 (1.32–1.72)**	**1.51 (1.34–1.70)**	**1.95 (1.38-2.75)**	**1.46 (1.14–1.88)**	**1.54 (1.31–1.81)**
	HT	**1.69 (1.60–1.78)**	**2.08 (1.84–2.36)**	**2.01 (1.79–2.25)**	**1.57 (1.39–1.76)**	**1.68 (1.38–2.06)**	**1.45 (1.26–1.68)**	**1.34 (1.20–1.51)**
	DL	**1.20 (1.14–1.27)**	**1.23 (1.09–1.39)**	**1.13 (1.01–1.26)**	1.05 (0.94–1.18)	**1.56 (1.25–1.94)**	**1.44 (1.23–1.67)**	**1.21 (1.08–1.36)**

Note: Adjusted for age, sex, residential areas, occupation, smoking, and comorbidities status in 2015. Bold font indicates statistical significance ($p < 0.05$).

Abbreviations: BMI, body mass index; CI, confidence interval; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; MetS, metabolic syndrome; ORs, odds ratio; Ref, reference.

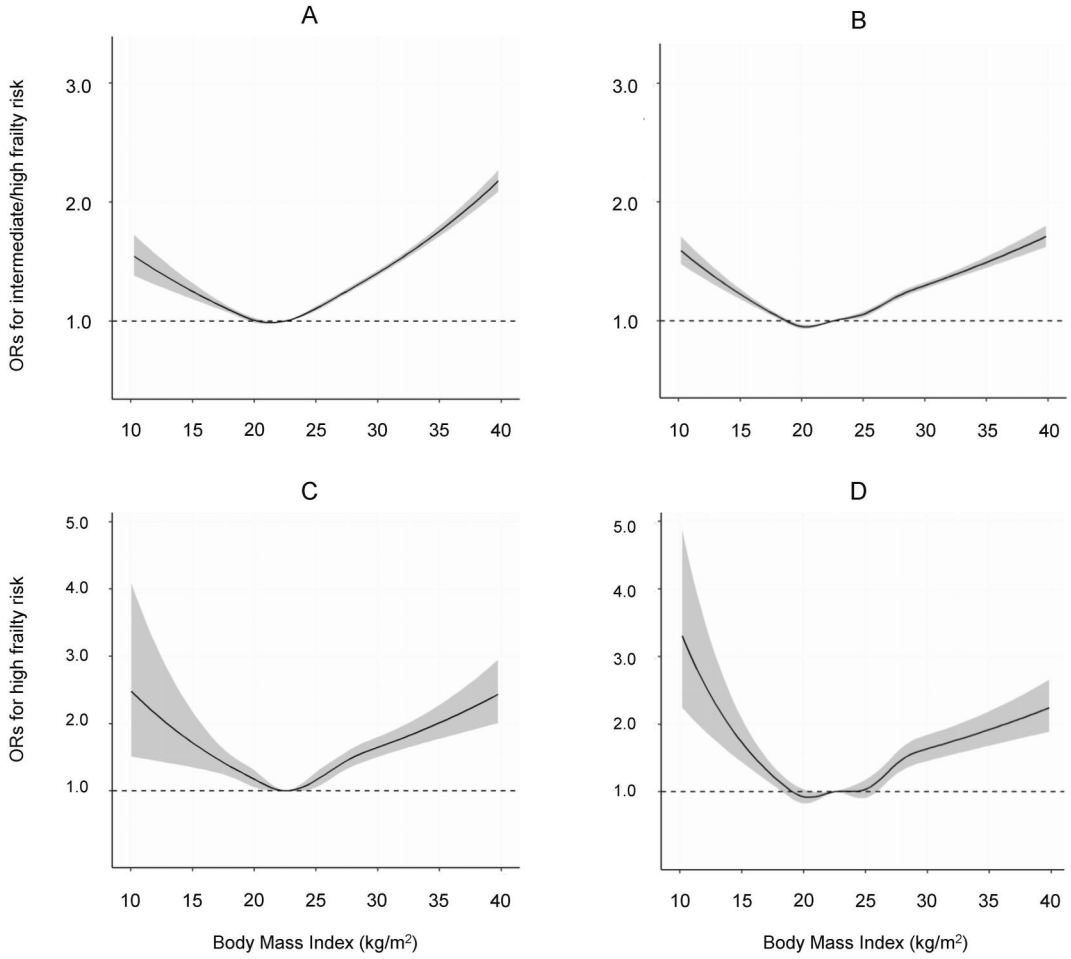

FIGURE 2 The relationship between body mass index (BMI) and frailty using a restricted cubic spline logistic regression model. (A), Intermediate/high-risk outcome in males, (B), intermediate/high-risk outcome in females, (C), high-risk outcome in males, and (D), high-risk outcome in females. Solid lines represent ORs, and dashed lines represent 95% CIs. BMI, body mass index; CI, confidence interval; ORs, odds ratio.

4 | DISCUSSION

This study examined the effect of overweight/obesity and MetS on frailty in the middle-aged and older Japanese adults using real-world data. The frailty score used in the present study was created based on the results of hierarchical cluster analysis, in which 22,139 older adult patients were classified into six clusters: frailty, elective cataracts, chronic heart problems, acute heart problems, cancer and lung disease, and mixed diagnoses, and 109 ICD-10-diagnosis codes with high prevalence in the frailty cluster were used to create the frailty score[17]; that is, the present frailty score is an independent indicator of cardiovascular diseases, such as chronic and acute heart problems. Furthermore, although cardiovascular diseases are associated with frailty risk,[20] the present results suggested that diabetes, hypertension, and dyslipidemia might be related to frailty for reasons other than the development of cardiovascular diseases.

A recent meta-analysis showed that the odds of incident frailty were 1.48 [95% CI, 1.33–1.64] in patients with diabetes.[21] Insulin resistance in diabetes causes skeletal muscular and vascular dysfunctions, leading to frailty.[22] Besides the effect on physical function, type 2 diabetes is also associated with an increased risk of dementia, which is one of the features of frailty.[23] However, the causality between hypertension and frailty has been unclear in previous studies. One possible mechanism is that hypertension is associated with dementia or cognitive impairment.[24] The present frailty score included kidney disease; thus, exacerbating kidney disease associated with hypertension may contribute to frailty.[25,26] Further studies are required to examine which components of the frailty score are affected by diabetes and hypertension.

Low HDL-C and high LDL-C levels are well-known risk factors for cardiovascular diseases, whereas low serum cholesterol levels also indicate malnutrition[27] which is associated with frailty.[28] Wu et al. showed that low LDL-C was associated with long-term all-cause mortality in a cohort of community-dwelling older Chinese adults and suggested the possibility that low LDL-C levels were partially a surrogate marker of frailty.[29] The present findings showing that both low HDL-C and LDL-C levels were related to intermediate/high risk of frailty risk in male supported this hypothesis. Nishimura et al. also

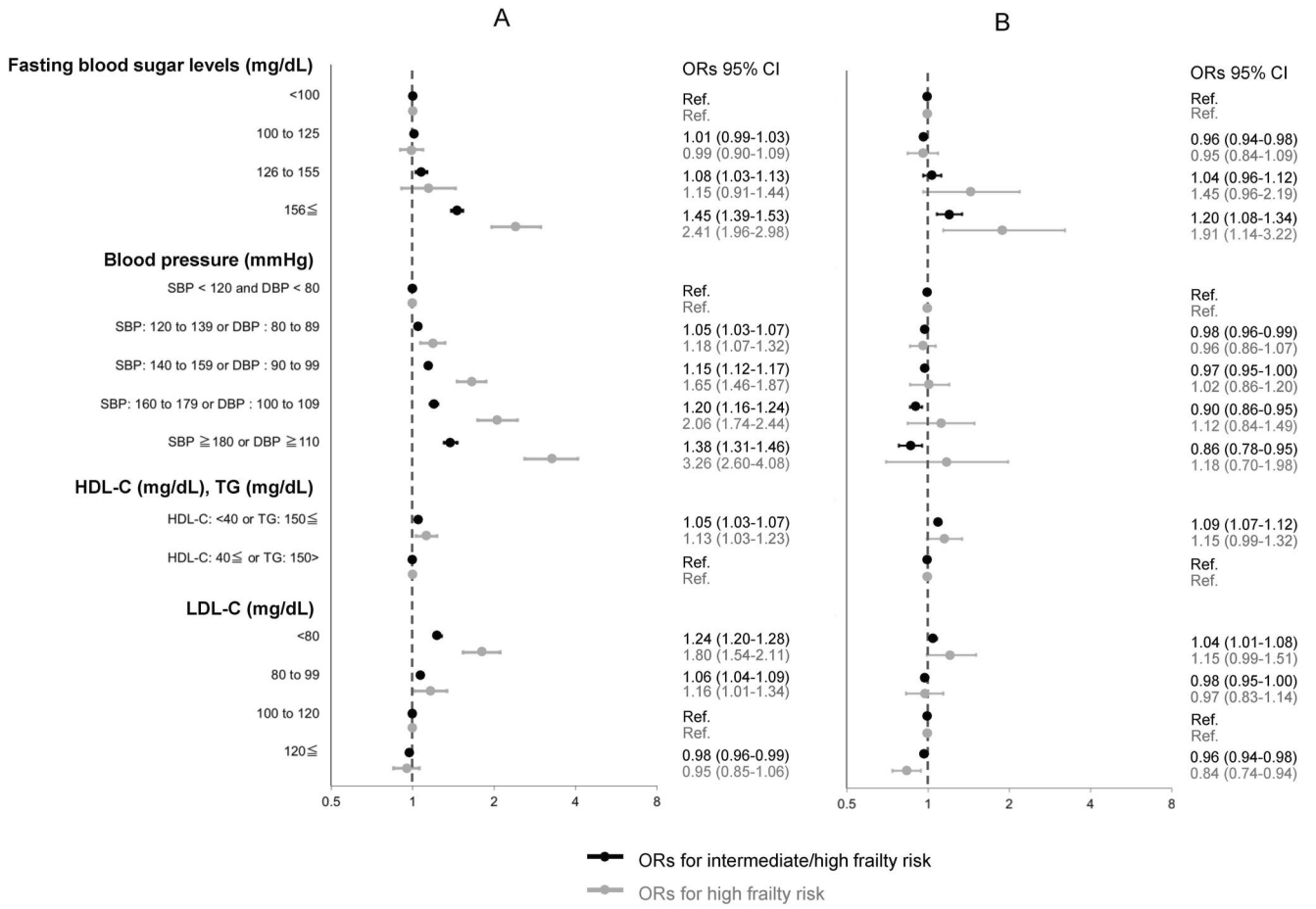

FIGURE 3 Forest plot of subgroup analyses for the risk factors associated with frailty. (A), Male and (B) female. The first odds ratio per carriable (black color) shows intermediate/high-risk outcomes. The second odds ratio per carriable (gray color) shows the high-risk outcomes. CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ORs, odds ratio; SBP, systolic blood pressure; TG, triglyceride.

demonstrated that low LDL-C level was a risk factor for frailty in older Japanese males with diabetes but not in females.[30] The lack of association between low LDL-C and frailty in females might be related to elevated serum total cholesterol and LDL-C levels after menopause.[31] Further studies should clarify the relationship between serum cholesterol levels and frailty.

The prevalence of frailty in older Japanese adults aged ≥65 years was higher in females than that in males,[2] consistent with findings in Western countries.[32] The current results, including middle-aged adults, also showed that the proportion of frailty was higher among females than that among males in all age categories. However, females showed less than half the prevalence of MetS and a smaller effect of MetS on frailty than males. This is partly because more than half of the participants were aged <50, including several premenopausal women whose estrogen levels are protective against obesity and MetS.[33,34] Frailty in the middle-aged female is caused by factors other than MetS.

In this study, the effects of MetS components on frailty were diminished with age. Kane et al.[14] showed that MetS was associated with frailty and mortality in the younger group (<65 years) but not in the older group (≥65 years), which is consistent with the results of the present study. The development of frailty in older adults is more influenced by factors other than MetS, various biological factors related aging as well as changes in socioeconomic status with retirement from full-time employment or multimorbidity.[35] Therefore, comprehensive care, apart from MetS intervention, is essential to prevent frailty in older adults.

Although weight loss is a major risk factor for frailty, the results of this study showed that a weight loss of <10% for 4 years prevented the development of frailty in participants with overweight/obesity and diabetes. Simpson et al. showed that lower HbA1c levels among individuals with diabetes were associated with a smaller increase in frailty scores over 8 years.[36] Accordingly, improving blood glucose levels with weight loss was considered effective in preventing frailty. Serra-Prat et al. examined the effectiveness of a weight-loss intervention in preventing frailty in community-dwelling adults with obesity aged 65–75 years in a randomized control trial[37]; the intervention allowed a reduction in inflammatory and insulin resistance markers with weight loss but was not demonstrated to be effective in preventing frailty owing to a short follow-up period

TABLE 4 Interactions between MetS components and weight change for frailty risk among participants with overweight/obesity (BMI ≥25 kg/m^2).

Variables	Male (n = 763,895) Adjusted ORs (95% CI)	Female (n = 256,870) Adjusted ORs (95% CI)
Weight change rate: <−10%	**1.42 (1.31–1.53)**	**1.69 (1.54–1.84)**
Weight change rate: −10% to −5%	**1.22 (1.15–1.29)**	**1.25 (1.17–1.35)**
Weight change rate: −5% to −3%	**1.09 (1.03–1.17)**	**1.13 (1.05–1.23)**
Weight change rate: −3% to +3%	Ref	
Weight change rate: +3% to +5%	0.99 (0.94–1.05)	0.95 (0.88–1.02)
Weight change rate: +5% to +10%	1.01 (0.96–1.07)	1.00 (0.94–1.07)
Weight change rate: +10%≤	**1.20 (1.11–1.31)**	**1.22 (1.11–1.33)**
DM*		
Weight change rate: <−10%	0.94 (0.86–1.03)	**0.85 (0.73–0.99)**
Weight change rate: −10% to −5%	**0.87 (0.82–0.93)**	**0.83 (0.74–0.93)**
Weight change rate: −5% to −3%	**0.88 (0.82–0.95)**	0.92 (0.81–1.05)
Weight change rate: −3% to +3%	Ref	
Weight change rate: +3% to +5%	**1.19 (1.08–1.32)**	1.12 (0.93–1.34)
Weight change rate: +5% to +10%	**1.16 (1.05–1.28)**	**1.24 (1.04–1.48)**
Weight change rate: +10%≤	**1.26 (1.06–1.51)**	**1.34 (1.01–1.77)**
HT*		
Weight change rate: <−10%	**1.32 (1.21–1.43)**	1.10 (0.98–1.24)
Weight change rate: −10% to −5%	**1.12 (1.05–1.19)**	1.08 (0.99–1.19)
Weight change rate: −5% to −3%	1.02 (0.96–1.10)	0.98 (0.89–1.09)
Weight change rate: −3% to +3%	Ref	
Weight change rate: +3% to +5%	0.96 (0.90–1.03)	0.99 (0.90–1.10)
Weight change rate: +5% to +10%	1.05 (0.99–1.12)	1.00 (0.92–1.10)
Weight change rate: +10%≤	1.06 (0.95–1.18)	1.02 (0.89–1.18)
DL*		
Weight change rate: <−10%	**1.11 (1.02–1.21)**	0.90 (0.80–1.02)
Weight change rate: −10% to −5%	0.99 (0.93–1.05)	0.96 (0.87–1.06)
Weight change rate: −5% to −3%	0.98 (0.92–1.05)	0.96 (0.87–1.07)
Weight change rate: −3% to +3%	Ref	
Weight change rate: +3% to +5%	0.96 (0.90–1.03)	0.94 (0.85–1.04)
weight change rate: +5% to +10%	1.00 (0.94–1.07)	1.01 (0.92–1.11)
Weight change rate: +10%≤	1.01 (0.91–1.12)	1.07 (0.91–1.25)

Note: Adjusted for age, residential areas, occupation, smoking, and comorbidities status in 2015. Bold font indicates statistical significance ($p < 0.05$).

Abbreviations: BMI, body mass index; CI, confidence interval; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; MetS, metabolic syndrome; ORs, odds, ratio; Ref, reference.

(24 months). Therefore, an extended period might be required to examine the effect of diabetes interventions on frailty prevention.

The strength of this study was the analysis of data from middle-aged and older adults prone to developing lifestyle-related diseases and the use of longitudinal analysis to clarify the relationship. Furthermore, this was the first attempt to examine the impact of MetS components on frailty using the hospital frailty risk score based on disease codes obtained from health insurance claims data. However, the present study had some limitations. First, the present database did not include socioeconomic status, such as income or education, associated with frailty mediated by depressive symptoms.[38] Second, this study did not include the alcohol consumption data as a covariate in this analysis because answering the question regarding alcohol consumption was not mandatory; thus, numerous values were missing. Third, the dietary information was not included in the database. Nevertheless, this database is expected to provide

further insights into MetS and frailty. Further studies should analyze the effect of the medication type and weight loss modality (intentional vs. unintentional) on the development of frailty.

5 | CONCLUSION

Obesity and MetS, and MetS components were independent risk factors for frailty in both sexes, whereas the influence of MetS components diminishes with age. Weight loss of up to 10% over 4 years prevented the development of frailty in participants with overweight/obesity and diabetes.

AUTHOR CONTRIBUTIONS

Yuki Nishida analyzed the data, contributed to conceptualization, and wrote the manuscript. Yosuke Yamada and Satoshi Sasaki contributed to the manuscript's conceptualization, discussion, review, and editing. Eiichiro Kanda and Yoshihiko Kanno contributed to the funding acquisition, discussion, review, and editing of the manuscript. Tatsuhiko Anzai, Kunihiko Takahashi, and Keita Yamauchi contributed to the funding acquisition, methodology, discussion, review, and editing of the manuscript. Fuminori Katsukawa contributed to the funding acquisition, conceptualization, methodology, discussion, review, and editing of the manuscript. Yuki Nishida and Fuminori Katsukawa were the guarantors of this work, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

FK received funding from the Japan Health Insurance Association. YN was funded by the Japan Health Insurance Association for one year, from April 2021 to March 2022. The other authors declared no conflict of interest.

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