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Dementia risk by combinations of metabolic diseases and body mass index: Japan Gerontological Evaluation Study Cohort Study

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ABSTRACT

Aims/Introduction: To compare the dementia risk associated with pre-existing diabetes, hypertension, dyslipidemia, obesity (body mass index [BMI] ≥25 kg/m^2) and underweight (BMI <18.5 kg/m^2) among older adults. We also explored the dementia risk associated with combinations of metabolic diseases and BMI.

Materials and Methods: We used data from the Japan Gerontological Evaluation Study. Participants completed a health checkup in 2010 and were followed for 5.8 years on average. Dementia was measured by municipal long-term care insurance registration. Diabetes, hypertension, dyslipidemia, obesity and underweight were diagnosed by medication use or health examination results. We calculated the incidence of dementia and adjusted hazard ratios (HRs).

Results: Among 3,696 participating older adults, 338 developed dementia. Adjusted HRs (95% confidence intervals) in men and women (reference: those without corresponding disease of normal weight) were as follows: 2.22 (1.26–3.90) and 2.00 (1.07–3.74) for diabetes; 0.56 (0.29–1.10) and 1.05 (0.64–1.71) for hypertension; 1.30 (0.87–1.94) and 0.73 (0.49–1.08) for dyslipidemia; 0.73 (0.42–1.28) and 0.82 (0.49–1.37) for BMI of 25–29.9 kg/m^2; and 1.04 (0.51–2.10) and 1.72 (1.05–2.81) for underweight. Dementia risk was significantly higher in underweight men with dyslipidemia (HR 4.15, 95% CI 1.79–9.63) compared with normal-weight men without dyslipidemia, and in underweight women with hypertension (HR 3.79, 1.55–9.28) compared with normal-weight women without hypertension. Dementia incidence was highest among underweight older adults with hypertension followed by dyslipidemia.

Conclusions: Among Japanese older adults, underweight and prevalent diabetes are risk factors for developing dementia. Lower BMI is also associated with a higher incidence of dementia.

INTRODUCTION

Dementia is a prevalent disease in older adults worldwide[1]. Researchers have investigated the dementia risk related to metabolic diseases[2]. Diabetes is known to impair cognitive function through several mechanisms[3–8], and there is debate as to whether hypertension in late-life increases or decreases the incidence of Alzheimer's disease[9,10]. Hypercholesterolemia might be a risk factor for dementia in mid-life, but not in late life[11]. Although dementia risk might increase with overweight or obesity in mid-life (relative risk 0.99–2.44)[12], the estimated risk for dementia associated with obesity in late-life varies (relative risk 0.24–1.13)[12]. However, separating individual dementia risk factors might be difficult, because metabolic diseases and obesity frequently overlap in older adults.

Being underweight might also be a risk factor for a reduced lifespan[13]. The Rotterdam Study carried out in the Netherlands suggested that a body mass index (BMI)

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<18.5 kg/m^2 (underweight) in older adults increased mortality[14]. A USA study reported high mortality among residents aged ≥65 years who were underweight or had unintentional weight loss[15]. Korean[16] and Japanese[17] older adults with low to normal-to-low BMI might also be at risk for a shorter lifespan. However, little is known about dementia risk among underweight older adults.

Some Asian older adults are underweight because of undernutrition[18] and underexercising[19], which might result in a shorter lifespan. Although Asians tend to be slimmer than Caucasians[20], they have a similar prevalence of diabetes and dyslipidemia[8,21,22]. Analyses of dementia risk associated with metabolic diseases and BMI have been carried out separately. However, evaluation of the risk for dementia among people with coexisting metabolic diseases and obesity/underweight is required. The present study aimed to compare the dementia risk associated with diabetes, hypertension, dyslipidemia and BMI (obesity and underweight) in a Japanese cohort. We also aimed to clarify the combinations of metabolic disease and BMI that had the highest risk for developing dementia.

METHODS

Participants

In 2010, the Japan Gerontological Evaluation Study randomly selected community-dwelling adults aged ≥65 years who were not registered by municipalities at baseline as requiring care under the long-term care insurance (LTCI) system[23]. In Japan, adults with incident dementia at age ≥40 years are covered by LTCI[24]. The benefits of LTCI range from support need levels 1 and 2 to care need levels 1–5[25], with a higher level indicating more care is required. As we describe below, the primary outcome of the present study was LTCI registration, diagnosis of dementia and a ranking of independence in daily life of ≥2b. Although a small number of participating older adults might have had slightly impaired cognitive function[24] at baseline, most were considered not to have dementia.

The present study included a subset of participants from the Japan Gerontological Evaluation Study cohort who received municipal health checkups in 2010 and were followed up over several years (average 5.8 years). Participants in this study were residents of Tokoname City and Minamichita Town in Aichi Prefecture, Japan, which had approximately 59,000 and 18,000 residents in 2018, respectively. In the health checkups, trained nurses measured blood pressure, collected blood samples and interviewed participants regarding prescribed medications. Serum cholesterol and glycated hemoglobin A1c levels were measured using laboratory testing devices with every-morning calibrations. BMI was calculated as the participant's weight in kilograms divided by their height in meters squared.

The protocol for this research project was approved by the suitably constituted ethics committees of the study institutions, and conformed to the provisions of the Declaration of Helsinki (ethics committee of the Chiba University School of Medicine, approval no. 2493; the ethics committee of the University of Yamanashi School of Medicine, approval no. 18150). Informed consent was obtained from all participants and/or their legal guardian(s). Data for participating older adults were anonymously analyzed and reported.

Measurements

Since 2000, all Japanese people aged ≥40 years have been required to pay a premium for coverage under the LTCI system[26]. This meant that they would be eligible for insurance benefits if they required long-term care, including dementia care[27]. When people need dementia care under this system, they are required to submit documentation prepared by a medical doctor and a LTCI certification investigator (accredited by the prefecture) who visit the older adult's home. These documents record dementia diagnosis and score for independence in daily life, which is ranked as 1, 2a, 2b, 3a, 3b, 4 or M; a higher rank indicates more dependence on others for assistance. For example, rank 2a indicates that the person has difficulty in daily life with symptoms, behaviors and communication outside the home (e.g., they might frequently lose their way or make mistakes with payments), but can lead an independent life with some care and support. If the difficulties described in rank 2a are both outside and inside the home, the person would be ranked 2b. Rank 4 indicates the older adult requires constant care. Therefore, we defined patients with dementia as those who had started to receive the LTCI benefit and were ranked from 2a to 4 as the outcome for the time-to-event analysis. Rank M indicates that people require specialized medical care for severe psychiatric symptoms, problematic behaviors or severe physical disorders; few people are certified with this rank, and we could not measure and include rank M as an outcome in the present study.

Health examinations that participants received in their municipalities were carried out by medical staff in medical institutions. We extracted data for diabetes, hypertension, dyslipidemia, underweight and obesity from the results of these examinations. Diabetes was defined as receiving the relevant medication or glycated hemoglobin A1c ≥6.5% (48 mmol/mol) according to a recommended guideline for epidemiological studies[28]. Hypertension was defined as receiving medication, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg[29]. Dyslipidemia was defined as receiving medication, serum low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL or triglyceride ≥150 mg/dL[30]. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2) or obese (≥25 kg/m^2), according to the recommended cut-off values for Japan[31,32]. When the sample size was sufficient for analysis, we further divided the obesity range to 25–29.9 kg/m^2 (obesity grade 1) or ≥30 kg/m^2 (obesity grades 2–4)[31,32].

Statistical analysis

We described participants' baseline characteristics using means (standard deviations [SD]) or numbers (percentages for proportions). We calculated hazard ratios (HR) with 95% confidence intervals (CI) for developing dementia for those with diabetes, hypertension, dyslipidemia, obesity and underweight stratified by sex. The HRs were adjusted for age, history of stroke, educational background, income, number of family members, marital status and frequency of meeting friends. As a sensitivity analysis, we carried out this analysis excluding the explanatory variable of history of stroke. We also calculated crude HRs for combinations of three metabolic diseases and BMI. In calculating HRs, participants who were lost to follow up were treated as censored data. Because dementia development was relatively common among underweight older adults, we calculated the dementia incidence rate (100 person-years) in those with and without diabetes, hypertension, and dyslipidemia to explore the profile with the highest risk. We also presented the incidence of dementia for combinations of three metabolic diseases and BMI. In this analysis, we calculated the *P*-value for trend for the association between BMI and total incidence of dementia, and that in each metabolic disease profile. Participants who had all data for the explanatory and response variables, and censored time were included in the analyses. All statistical analyses were carried out with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were reported as means and SDs. We used the SAS PROC PHREG procedure to calculate HRs. All reported *P*-values were two-sided; *P*-values < 0.05 were considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of participants who were followed up. In total, there were 3,696 participants (42.8% men); 338 developed dementia. Participants' mean age at baseline was 73.4 years (SD 5.8 years), and the mean follow-up duration was 5.8 years (SD 1.3 years). Dyslipidemia was the most common and obesity the second most common among three metabolic diseases and BMI abnormalities (obesity and underweight).

Table 2 shows the HRs for developing dementia with diabetes, hypertension, dyslipidemia, obesity and underweight by sex. Men and women with diabetes had a statistically significant doubled risk for dementia compared with those without diabetes. Underweight women had a HR for dementia of 1.72 compared with those with normal weight, and this result was statistically significant. None of the covariates for adjustment were significantly associated with the incidence of dementia. In the sensitivity analysis excluding the explanatory variable of history of stroke, HRs (95% CIs) in men and women were as follows: 2.21 (1.26–3.88) and 2.00 (1.07–3.74) for diabetes; 0.65 (0.35–1.23) and 1.02 (0.62–1.66) for hypertension; 1.31 (0.88–1.95) and 0.72 (0.49–1.07) for dyslipidemia; 0.90 (0.12–6.52) and 0.62 (0.09–4.44) for BMI $\geq$30 kg/m^2; 0.74 (0.42–1.28) and 0.81 (0.49–1.36) for BMI 25–29.9 kg/m^2; and 1.04 (0.51–2.1) and 1.73 (1.06–2.83) for BMI <18.5 kg/m^2, respectively.

Table 3 shows the HRs for dementia in various combinations of metabolic diseases and body types stratified by sex. In brief, there was a statistically significant large HR in underweight men with dyslipidemia (HR 4.15, 95% CI 1.79–9.63) compared with normal-weight men without dyslipidemia. In addition, the large HR for underweight women with hypertension (HR 3.79, 95% CI 1.55–9.28) was statistically significant compared with normal-weight women without hypertension.

Table 4 shows the incidence rate for combinations of metabolic diseases and BMI. The highest incidence was in underweight participants with hypertension, followed by underweight participants with dyslipidemia. There were statistically significant trends of lower BMI and a higher incidence of dementia in all participants, and in those without diabetes, with hypertension, without hypertension, with dyslipidemia and without dyslipidemia.

Table 5 shows the results of Table 4 stratified by sex. There were statistically significant trends of lower BMI and a higher incidence of dementia in both sexes, and in men and women without diabetes, women with hypertension, men and women without hypertension, men and women with dyslipidemia, and men and women without dyslipidemia.

DISCUSSION

The present study showed that among older adults with metabolic diseases and body types, those with diabetes had the highest HR for dementia (Table 2). Among the various metabolic disease and body type profiles, underweight participants with hypertension had the highest incidence of dementia, followed by underweight participants with dyslipidemia (Table 4). In the combinations of metabolic disease and body type by sex, the highest HR was found in underweight men with dyslipidemia, followed by underweight women with hypertension (Table 3). Among all participants, lower BMI was associated with a higher incidence of dementia (Tables 4,5).

Previous research has shown that prevalent diabetes increased the risk for dementia, and one-third of general older adults have cerebrovascular amyloidosis[33]. In a mouse model, amyloidosis manifested significantly in mice with diabetes compared with those without diabetes[34]. Epidemiological studies have shown that people with diabetes are at 1.5–1.7-fold greater risk for dementia than people without diabetes[2,35]. Presumed mechanisms for the high dementia incidence in patients with diabetes include oxidant stress from steep glycemic excursion and production of reactive oxygen species[4], reduction of insulin transportation to the brain[5,7], inflammation of cerebral tissue, reduction of insulin signaling[6], and atherosclerosis from hypertension and hypercholesterolemia[8]. Consistent with previous studies, participants with diabetes in the present study had a doubled risk for dementia (Table 2). These data suggest that controlling diabetes in older adults would contribute to reducing the risk for dementia.

Table 1 | Baseline characteristics of participating Japanese older adults who were followed up in this study

Baseline characteristics of followed older adults	Men (n = 1,582)	Women (n = 2,114)
Age, years (mean ± SD)	73.4 ± 5.7	73.5 ± 5.8
BMI ≥30 kg/m^2, n (%)	20 (1.3)	49 (2.3)
BMI 25–29.9 kg/m^2, n (%)	336 (21.2)	417 (19.7)
BMI 18.5–24.9 kg/m^2, n (%)	1,134 (71.7)	1,462 (69.2)
BMI ≤18.4 kg/m^2, n (%)	92 (5.8)	186 (8.8)
Diabetes, n (%)	146 (9.2)	127 (6.0)
Hypertension, n (%)	277 (17.5)	389 (18.4)
Dyslipidemia, n (%)	752 (47.5)	961 (45.5)
Medication for diabetes, n (%)	51 (3.2)	40 (1.9)
Medication for hypertension, n (%)	201 (12.7)	282 (13.3)
Medication for dyslipidemia, n (%)	73 (4.6)	150 (7.1)
History of stroke, n (%)	32 (2.0)	19 (0.9)
Dementia, n (%)	131 (8.3)	207 (9.8)
Follow-up duration, years (mean ± SD)	5.7 ± 1.4	5.9 ± 1.2

BMI, body mass index; SD, standard deviation.

Table 2 | Hazard ratios (95% confidence intervals) for dementia in older adults with diabetes, hypertension, dyslipidemia, obesity and underweight

Metabolic disease	Univariate	Adjusted in model 1†	Adjusted in model 2†
Men			
Diabetes	1.42 (0.84–2.39)	1.72 (1.01–2.90)	2.22 (1.26–3.90)
Hypertension	0.74 (0.45–1.22)	0.63 (0.37–1.07)	0.56 (0.29–1.10)
Dyslipidemia	1.09 (0.77–1.53)	1.36 (0.96–1.93)	1.30 (0.87–1.94)
BMI ≥30 kg/m^2	0.58 (0.08–4.12)	0.66 (0.09–4.72)	0.91 (0.13–6.64)
BMI 25–29.9 kg/m^2	0.62 (0.38–1.02)	0.72 (0.44–1.18)	0.73 (0.42–1.28)
BMI 18.5–24.9 kg/m^2	Ref	Ref	Ref
BMI <18.5 kg/m^2	1.64 (0.90–2.98)	0.95 (0.52–1.75)	1.04 (0.51–2.10)
Women			
Diabetes	1.76 (1.11–2.79)	2.16 (1.36–3.44)	2.00 (1.07–3.74)
Hypertension	1.00 (0.70–1.42)	1.10 (0.77–1.58)	1.05 (0.64–1.71)
Dyslipidemia	0.68 (0.51–0.90)	0.88 (0.66–1.18)	0.73 (0.49–1.08)
BMI ≥30 kg/m^2	0.63 (0.20–1.99)	0.85 (0.27–2.66)	0.61 (0.09–4.43)
BMI 25–29.9 kg/m^2	0.75 (0.51–1.11)	0.81 (0.55–1.19)	0.82 (0.49–1.37)
BMI 18.5–24.9 kg/m^2	Ref	Ref	Ref
BMI <18.5 kg/m^2	1.99 (1.35–2.92)	1.52 (1.03–2.24)	1.72 (1.05–2.81)

†Model 1 adjusted for age and history of stroke; model 2 adjusted for model 1 plus educational background, income, number of family members, marital status and frequency of meeting friends. BMI, body mass index.

The present study also showed that underweight women were at risk for dementia (Table 2). We further analyzed our data to answer the question, "Which groups of underweight individuals with comorbid metabolic diseases suffer from dementia?" (Table 3). The results suggested that underweight men with dyslipidemia and underweight women with hypertension had a higher risk for dementia. These older adults might therefore need to be targeted for interventions for metabolic diseases to reduce dementia risk.

Reasons for older adults being underweight might include combinations of shortage of food intake, underexercising, digestion and absorption disorders, loss of teeth, endocrinological diseases, and debilitating diseases (e.g., cancer or infection)[36]. In particular, undernutrition among older adults has been recognized as a major reason for decline in muscle mass and weight[37]. A previous study showed that muscle-releasing hormones (myokines) played an important role in recovery of injured brain tissue, and exercise improved cognitive performance[38]. The high risk for dementia among those with low BMI in the present study emphasized the importance of maintaining muscle mass to preserve cognitive function[39]. This suggests that it might be important to encourage older adults to consume more protein than younger to middle-aged adults[40].

Table 3 | Hazard ratios for dementia in older adults with combinations of diabetes, hypertension, dyslipidemia, obesity, and underweight

DM	HT	DL	BMI	No.†	vs	DM	HT	DL	BMI	No.†	HR (95% CI)
Men											
(+)			Obese	5/48	vs	(–)			NW	88/1,038	1.17 (0.48–2.89)
(+)			Underweight	0/2	vs	(–)			NW	88/1,038	–‡
	(+)		Obese	3/85	vs		(–)		NW	84/948	0.38 (0.12–1.21)
	(+)		Underweight	0/6	vs		(–)		NW	84/948	–‡
		(+)	Obese	17/228	vs			(–)	NW	57/629	0.80 (0.47–1.38)
		(+)	Underweight	6/19	vs			(–)	NW	57/629	4.15 (1.79–9.63)
(+)	(+)		Obese	1/16	vs	(–)	(–)		NW	77/800	0.94 (0.24–3.72)
(+)	(+)		Underweight	0/1	vs	(–)	(–)		NW	77/800	–‡
(+)		(+)	Obese	4/37	vs	(–)		(–)	NW	51/576	1.34 (0.53–3.38)
(+)		(+)	Underweight	0/0	vs	(–)		(–)	NW	51/576	–‡
	(+)	(+)	Obese	3/67	vs		(–)	(–)	NW	50/549	0.43 (0.14–1.39)
	(+)	(+)	Underweight	0/0	vs		(–)	(–)	NW	50/549	–‡
(+)	(+)	(+)	Obese	1/15	vs	(–)	(–)	(–)	NW	47/509	–‡
(+)	(+)	(+)	Underweight	0/0	vs	(–)	(–)	(–)	NW	47/509	–‡
Women											
(+)			Obese	5/39	vs	(–)			NW	126/1,384	1.37 (0.56–3.35)
(+)			Underweight	0/10	vs	(–)			NW	126/1,384	–‡
	(+)		Obese	4/112	vs		(–)		NW	112/1,204	0.37 (0.14–1.01)
	(+)		Underweight	5/19	vs		(–)		NW	112/1,204	3.79 (1.55–9.28)
		(+)	Obese	15/249	vs			(–)	NW	89/803	0.52 (0.30–0.91)
		(+)	Underweight	9/53	vs			(–)	NW	89/803	1.68 (0.85–3.34)
(+)	(+)		Obese	0/11	vs	(–)	(–)		NW	102/1,051	0.52 (0.11–2.40)
(+)	(+)		Underweight	0/2	vs	(–)	(–)		NW	102/1,051	0.74 (0.24–2.33)
(+)		(+)	Obese	2/21	vs	(–)		(–)	NW	79/768	0.74 (0.24–2.33)
(+)		(+)	Underweight	0/2	vs	(–)		(–)	NW	79/768	–‡
	(+)	(+)	Obese	3/94	vs		(–)	(–)	NW	75/718	0.30 (0.11–0.83)
	(+)	(+)	Underweight	2/8	vs		(–)	(–)	NW	75/718	2.69 (0.91–7.91)
(+)	(+)	(+)	Obese	0/9	vs	(–)	(–)	(–)	NW	67/691	0.24 (0.01–4.67)
(+)	(+)	(+)	Underweight	0/0	vs	(–)	(–)	(–)	NW	67/691	–‡

†Number of dementia onset/number of aged adults at risk. ‡Hazard ratio could not be calculated because of the small sample size. Hazard ratios for dementia in older adults with one to several metabolic disease(s) were provided, compared with normal-weight older adults without corresponding metabolic disease(s), shown as (–). BMI, body mass index; CI, confidence interval; DL, dyslipidemia; DM, diabetes mellitus; HR, hazard ratio; HT, hypertension; NW, normal weight. Obese, body mass index ≥25 kg/m^2; normal weight, body mass index 18.5–24.9 kg/m^2; underweight, body mass index <18.5 kg/m^2.

Table 4 | Incidence of dementia (per 100 person-years) among older adults stratified by body mass index and disease

BMI (kg/m^2)	<18.5 (n = 278)	18.5–24.9 (n = 2,596)	25.0–29.9 (n = 735)	≥30.0 (n = 69)	P for trend
All	2.92	1.58	1.11	0.99	<0.0001
DM (+) (n = 273)	0	2.71	1.91	1.92	0.36
DM (–) (n = 3,423)	3.05	1.51	1.02	0.85	<0.0001
HT (+) (n = 666)	4.08	1.70	0.65	0	0.0002
HT (–) (n = 3,030)	2.82	1.56	1.25	1.36	0.0005
DL (+) (n = 1,713)	3.88	1.38	1.18	0.48	0.0015
DL (–) (n = 1,983)	2.59	1.75	1.01	1.54	0.0011

BMI, body mass index; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension.

Among the disease and body type profiles investigated, there was a significant increase in dementia in underweight women with hypertension (Tables 3,5). Reportedly, the BMI of Swedish women with ε4 allele of the apolipoprotein E gene (ApoE4$^+$), a major risk factor for Alzheimer's disease, declined after age 70 years[41]. This allele has also been associated with aortic

Table 5 | Incidence rate of dementia (per 100 person-years) among older adult men and women stratified by body mass index and non-communicable diseases

BMI (kg/m^2)	<18.5	18.5–24.9	25.0–29.9	≥30.0	*P* for trend
Men (*n*)	448	1,582	356	20	
All	2.44	1.52	0.96	0.88	0.004
DM (+) (*n* = 146)	0.00	2.11	1.86	0.00	0.36
DM (–) (*n* = 1,436)	2.51	1.47	0.82	1.04	0.002
HT (+) (*n* = 277)	0.00	1.41	0.65	0.00	0.12
HT (–) (*n* = 1,305)	2.62	1.55	1.05	1.41	0.013
DL (+) (*n* = 752)	6.30	1.45	1.35	0.00	0.020
DL (–) (*n* = 830)	1.52	1.58	0.28	2.61	0.029
Women (*n*)	186	1,462	417	49	
All	3.15	1.63	1.23	1.04	0.0002
DM (+) (*n* = 127)	0.00	3.42	1.99	2.88	0.45
DM (–) (*n* = 1,987)	3.35	1.55	1.16	0.78	<0.0001
HT (+) (*n* = 389)	5.54	1.91	0.65	0.00	0.0004
HT (–) (*n* = 1,725)	2.92	1.57	1.41	1.35	0.008
DL (+) (*n* = 961)	3.09	1.32	1.02	0.75	0.013
DL (–) (*n* = 1,153)	3.18	1.88	1.48	1.28	0.007

BMI, body mass index; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension.

stenosis[42]. The Rotterdam Study showed that residents with an abnormal increase in blood pressure from approximately age 55 years had a higher risk for future stroke[43]. In a USA study of aged adults, hetero- or homozygous ε4 allele(s) were detected in 38.7% of patients with Alzheimer's disease, 44.8% of those with cerebrovascular dementia and 24.1% of people without dementia. The present study did not identify Alzheimer's disease and ApoE4$^+$. However, we presume that this allele might have influenced the correlations among the decline in BMI, increase in blood pressure and high dementia risk.

In the present study, underweight men with dyslipidemia were also at a statistically significant high risk for dementia (HR 4.15, 95% CI 1.79–9.63; Table 3). However, some participants with dyslipidemia had received medications from mid- or late-life, whereas others had not received pharmacological interventions. A previous meta-analysis showed that statin use had a risk reduction of 38% and 24% in dementia and Alzheimer's disease, respectively[44]. This might suggest that early pharmacological intervention for middle-aged adults with dyslipidemia should be encouraged. With regard to high serum cholesterol levels, diet-induced hypercholesterolemia in white rabbits showed increased levels of brain amyloid beta protein and apolipoprotein E (clinical manifestations of Alzheimer's disease)[45]. A Finnish epidemiological study showed that hypercholesterolemia in mid-life was an independent risk factor for Alzheimer's disease[46]. However, there is no evidence that Japanese underweight older men have a high probability of untreated dyslipidemia. Dyslipidemia might contribute to dementia related to both Alzheimer's disease and stroke.

The present results showed that other than diabetes, no metabolic disease consistently presented a high risk for dementia (Tables 2,3). Epidemiological evidence suggests that metabolic syndrome might be an independent risk factor for dementia[47,48]. Accumulation of obesity, hypertension and hypercholesterolemia in mid-life increases the risk for dementia[49]. However, few studies have compared the risk for dementia in late-life in people with obesity versus non-obesity. The results of two USA studies investigating this topic were inconsistent[50,51], and another recent USA study suggested that higher late-life BMI was associated with a lower risk for dementia[52]. The present study investigating Japanese older adults showed that being underweight in late-life was a risk factor for dementia, whereas obesity was not (Table 5).

Hypertension in late-life is a risk factor for stroke and therefore cerebrovascular dementia, and was previously suspected to be a risk factor for Alzheimer's disease[53]. However, a recent systematic review did not detect late-life hypertension as a risk factor[9]. There is some consensus from diverse epidemiological results that hypercholesterolemia in mid-life might be an independent risk factor for Alzheimer's disease[54]. Literature suggests that ApoE4$^+$ might increase the serum lipid level[55]. However, evidence for the association between late-life dyslipidemia and dementia incidence is scarce. The present study concluded that hypertension and dyslipidemia in late-life were not consistent risk factors for dementia in all older adults (underweight to obese; Tables 2,5).

We found that obese women with dyslipidemia, and with dyslipidemia and hypertension were at statistically significant low risks for dementia (HR 0.52, 95% CI 0.30–0.91; HR 0.30, 95% CI 0.11–0.83, respectively; Table 3).The present results for separate metabolic diseases or BMI categories (Table 2) showed that obesity, hypertension and dyslipidemia were not risk or protective factors for dementia in women in late-life. The reason for the low HR (0.52) in women with obesity and

dyslipidemia is unknown. However, as the metabolic disease groups included participants who could afford medical care expenses for those diseases, Japanese older adult women with obesity might have a higher level of education[56] and a sufficient diet, and therefore good health status.

Adjusted HRs (Table 2) of diabetes for dementia in men (2.22, 95% CI 1.26–3.90) versus women (2.00, 95% CI 1.07–3.74) were similar, whereas the HR and incidence of underweight were higher in women (1.72, 95% CI 1.05–1.81) than in men (1.04, 95% CI 0.51–2.10). The present data also suggested that there was a higher incidence of dementia in women not with diabetes or dyslipidemia, but with hypertension (Table 5). The frequency of ApoE4^{+} appeared to be similar between Japanese men and women[57]. Worldwide, the incidence of Alzheimer's disease is considered to be similar between the sexes[58]. However, the incidence of Alzheimer's disease tends to be higher in women in Japan, although vascular dementia is similar in both sexes, as men die at a faster rate with aging[59]. The reasons for our finding of a higher dementia risk among underweight women are likely to be complex. For example, there are neuroanatomical, neurochemical, psychological, behavioral and cognitive differences between the sexes[58]. The susceptibility to risk factors for dementia might also differ between the sexes[60]. The design of the present study did not elucidate underlying reasons for the high incidence of dementia among underweight women with and without cardiometric factors.

Social role might also affect the difference between men and women in terms of the relationship between underweight and dementia. When older adult women experience decreased cognitive function, there might be a corresponding loss of a balanced healthy diet. In Japan, women are traditionally expected to cook meals for their families[61]. Therefore, it is likely that older adult men with dementia who have a spouse might have a good diet, whereas older adult women with dementia (with and without a spouse) might not have a healthy diet. A limitation of the present cohort study was that it was difficult to strictly exclude people with dementia from the baseline participants. The significantly larger HR (1.72) for underweight and dementia onset in women (Table 2) might reflect this situation. Furthermore, it might be less effective for health professionals to recommend protein intake and exercise to prevent sarcopenia and dementia progression for Japanese women with mild dementia.

Older adults tend to have decreased digestion and absorption capacity[36,62]. Without sufficient protein intake and exercise, they are prone to lose muscle mass[63]. Underweight is also considered to reflect inactivity, frailty and sarcopenia, which is defined as age-related decline of skeletal muscle, muscle strength and physical performance[64,65]. The present results showed that older underweight women were at a high risk for dementia (Table 2). It might be important to recommend exercise for older adults to better control comorbid metabolic diseases, and reduce the risk for dementia[9], coronary heart disease, stroke, type 2 diabetes and several forms of cancer[66].

People are becoming increasingly concerned about modifying obesity to prevent non-communicable diseases and cancer[67]. For older adults, major health outcomes are longevity and a healthy lifespan. Because older adults are vulnerable to illness, and have high mortality and weak organs, guidelines for disease prevention and management for middle-aged adults have recently been customized for older adults[29,30,68–73]. However, we consider that medical guidelines for older adult patients with various metabolic and debilitating diseases require systemic evaluation, so that mortality risk from reducing a single disease does not increase other mortality risks. Dementia[74], sarcopenia and frailty[75] present major mortality risks for older adults. Many guidelines for the prevention or management of diseases require health professionals to intervene with older adults based on their disease profiles. Furthermore, health professionals need to support their patients individually to accomplish longer healthy lifespans, consistent with the recommendations of various medical guidelines.

The present study had several strengths. First, metabolic diseases were identified in medical examinations, and the diagnostic standards applied in this study were based on guidelines used by medical doctors. Second, the sample size was relatively large, especially in the Japanese context where databases for usual medical treatment, municipal health examinations and long-term care for older adults are not usually linked. The linking of these databases enabled us to compare the risk for dementia among older adults with several metabolic diseases and different BMI groups, and evaluate which groups were at the highest risk (Tables 2,4,5). Further analyses with these linked databases are required to support the present results.

The present study also had several limitations. First, the endpoint (dementia) was gathered from municipal LTCI registrations, and it is possible that not all older adults with dementia applied to receive the LTCI benefit. As described in the Methods section, older adults with slightly impaired cognitive function might have been included as participants at baseline. However, as dementia progresses, patients tend to require support and it is therefore likely that patients or their caregivers would have applied for long-term care. Although this measurement of dementia onset might have been indirect, we consider that most cases of dementia onset were detected in this cohort. Second, the primary cause of dementia was not measured. For example, the etiology of cerebrovascular dementia differs from that of Alzheimer's disease, and the respective risk factors would be different. Third, the sample population was older adults living in two municipalities, and the results might not be generalizable. Fourth, it is possible that some older adults who were underweight at baseline were already mildly demented, and this might have impacted our findings. Fifth, the amount of muscle mass was not evaluated. A meta-analysis of randomized controlled trials of healthy older adults showed that exercise assisted in preserving reasoning ability[76]. Measurement of muscle mass is therefore likely to have improved the interpretation of the present results. Sixth, longitudinal changes in

metabolic disease profiles were not measured and built into the analyses. Finally, we did not adjust for risk factors for dementia other than history of stroke and metabolic status. However, we believe that overadjustment with many covariates would have biased the results, as would underadjustment. In addition, all cohort studies have such bias.

In conclusion, in a Japanese older adult population, being underweight and prevalent diabetes might be risk factors for dementia. Clinicians need to evaluate the reasons for their patients being underweight, and provide interventions according to their disease profiles.

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DISCLOSURE

The authors declare no conflict of interest.

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