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RESEARCH ARTICLE

Body mass index, weight change in midlife, and dementia incidence: the Japan Public Health Center-based Prospective Study

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Abstract

INTRODUCTION: Insufficient evidence exists on the sex-specific associations of body mass index (BMI) and weight change through midlife with dementia incidence, especially in Asian populations.

METHODS: For 37,414 Japanese residents aged 40 to 59 years, BMIs at baseline (year 1990 or 1993) and 10-year follow-ups were obtained. Weight changes between baseline and 10-year follow-ups were determined. Disabling dementia incidence from 2006 to 2016 was ascertained using long-term care insurance (LTCI) certifications. Hazard ratios (HRs) were computed.

RESULTS: Increased dementia risk was observed with obesity at baseline and with underweight at 10-year follow-ups. Weight loss after baseline was at greater risk than weight gain. No sex difference was observed.

DISCUSSION: In both sexes, obesity in midlife increased the risk of developing dementia with increasing impacts of weight loss after midlife. A healthy body weight throughout adulthood is beneficial for dementia prevention.

KEYWORDS
body mass index, dementia, JPHC Study, life course, weight change

Highlights

- Obesity in midlife is a risk factor for incident dementia.
- Weight loss is a bigger risk factor than weight gain in later midlife.
- Association of BMI and weight change in midlife with dementia does not vary by sex.

1 | BACKGROUND

The number of individuals with dementia has increased rapidly, reflecting the fact that populations worldwide are aging. Up to 40% of dementia is attributable to a combination of modifiable risk factors.[1] Using a life-course perspective is vital in assessing these risk factors as some risk factors may impact later dementia based on the age at which they are measured.[2] For instance, the harmful effects of midlife obesity as a modifiable risk factor for dementia are well established.[1] However, many studies on the association between body mass index (BMI) in late life and dementia incidence have reported a decreased risk associated with obesity.[3–7] Weight loss from midlife to late life[8] or after

65 years of age[4,9] has been reported to be related to later dementia. These relationships observed after midlife may be affected by reverse causation.[10]

Studies on sex-related differences in the association between BMI and dementia incidence are limited and have shown conflicting results, with some suggesting that higher BMI levels predicted later dementia or Alzheimer's disease (AD) more strongly among women.[11–13] In contrast, one study found that being overweight or obese in midlife only created a higher risk among men and not women.[14] Further, a recent meta-analysis has questioned whether sex differences exist.[15] Moreover, few studies have examined sex-related differences in the relationship between weight change after midlife with later dementia and have shown mixed results.[16,17]

Asian populations generally have lower BMI levels and greater tendencies toward abdominal obesity than non-Asian populations.[18] However, evidence regarding how body weight[19] and weight changes during adulthood affect the incidence of dementia in Asian populations is scarce.

Using data from a nationwide prospective cohort study in Japan, we aimed to examine sex-specific associations of BMI levels at various periods of adulthood and weight change before and after midlife with dementia incidence. In this study, dementia incidence was identified based on certifications in Japan's long-term care insurance (LTCI) system.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched online databases, including PubMed, and the available literature on the association of BMI or weight change over adulthood with dementia incidence was cited.
2. **Interpretation**: Our findings showed that being underweight or slender in midlife was associated with higher dementia risk as well as midlife obesity. After a decade, weight loss was more strongly associated with dementia incidence compared with weight gain, with increased dementia risk among underweight individuals. We found no sex-related differences in these associations.
3. **Future directions**: Future studies are needed to explore the relationship of BMI in early adulthood and weight change from early to midlife with dementia incidence. The mechanism of weight change underlying the associations with dementia incidence and the timing may also require further research.

2 | METHODS

2.1 | Study population

The Japan Public Health Center-based Prospective Study (JPHC Study) is a prospective cohort study of 140,420 residents from 11 public health center areas in Japan. Cohort I included residents aged 40 to 59 years in five regions beginning in 1990, and Cohort II included residents aged 40 to 69 years in six regions starting in 1993.[20] The protocol of the JPHC Disabling Dementia Study, a component of the JPHC Study, was approved by the Institutional Review Boards of the National Cancer Center, Japan, and Kochi University Medical School (Approval No. 2015-312 and 28-132, respectively). Study participants were informed of the purpose of the study; those who completed questionnaires were regarded as having consented to participation.

This study comprised 53,791 participants aged 40 to 59 years who resided in the following eight areas where dementia incidence data were available: Omonogawa and Yokote Districts, Yokote City, Akita Prefecture; Iwase District, Sakuragawa City, and Tomobe District, Kasama City, Ibaraki Prefecture; Usuda District, Saku City, Nagano Prefecture; Kagami and Noichi Districts, Konan City, Kochi Prefecture; and Gushikawa District, Uruma City, Okinawa Prefecture. We excluded ineligible participants, including those of non-Japanese nationality, who were not present from baseline, had incorrect birth data, or had duplicate enrollments ($n = 119$). Additionally, those who had died, had moved out of the study area, or had been lost to follow-up prior to the ascertainment of dementia were excluded (April 1, 2009 for Saku and January 1, 2006 for the other areas) ($n = 9506$). We excluded participants who did not respond to the self-administered questionnaire containing items for height, body weight, lifestyles, and medical histories at baseline ($n = 6464$). Ultimately, 37,414 participants were included in analyses after additional exclusions of participants whose BMIs at baseline were ineligible (<14.0 or ≥40.0) ($n = 29$) or missing ($n = 259$) (Figure 1).

2.2 | Exposure assessment

Participants answered self-administered questionnaires at baseline, 5-year follow-ups, and 10-year follow-ups. We used baseline and 10-year follow-up BMIs for analyses, which were calculated as self-reported weights (in kilograms) divided by self-reported height (in square meters) at each survey time point. Self-reported BMI in the JPHC Study was highly correlated with actual BMI, where the Spearman's rank correlation coefficients were 0.89 in men and 0.91 in women ($n = 15,311$).[21]

Additionally, we calculated the percent weight change between baseline and 10-year follow-up as follows: ((weight at 10-year follow-up) − (weight at baseline))/(weight at baseline) × 100.

At 10-year follow-ups, recalled weights at age 20 were also collected. BMIs at age 20 years were calculated using recalled weights at age 20 and self-reported heights at baseline. Annual percent weight change between 20 years of age and baseline (ie, weight change before baseline) was calculated as follows: (((weight at baseline) − (weight at age 20))/(weight at age 20))/((age at baseline) − 20) × 100.

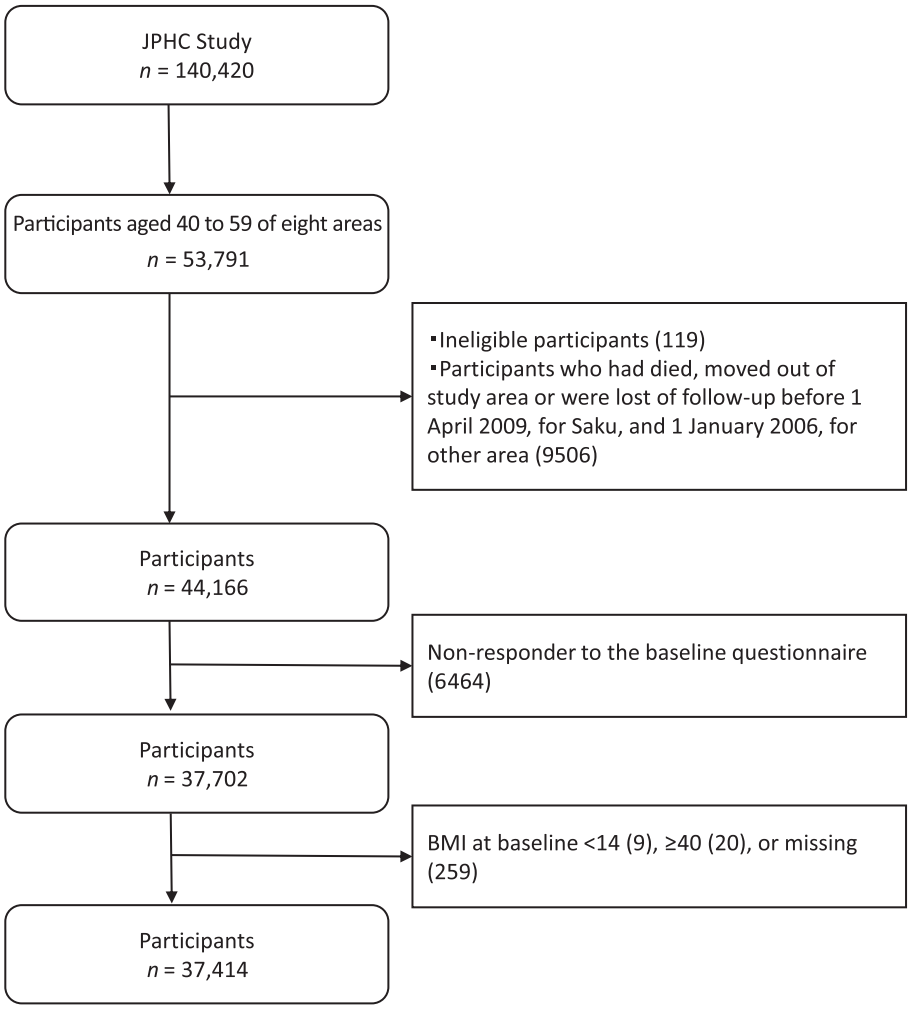

FIGURE 1 Flowchart of study participants.

2.3 | Disabling dementia case ascertainment

Participants with disabling dementia were identified through certification records found in the LTCI system. This insurance system, used throughout the country, was implemented on April 1, 2000, and aimed to support people with physical and mental disabilities related to aging.[22] Individuals aged ≥65 years and between 40 and 64 years with specific age-related diseases, including dementia, that require support or long-term care can benefit from the system. Municipalities provide certifications regarding long-term care requirements for those eligible for benefits based on investigations of their physical and mental condition as well as opinions of a primary care physician. Information on the cause of dementia is not included in the dementia incidence data. We defined disabling dementia as certifications of any level that required long-term care (Care Levels 1 to 5), within the range of severity of cognitive disability (Grades IIa, IIb, IIIa, IIIb, IV, or M) on the dementia rating scale, based on opinions of primary care physicians. Cognitive disability was divided into the following grades: no dementia; some dementia but almost independent in daily life (Grade I); dementia with some difficulty in communicating but with independence in daily living with minimal observation (Grade IIa and IIb); dementia with some difficulty in communicating and a need for partial care (Grade IIIa and IIIb); severe dementia with difficulty in communicating and a need for complete care (Grade IV); and significant psychiatric symptoms, behavioral problems, or serious physical illness and need for specialized medical care (grade M).[23,24] A community-based study ($n = 623$) showed that Grade IIa or higher on the dementia rating scale along with certifications of any level that required long-term care had a sufficient degree of validity concerning dementia diagnoses by neuropsychiatrists: the sensitivity was moderate (73%), and the specificity was high (96%).[24]

In this study, certification records from the LTCI system between 2006 and 2016 were available for most locations, while records from Saku were available only from 2009. Therefore, the starting point for dementia incidence observation was noted as January 1, 2006 (or April 1, 2009, in Saku), and the incidence dates were noted as the date of initial certification that satisfied the disabling dementia criteria, from January 1, 2006 to December 31, 2016.

2.4 | Covariates

Information on covariates at BMI assessment time points was obtained from self-administered questionnaires and included smoking, alcohol intake, and medical histories. Smoking was grouped into five categories: never, former smoker, current smoker of <20 pack-years, current smoker of ≥20 pack-years, and missing. Alcohol drinking habit was also classified into five categories: non-drinker, occasional drinker (one to three times/month), regular drinker (1 to <150 g ethanol/week, ≥150 g ethanol/week), and missing. Medical histories included the following: diabetes mellitus, hypertension, stroke, ischemic heart disease, cancer, and gastrointestinal ulcers. These conditions have been reported as being associated with dementia risk or weight change.[1,4,25] Participants were asked whether they had been diagnosed with each of the aforementioned diseases (yes, no, or missing), except for hypertension, which was defined based on medication use (yes, no, or missing). We examined the validity of self-reporting of disease prevalence and found mixed results (sensitivity and positive predictive values (%), respectively: 83 ($n = 93$) [26] and 94 ($n = 5927$)[27] for diabetes, 53 and 60 for total cancers ($n = 3340$),[28] 73 and 57 for stroke ($n = 1447$),[29] and 82 and 43 for myocardial infarction ($n = 342$).[29] Data on the highest levels of educational achievement (junior high school, high school or more, and others or missing) were available only for participants in Cohort I.

2.5 | Statistical analysis

BMIs at baseline and 10-year follow-ups were divided into the following five categories, according to a recent JPHC Study report[30]: 14.0 to 18.9 kg/m^2 (underweight), 19.0 to 22.9 kg/m^2 (slender), 23.0 to 24.9 kg/m^2 (normal: reference), 25.0 to 26.9 kg/m^2 (overweight), and 27.0 to 39.9 kg/m^2 (obese). Weight changes between baseline and 10-year follow-ups were grouped into three categories based on sex-specific quartiles: lowest quartile (weight loss), interquartile range, and highest quartile (weight gain).

Person-years of follow-up were calculated for each participant from the starting point until the dates of the first occurrence: diagnosis of disabling dementia, migration from a study area, death, or the end of follow-up. We used a Cox proportional hazards model to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). A test based on Schoenfeld residuals did not violate the proportional hazards assumption. We also checked the interactions between each exposure (the five BMI categories at baseline and 10-year follow-up; the three categories of weight change between baseline and 10-year follow-ups) and sex; men and women were analyzed separately.

Three models were considered. Model 1: age was adjusted for. Model 2: additional adjustments were made for smoking and alcohol intake. Model 3: additional adjustments were made for medical histories. Differences in baseline hazards by study area were assumed, and the public health center area was treated as a stratification variable in all models. In Model 2, lifestyle-related covariates were derived from each survey. Medical histories obtained from baseline surveys were used for Model 3, except for analyses of BMI at 10-year follow-ups. In these analyses, participants were considered as having a history of each disease at 10-year follow-ups when the disease was reported at either the 5- or 10-year follow-ups. Models for weight change also included initial BMI levels. We assigned median values in each category to test for a linear trend across exposure categories and treated them as a continuous variable.

We performed supplementary analyses. (1) We calculated HRs and 95% CIs of disabling dementia incidence according to the BMI at 20 years of age and annual percent weight changes between 20 years of age and age at baseline. The exposure categories and the models were the same as those used in the main analyses. Information about covariates at 20 years of age was not available, so we adjusted for smoking, alcohol intake, and medical histories obtained at baseline. (2) Aiming to consider the dementia subtype, we divided the disabling dementia cases into post-stroke dementia and dementia without a history of stroke, intending to represent vascular and non-vascular dementia, respectively. Stroke history was ascertained using the JPHC Study stroke registry from 2006 to 2009 for Cohort I and 2006 to 2012 for Cohort II.[31] However, follow-up periods were limited due to the availability of stroke registry data. Stroke was eliminated as a covariate in Model 3. (3) Educational background was added as a covariate in Cohort I.

Two-tailed p values of $< .05$ were considered statistically significant. All statistical analyses were performed using STATA version 15.1 (STATA Corporation, College Station, TX, USA).

3 | RESULTS

3.1 | Characteristics of study population

Of the 37,414 participants, 3019 (1331 men and 1688 women) had incident-disabling dementia during the 363,023 person-years of follow-up. Among the 37,414 participants, 19,864 (53.1%) were women, and at baseline, the mean age (standard deviation (SD)) was 48.8 (5.8) years for men and 49.2 (5.8) years for women. Sex-specific descriptive statistics for the BMI category at baseline are shown in Table 1. Among women, the average age increased as BMI levels increased, which was not observed among men. Underweight men and women had the highest proportion of current smokers (<20 pack-years and ≥20 pack-years). Underweight men and obese women had the highest proportions of non-drinkers. Men and women with higher BMI levels had higher proportions of hypertension but were less likely to have gastrointestinal ulcers. Moreover, among both sexes, those with obesity had the highest proportions of diabetes mellitus, and underweight and obese women had higher proportions of stroke history.

TABLE 1 Sex-specific baseline characteristics of participants according to body mass index (BMI) at baseline.

	Men						Women					
	BMI at baseline						BMI at baseline					
	Underweight	Slender	Normal	Overweight	Obese		Underweight	Slender	Normal	Overweight	Obese	
Variables	14.0 to 18.9	19.0 to 22.9	23.0 to 24.9	25.0 to 26.9	27.0 to 39.9	*P*	14.0 to 18.9	19.0 to 22.9	23.0 to 24.9	25.0 to 26.9	27.0 to 39.9	*P*
N (%)	625 (3.6)	7007 (39.9)	5038 (28.7)	3062 (17.5)	1818 (10.4)		1074 (5.4)	8548 (43.0)	4899 (24.7)	2936 (14.8)	2407 (12.1)	
Age, mean (SD)	48.8 (6.1)	48.9 (5.9)	48.9 (5.8)	48.8 (5.7)	48.7 (5.6)	.666	48.2 (6.0)	48.6 (5.8)	49.5 (5.8)	49.8 (5.7)	50.4 (5.7)	**<.001**
Smoking status (%)						**<.001**						**<.001**
Never	18.1	20.2	23.5	26.3	26.0		87.2	91.8	92.5	91.7	90.4	
Former smoker	13.6	19.3	24.8	25.9	27.7		1.6	1.1	1.5	1.9	1.9	
Current smoker, <20 pack-years	15.5	11.8	10.1	10.6	7.9		7.4	4.7	3.8	4.0	4.9	
Current smoker, ≥20 pack-years	51.8	47.5	40.6	36.5	37.4		3.5	1.8	1.6	1.7	2.2	
Missing	1.0	1.2	1.0	0.8	1.1		0.4	0.6	0.7	0.7	0.6	
Alcohol drinking habit (%)						**<.001**						**<.001**
Non-drinker	27.7	19.7	18.8	19.7	22.2		75.1	72.3	74.3	74.5	79.9	
Occasional drinker (1 to 3 times/month)	7.5	8.0	10.1	11.3	14.2		8.9	11.8	11.8	11.9	9.9	
Regular drinker, <150 g/week	18.9	21.7	21.3	20.4	19.2		9.6	11.2	10.0	9.8	6.4	
Regular drinker, ≥150 g/week	43.5	47.8	47.3	46.3	42.2		4.2	3.0	2.5	2.3	2.7	
Missing	2.4	2.8	2.5	2.2	2.3		2.1	1.6	1.5	1.5	1.2	
Medical history (%)												
Diabetes mellitus	4.3	4.1	5.0	5.5	6.8	**<.001**	2.0	1.7	1.8	3.2	4.9	**<.001**
Hypertension	6.4	10.6	14.5	19.2	21.7	**<.001**	4.8	8.5	13.3	17.4	25.0	**<.001**
Stroke	0.3	0.3	0.5	0.4	0.4	.480	0.4	0.1	0.2	0.1	0.5	**.014**
Ischemic heart disease	0.5	0.7	0.9	1.2	1.4	**.019**	0.7	0.6	0.6	0.8	0.7	.627
Cancer	1.4	1.1	0.9	1.2	0.6	.194	2.9	2.1	2.6	2.2	2.6	.337
Gastrointestinal ulcer	20.5	15.1	11.1	10.7	10.0	**<.001**	10.9	6.5	5.1	4.1	4.7	**<.001**

Note: Analysis of variance for age and chi-squared test for the other variables. Bold figures mean *p* values of < .05. Abbreviation: SD, standard deviation.

3.2 | BMI and incident dementia

The interaction between the BMI category and sex was not statistically significant regardless of the survey (Table 2). Table 2 shows sex-specific results for BMI at baseline and 10-year follow-up. Regarding the BMI at baseline, slender men (HR 1.27, CI 1.11 to 1.45 in Model 3), underweight women (HR 1.31, CI 1.03 to 1.66 in Model 3), and obese men and women (men: HR 1.31, CI 1.08 to 1.58; women: HR 1.37, CI 1.18 to 1.59; Model 3) had an increased risk of dementia. The *p* value for the apparent linear trend across the various BMI categories was not significant in either sex. In men, the risk of dementia in the underweight category was as high as that in the slender category; however, the HR for underweight versus normal weight categories was not statistically significant. Regarding BMIs at the 10-year follow-ups, obesity among men was no longer associated with a greater dementia risk. The risk remained among women (HR 1.20, CI 1.02 to 1.42 in Model 3), although the absolute HR value at the 10-year follow-up mark was smaller than that at the baseline. In contrast, among both sexes, the absolute HR values in underweight participants at the 10-year follow-up mark increased compared with those at baseline (HR 1.68 vs 1.30 for men and HR 1.67 vs 1.31 for women in Model 3, respectively). A significant negative linear trend was observed in men but not women.

3.3 | Weight change and incident dementia

Table 3 shows sex-specific results for weight change between baseline and the 10-year follow-up. Interactions between weight change and sex were not significant. In the period after baseline, both men and women with the lowest and highest quartiles of weight change had an increased dementia risk. Additionally, Model 3 HRs for the lowest quartiles were greater than those for the highest quartiles (HR 1.49 vs 1.23 in men; HR 1.51 vs 1.21 in women, respectively), with significant negative linear trends noted among both men and women ($p = .007$ and $p < .001$, respectively).

3.4 | Supplementary analyses

The age-adjusted HRs showing the association between obesity at 20 years of age and disabling dementia risk increased in both sexes (Table SA). Among women, however, this association became borderline significant after adjustments for medical history. Regarding weight change before baseline, the lowest quartile (weight loss) among men and the highest quartile (weight gain) among women were at a higher dementia risk (Table SB).

The results of analyses based on the stroke registry are shown in Tables SC and SD. Men with obesity and those who were overweight at 20 years of age and women who were with underweight at 10-year follow-ups were at a high risk of dementia without a stroke history. In contrast, obesity at baseline among men was associated with increased

TABLE 2 Sex-specific hazard ratios (95% confidence intervals) of disabling dementia incidence according to body mass index (BMI) at baseline and 10-year follow-up.

	Men, BMI status						Women, BMI stauts						*P* for interaction between BMI status and sex
Models	Underweight 14.0 to 18.9	Slender 19.0 to 22.9	Normal 23.0 to 24.9	Overweight 25.0 to 26.9	Obese 27.0 to 39.9	*P* for trend	Underweight 14.0 to 18.9	Slender 19.0 to 22.9	Normal 23.0 to 24.9	Overweight 25.0 to 26.9	Obese 27.0 to 39.9	*P* for trend	
BMI at baseline (ages 40 to 59)													
Cases/N	49/625	555 /7007	338 /5038	234 /3062	155 /1818		86/1074	633 /8548	386 /4899	276 /2936	307 /2407		
Model 1	1.28 (0.95 to 1.73)	**1.25 (1.09 to 1.43)**	Reference	1.17 (0.99 to 1.38)	**1.32 (1.09 to 1.60)**	.712	**1.31 (1.03 to 1.65)**	1.09 (0.96 to 1.24)	Reference	1.14 (0.98 to 1.33)	**1.47 (1.27 to 1.71)**	**0.005**	.460
Model 2	1.20 (0.89 to 1.62)	**1.20 (1.05 to 1.38)**	Reference	1.18 (0.9994 to 1.40)	**1.37 (1.13 to 1.67)**	.537	1.26 (0.998 to 1.60)	1.09 (0.96 to 1.24)	Reference	1.13 (0.97 to 1.32)	**1.45 (1.25 to 1.69)**	**0.005**	.864
Model 3	1.30 (0.96 to 1.76)	**1.27 (1.11 to 1.45)**	Reference	1.17 (0.99 to 1.38)	**1.31 (1.08 to 1.58)**	.519	**1.31 (1.03 to 1.66)**	1.11 (0.97 to 1.26)	Reference	1.11 (0.95 to 1.30)	**1.37 (1.18 to 1.59)**	0.084	.792
BMI at 10-year follow-up (ages 50 to 69)													
Cases/N	63/581	461 /5851	291 /4461	203 /2828	139 /1866		104 /1014	512 /7192	327 /4390	251 /2948	255 /2481		
Model 1	**1.72 (1.31 to 2.26)**	**1.22 (1.05 to 1.41)**	Reference	1.10 (0.92 to 1.32)	1.19 (0.97 to 1.46)	**.043**	**1.60 (1.28 to 1.99)**	1.08 (0.94 to 1.24)	Reference	1.10 (0.93 to 1.30)	**1.30 (1.10 to 1.53)**	0.850	.725
Model 2	**1.61 (1.22 to 2.12)**	**1.18 (1.02 to 1.37)**	Reference	1.12 (0.94 to 1.34)	1.21 (0.99 to 1.48)	.195	**1.57 (1.26 to 1.96)**	1.07 (0.93 to 1.23)	Reference	1.10 (0.93 to 1.29)	**1.29 (1.10 to 1.53)**	0.746	.890
Model 3	**1.68 (1.28 to 2.22)**	**1.24 (1.07 to 1.43)**	Reference	1.11 (0.92 to 1.32)	1.17 (0.96 to 1.44)	**.031**	**1.67 (1.33 to 2.08)**	1.09 (0.95 to 1.26)	Reference	1.08 (0.91 to 1.27)	**1.20 (1.02 to 1.42)**	0.334	.905

Note: Model 1 was adjusted for age at baseline and public health center area.
Model 2 was adjusted for age at baseline, public health center area, smoking, and alcohol drinking habit at each survey.
Model 3 was adjusted for age at baseline, public health center area, smoking, alcohol drinking habit, and each history of medical conditions (diabetes mellitus, hypertension, stroke, ischemic heart disease, cancer, and gastrointestinal ulcer) at each survey. In analyses of BMI at 10-year follow-up, participants were considered to have history of each disease at 10-year follow-up when they reported the disease in either 5- or 10-year follow-up. Bold figures mean *p* values of <.05 or hazard ratios with *p* values of <.05.

TABLE 3 Sex-specific hazard ratios (95% confidence intervals) of disabling dementia incidence according to percent weight change between baseline and 10-year follow-up.

	Men				Women				
Models	Quartile 1 Weight loss	Quartiles 2 and 3	Quartile 4 Weight gain	*P* for trend	Quartile 1 Weight loss	Quartiles 2 and 3	Quartile 4 Weight gain	*P* for trend	*P* for interaction between weight change and sex
Range, %	≤ −3.44	−3.43 to 4.00	>4.00		≤−3.70	-3.69 to 4.26	> 4.26		
Cases/N	401/3930	484/7804	272/3853		521/4566	616/8990	312/4469		
Model 1	**1.57 (1.37 to 1.79)**	Reference	**1.26 (1.08 to 1.46)**	**.002**	**1.52 (1.35 to 1.71)**	Reference	**1.22 (1.06 to 1.40)**	**<.001**	.802
Model 2	**1.53 (1.34 to 1.75)**	Reference	**1.23 (1.06 to 1.43)**	**.003**	**1.52 (1.35 to 1.71)**	Reference	**1.21 (1.06 to 1.39)**	**<.001**	.835
Model 3	**1.49 (1.30 to 1.70)**	Reference	**1.23 (1.06 to 1.43)**	**.007**	**1.51 (1.35 to 1.70)**	Reference	**1.21 (1.06 to 1.39)**	**<.001**	.724

Note: Model 1 was adjusted for age at baseline, public health center area, and BMI category at baseline.
Model 2 was adjusted for age at baseline, public health center area, BMI category, smoking, and alcohol drinking habit at baseline.
Model 3 was adjusted for age at baseline, public health center area, BMI category, smoking, alcohol drinking habit, and each history of medical conditions (diabetes mellitus, hypertension, stroke, ischemic heart disease, cancer, and gastrointestinal ulcer) at baseline. Bold figures mean *p* values of <.05 or hazard ratios with *p* values of <.05.

post-stroke dementia risk (Table SC). Moreover, a high risk of dementia was observed with weight loss after baseline among both sexes, but only in those with dementia without a stroke history (Table SD).

Adding educational background to the model did not materially alter the results among the participants in Cohort I (Table SE for BMIs and Table SF for weight change).

4 | DISCUSSION

We examined the associations of BMI at and after midlife and weight changes through midlife with later dementia incidence among a Japanese population. At midlife, while those with obesity were at high risk, participants in the slender or underweight categories were also associated with a greater risk than those with normal BMI. After midlife, the risk associated with obesity was attenuated, while the risk associated with underweight participants was strengthened. Consistent with these patterns of change through midlife, weight loss after midlife was associated with a more significant dementia risk than weight gain.

Consistent with our results, studies on BMI trajectory starting at midlife had indicated that BMIs measured distally to dementia onset were positively associated with dementia. Simultaneously, there was an inverse relationship when BMI measurements were more proximal to dementia onset.[7,10,32] Regarding weight changes after midlife, increased risk of dementia incidence with weight loss after midlife has been consistently reported among all-type dementia[4,8,9,15,33,34] and AD.[3,8,16] An association confounded by weight loss during preclinical dementia phases (ie, reverse causation) may partially explain the attenuated or reversed risk of dementia associated with obesity in later life.[10,32]

The unique findings of our study include a risk increase associated with weight gain in later midlife and a risk increase in lower BMI categories in midlife.

Despite the attenuated risk of obesity at the 10-year follow-up, we found an increased risk associated with greater weight gain after midlife, although the HRs were considerably smaller than those of weight loss. Consistent with our findings, recent studies have found increased dementia risk with weight gain, even among older individuals.[17,35] Weight gain in older adulthood may be associated with physical inactivity,[35] which may also be a consequence of the preclinical phase of dementia.[36]

The higher dementia risk noted with lower BMIs at midlife has scarcely been reported in studies of middle-aged populations in Western countries. One nested case-control study in Asia obtained results similar to ours regarding low BMI in midlife, where BMIs of <20.5, 23.0 to 25.4, and ≥25.5 were related to increased dementia risk.[37] Studies from Western countries raise concerns about not having enough individuals to assess the effect of being underweight.[8,38] Asian populations typically have lower BMIs compared with non-Asian populations.[18] Therefore, studies with Asian populations may be able to elucidate the impacts of being underweight in midlife on dementia incidence.

We demonstrated that the associations of weight measures, that is, BMI at and after midlife and weight change through midlife, with dementia incidence were similar in both sexes. This finding is consistent with a recent meta-analysis that found no evidence of sex difference in the relationship between body size, weight change, and dementia.[15] However, previous studies were inconsistent in terms of sex-related differences in obesity and later dementia association. Further studies would be worth conducting.

Furthermore, the mechanism linking adiposity and dementia is poorly understood. Some studies have found associations between obesity and brain pathologies related to dementia.[39,40] Excess adipose tissue may influence brain function and the development of dementia via several mechanisms: harmful vascular effects, adipokines secreted by adipose tissue, and peripheral and brain insulin resistance.[41–43] Abdominal obesity is particularly highly associated with insulin resistance, cardiovascular disease, increased adipocytokines, and inflammatory markers, which may contribute to the development of dementia.[12] Other studies on AD have also indicated that weight loss during the preclinical phase may occur downstream of AD pathology, such as the amyloid beta (Aβ) burden.[44] Aβ burden, or Aβ-associated tau pathology, may cause weight loss by interfering with the functioning of the hypothalamus and/or decreasing food intake via olfactory impairment, increased anxiety, or apathy.[45]

The strengths of our study included its prospective cohort design and long follow-up periods. We controlled for any medical history that may cause weight changes and observed no alterations in results (Model 3). Additionally, the large number of participants allowed the analysis of men and women separately, and we demonstrated no sex-related difference in the associations. However, the study also had limitations. First, BMI, which was assessed at only two time points during the follow-ups, was calculated using self-reported body weights and heights. Although self-reported BMI at midlife in the JPHC study is at a sufficient level of validity, the results are not free from influences of misclassification of BMI and weight change. Second, the supplementary analysis for weight at age 20 and weight change before baseline might be affected by misclassification due to recalled weight and residual confounding due to lack of availability to smoking, drinking, and medical histories at 20 years of age. The association between obesity at younger age and dementia incidence has not been established.[13,46] Further research is needed to investigate relationships between the trajectory of body weight from early life and later dementia. Third, we do not have concrete information about the accuracy of our subtype classification of disabling dementia into post-stroke dementia and dementia without a stroke history in relation to vascular dementia and non-vascular dementia, respectively. Another weakness of this classification is no consideration of other types of dementia, such as Lewy body dementia.

Obesity in midlife was related to a higher risk of dementia. However, more robust associations between underweight and dementia incidence were noted as age increased. Moreover, weight loss after midlife was associated with dementia incidence, and the risk associated with obesity was weakened. The relationships did not differ by sex. Monitoring weight changes and body weight throughout adulthood may contribute to dementia prevention and identifying individuals at risk.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information

CONSENT STATEMENT

All study participants were informed of the purpose of the study, participants who completed survey questionnaires were regarded as consenting to participation, and the study design was approved by the appropriate ethics review board.

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SUPPORTING INFORMATION

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

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