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RESEARCH ARTICLE

Weight loss and risk of dementia in individuals with versus without obesity

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ABSTRACT

INTRODUCTION: Using nationwide cohort data, we aimed to elucidate whether baseline obesity altered the relationship between loss in body mass index (BMI) or waist circumference (WC) and risk of dementia.

METHODS: Among 9689 participants whose BMIs and WCs were repeatedly measured over 1 year, 1:1 propensity score matching was conducted between participants with and without obesity ($n = 2976$ per group, mean age 70.9). For each group, we explored the association between loss in BMI, or WC, and incidence of dementia during an approximately 4-year follow-up period.

RESULTS: BMI loss was associated with an increased risk of all-cause dementia and Alzheimer's disease in participants without obesity; however, this association was absent in participants with obesity. WC loss was associated with decreased Alzheimer's disease risk only in participants with obesity.

DISCUSSION: Only unfavorable loss (loss from non-obese state) in BMI, not WC, can be a metabolic biomarker of prodromal dementia.

KEYWORDS
Alzheimer's disease, body mass index, dementia, obesity, waist circumference, weight loss

1 | INTRODUCTION

Obesity is a morbid metabolic condition and is considered one of the potentially modifiable risk factors for all-cause dementia, including Alzheimer's disease (AD) and vascular dementia (VaD).[1,2] This increased adiposity can provoke dementia via various mechanisms such as microvascular injury, chronic inflammation, and the adipokine signaling pathway.[1] Therefore, it seems obvious that weight reduction is a reasonable strategy to reduce the risk of dementia,[2] cardiovascular disease, and mortality in obese individuals.[3,4]

However, opposite results have also been reported in studies of older adults (see Supplementary Table 1). Longitudinal cohort studies have observed that obesity or high body mass index (BMI) at age 65 or older is associated with decreased risk of dementia,[5–15] yielding the concept of the "obesity paradox."[7] In addition to the reverse relationship between obesity and dementia, several longitudinal cohort studies have reported that weight began to fall 6–10 years before diagnosis of dementia,[16–20] leading to the proposal of weight loss as a prodromal sign of dementia.[21] A recent prospective cohort study with BMI trajectory and brain autopsy supported this suggestion, revealing that individuals with a higher burden of AD pathology underwent steeper BMI loss before death than those with a lower burden.[22]

These conflicting findings from longitudinal observational studies should be taken seriously by clinicians. Should weight loss be regarded as a warning sign of dementia in obese individuals? To address this issue, we assumed that losing body weight was either metabolically favorable or unfavorable. The former was decreased weight from the obese state, and the latter was weight loss from the non-obese state,

since low BMI may be associated with increased cardiovascular risk and mortality.[23,24]

Therefore, we explored the relationship between weight loss (defined as BMI loss in this study) and subsequent dementia incidence, stratifying participants by baseline obesity using a nationwide cohort of older adults. In addition to BMI loss, we also investigated waist circumference (WC) loss as reduced central adiposity, which might provide an obesity-related health status better than BMI.[25]

2 | METHODS

2.1 | Data source and study design

Data were retrieved from the National Health Insurance Service-Elderly Cohort (NHIS-EC), a nationwide Korean population-based cohort of individuals aged ≥ 60 years in 2002. The National Health Insurance Service (NHIS) is the only required public health insurance system in South Korea. A small number of individuals who cannot afford NHIS are supported by the Medical Aid Program run by the Korean government. Thus, the whole population is covered by NHIS or the Medical Aid Program. The NHIS-EC included a randomly selected 10% of all elderly individuals from both NHIS and the Medical Aid Program. The NHIS-EC data contain sociodemographic conditions, insurance status, medical records of diagnosis (as defined by the 10th revised code of the International Classification of Diseases [ICD-10]) and medical service (treatment and procedure), and costs claimed by hospitals.

Individuals in the NHIS-EC were eligible for regular annual health checkups, including body weight, height, WC, blood pressure, and self-reported smoking history, alcohol consumption, and exercise frequency, which were used in this study. Health checkups were held in authorized institutions or hospitals designated by the Ministry of Health and Welfare in South Korea. Despite the availability of data in NHIS-EC ranging from 2002 to 2013, we focused our analysis on the data from 2008 as WCs were measured from this year. The changes in BMI or WC were measured over a 1-year period (between 2008 and 2009), as significant weight loss within 1 year has been linked to morbidity and mortality in older adults.[26] Thus, we observed our study population from their individual health checkup dates in 2009 (the second measurement of both BMI and WC) until the end of NHIS-EC (December 31, 2013). This study was approved by the Institutional Review Board of Yonsei University Health System (4-2021-1051), and the requirement of informed consent was waived. All study procedures were performed in accordance with the Declaration of Helsinki in 1975, revised in 2013.

2.2 | Study population selection

A flow chart for study population selection is shown in Supplementary Figure 1. Individuals (n = 11,539) who underwent health checkups in both 2008 and 2009 were screened for eligibility to be included in this study. We excluded 1701 individuals for the following reasons: (i) missing BMI or WC data (n = 59), (ii) death before the end of 2009 (n = 570), or (iii) diagnosis of cerebrovascular disease (n = 1315) or all-cause dementia (n = 455) before the end of 2009. Additionally, considering the gradual onset of dementia, those who died or were diagnosed with dementia within a year of their second health checkups were excluded (n = 149). Of the remaining 9689 participants, 3089 were obese (BMI ≥ 25 kg/m^2) in 2008, and 6600 were not obese (BMI < 25 kg/m^2) according to the World Health Organization obesity criteria for Asian adults.[27] Among these 9689 participants, 3143 had central obesity and 6546 did not in 2008 (Supplementary Figure 2). Central obesity was defined as WC ≥ 90 cm for males and ≥ 85 cm for females, according to the criteria for Korean adults.[28]

2.3 | Key explanatory variables

BMI was calculated using height and weight measurements, expressed in kg/m^2. BMI change was defined as follows: [(BMI in 2009 − BMI in 2008)/BMI in 2008] × 100 (%). Participants with BMI change < 0 were regarded as those with BMI loss. The amount of BMI loss as a continuous variable was defined as -1 × BMI change (%). To distinguish between minor fluctuations and substantial changes, we also classified BMI change for 1 year as five categories following a previous recommendation:[29] large BMI loss (> 5%), small BMI loss (> 3% to 5%), stable BMI (loss or gain ≤ 3%), small BMI gain (> 3% to 5%), and large BMI gain (> 5%).

WC was measured in centimeters (cm) at the slimmest location between the bottom of the rib cage and the iliac crest, recorded while breathing quietly. WC change was calculated as follows: [(WC in 2009 − WC in 2008)/WC in 2008] × 100 (%). Participants with WC change < 0 were considered those with WC loss, and the amount of WC loss as a continuous variable was −1 × WC change (%).

2.4 | Outcome

All-cause dementia was defined using the following ICD-10 codes: F00 or G30 for AD, F01 for VaD, and F03 or G31 for other types of dementia. For the validity of diagnosis, we considered participants to have dementia when they were diagnosed with the corresponding code(s) at least twice. Unlike those with AD or VaD, participants with other types of dementia were not analyzed separately because of the heterogeneous disease entities and small sample size.

2.5 | Other variables

To adjust for the potential effect of comorbidities such as cardiovascular disease, malignancies, and diabetes mellitus, we used Quan's updated Charlson Comorbidity Index (CCI) algorithm.[30] Since dementia is our primary outcome variable, we calculated CCI, except for dementia, which was included in the original CCI calculation. In addi-

tion to CCI, a history of psychiatric (mood, anxiety, and psychotic disorders) and sleep disorders was considered as covariates.

To account for changes in BMI due to medication, we calculated the cumulated defined daily dose (cDDD) of medications that have the potential to cause either weight gain or loss. We regarded the following medications as having the potential to cause weight gain:[31] olanzapine, clozapine, nortriptyline, imipramine, doxepin, mirtazapine, paroxetine, levetiracetam, valproic acid, prednisone, prednisolone, methylprednisolone, dexamethasone, and betamethasone. On the other hand, the following medications were considered to have the potential to cause weight loss:[31] topiramate, liraglutide, metformin, bupropion, and naltrexone.

This study also assessed factors such as blood pressure, socioeconomic status (income level ≤ 20th percentile or > 20th percentile), region of residence (city or rural), and self-reported smoking history (no smoking, ever smoking, or current smoking) and alcohol consumption (no drinking, 2 to 3 times a month, 1 to 2 times a week, 3 to 4 times a week, or almost daily). Additionally, exercise frequency (< 3 times a week or ≥ 3 times a week) was self-reported by participants.

2.6 | Statistical analysis

To correct for the potential confounding effect of baseline characteristic differences between participants with and without obesity (defined by BMI), the propensity scores were matched. Each participant's propensity score was calculated using logistic regression adjusted for baseline age, sex, income, region of residence, smoking history, alcohol consumption, exercise frequency, systolic blood pressure, CCI, history of psychiatric and sleep disorders, and cDDD of medications with potential to cause weight gain and loss. Based on the propensity scores, we matched participants without obesity to those with obesity in a 1:1 ratio using the local optimal algorithm. This matching yielded an equal sample size of 2976 in the obesity and non-obesity groups (Supplementary Figure 1).

Baseline demographics and comorbidities between participants with and without obesity were characterized using descriptive statistics and compared using the absolute standardized difference (ASD). Multivariable Cox proportional hazard regression models were used to explore the association between BMI loss and risk of dementia. The main explanatory variable was the presence or absence of BMI loss or the amount of BMI loss, either expressed as a continuous variable (%) or a categorical variable (ie, large loss [> 5%], small loss [> 3% to 5%], stable [loss or gain ≤ 3%], small gain [> 3% to 5%], and large gain [> 5%]). The models were adjusted for baseline age, sex, income, region of residence, smoking history, alcohol consumption, exercise frequency, systolic blood pressure, CCI, history of psychiatric and sleep disorders, and cDDD of medications with potential to cause weight gain and loss. We applied Cox regression models after stratifying participants with and without obesity The proportional hazard assumption was tested using the Schoenfeld residuals.

We conducted three sensitivity analyses to assess the robustness of the association between baseline obesity, BMI loss, and risk of dementia. In Sensitivity Model 1, we redefined patients with dementia as those who were prescribed anti-dementia medications (donepezil, rivastigmine, galantamine, or memantine) with corresponding ICD-10 codes. This definition was validated for the diagnosis of all-cause dementia with a positive predictive value of 94.7% in a previous study.[32] In Sensitivity Model 2, participants with severe obesity (BMI ≥ 30 kg/m^2) or underweight (BMI < 18.5 kg/m^2) at baseline were excluded to eliminate the influence of baseline cachexic or morbidly obese conditions. In Sensitivity Model 3, we only used data in which diagnosis of dementia was made by psychiatrists or neurologists to ensure the accuracy of code-based diagnostic classification.

In addition to BMI loss, we investigated the association between WC loss and risk of dementia in the same 1:1 propensity score-matched study sample (by BMI, n = 2976 for each group). For each group, we applied Cox regression models, where the presence or absence of WC loss or the amount of WC loss as a continuous variable was the main explanatory variable with the same covariates. An additional 1:1 propensity score matching was conducted between participants with and without central obesity (by WC) among the original 9839 participants (n = 3048 per group, Supplementary Figure 2). We then applied the same Cox regression models to participants with and without central obesity.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.2 (R Foundation for Statistical Computing), with statistical significance set at p value < .05. All missing data were addressed through listwise deletion.

3 | RESULTS

3.1 | Baseline characteristics of study participants

The baseline characteristics of the study sample (year 2008) are presented in Table 1. Before propensity score matching, participants without obesity were older and predominantly male, had lower systolic and higher diastolic blood pressure, were more smokers and alcohol drinkers, and had higher mortality (ASDs > 0.1, Table 1, left panel) than those with obesity. The incidences of all-cause dementia, AD, and VaD were not different between the two groups. After propensity score matching, significant differences disappeared in baseline characteristics between participants with and without obesity except for alcohol consumption (ASDs < 0.1, Table 1, right panel). The mean age of the propensity score-matched participants was 70.9 (standard deviation of 3.38) years, and males predominated (54.4%). Follow-up BMI and WC assessments were conducted at an average of 12.1 months. The mean BMI and WC in participants without obesity were 22.1 kg/m^2 and 80.7 cm, respectively, while those in participants with obesity were 27.1 kg/m^2 and 90.3 cm, respectively.

3.2 | BMI loss and risk of dementia: stratified by baseline obesity

Figure 1 depicts Cox regression models of the association between BMI loss and risk of dementia in the propensity score-matched

TABLE 1 Demographic and clinical characteristics of participants at baseline

	Before propensity score matching			After propensity score matching		
	Participants without obesity ($n = 6600$)	Participants with obesity ($n = 3089$)	ASD	Participants without obesity ($n = 2976$)	Participants with obesity ($n = 2976$)	ASD
Age	71.4 (3.83)	70.9 (3.37)	0.126	70.9 (3.38)	70.9 (3.38)	0.020
Sex			0.164			0.013
Male	4137 (62.7%)	1687 (54.6%)		1629 (54.7%)	1610 (54.1%)	
Female	2463 (37.3%)	1402 (45.4%)		1347 (45.3%)	1366 (45.9%)	
Systolic blood pressure (mmHg)	130.2 (16.47)	134.3 (16.29)	0.253	133.9 (16.95)	134.1 (16.10)	0.012
Diastolic blood pressure (mmHg)	78.5 (10.14)	80.6 (10.12)	0.210	80.2 (10.46)	80.5 (10.11)	0.033
BMI (kg/m^2)	22.1 (1.97)	27.1 (1.82)	2.612	22.3 (1.93)	27.1 (1.82)	2.566
BMI change (%)	0.4 (5.82)	−1.3 (4.73)	0.327	0.5 (5.85)	−1.3 (4.71)	0.339
WC (cm)	80.7 (6.97)	90.3 (6.66)	1.410	80.7 (6.95)	90.3 (6.70)	1.404
WC change (%)	0.1 (5.49)	−1.3 (4.41)	0.063	0.2 (5.62)	−1.3 (4.38)	0.056
Time to next measurement of BMI and WC (month)	12.1 (3.81)	12.2 (3.83)	0.021	12.3 (3.84)	12.2 (3.82)	0.024
CCI	0.8 (1.23)	0.9 (1.26)	0.075	0.8 (1.29)	0.9 (1.25)	0.044
Income level by insurance fee			0.060			0.017
Bottom 0 to 20th percentile	2308 (35.0%)	993 (32.1%)		979 (32.9%)	956 (32.1%)	
Bottom 20th to 100th percentile	4292 (65.0%)	2096 (67.9%)		1997 (67.1%)	2020 (67.9%)	
Region of residence			0.066			0.021
Rural area	2103 (31.9%)	891 (28.8%)		832 (28.0%)	860 (28.9%)	
Urban area	4497 (68.1%)	2198 (71.2%)		2144 (72.0%)	2116 (71.1%)	
Smoking			0.183			0.041
No smoking	4736 (74.9%)	2449 (81.7%)		2482 (83.4%)	2427 (81.6%)	
Ever smoking	530 (8.4%)	214 (7.1%)		174 (5.8%)	214 (7.2%)	
Current smoking	1061 (16.8%)	336 (11.2%)		320 (10.8%)	335 (11.3%)	
Missing	273	90		0	0	
Alcohol consumption			0.162			0.101
No drinking	4382 (67.0%)	2175 (71.0%)		2193 (73.7%)	2128 (71.5%)	
2 to 3/month	610 (9.3%)	299 (9.8%)		239 (8.0%)	287 (9.6%)	
1 to 2/week	762 (11.7%)	324 (10.6%)		290 (9.7%)	310 (10.4%)	
3 to 4/week	384 (5.9%)	147 (4.8%)		123 (4.1%)	136 (4.6%)	
Almost daily	400 (6.1%)	117 (3.8%)		131 (4.4%)	115 (3.9%)	
Missing	62	27		0	0	
Exercise frequency			0.024			0.013
0 to 2/week	4880 (74.6%)	2254 (73.6%)		2204 (74.3%)	2191 (73.7%)	
≥ 3/week	1662 (25.4%)	810 (26.4%)		763 (25.7%)	781 (26.3%)	
Missing	58	25		9	4	
History of psychiatric diseases	1382 (20.9%)	651 (21.1%)	0.003	643 (21.6%)	630 (21.2%)	0.011
History of insomnia	857 (13.0%)	418 (13.5%)	0.016	399 (13.4%)	409 (13.7%)	0.010
cDDD of medications with potential to cause weight gain	3.1 (12.79)	3.3 (15.19)	0.013	3.1 (13.68)	3.3 (15.31)	0.010
cDDD of medications with potential to cause weight loss	4.5 (22.94)	7.0 (28.40)	0.098	6.4 (28.07)	7.0 (28.20)	0.020
Follow-up months	49.7 (8.99)	50.1 (8.31)	0.050	50.0 (8.39)	50.1 (8.34)	0.016

(Continues)

TABLE 1 (Continued)

	Before propensity score matching			After propensity score matching		
	Participants without obesity ($n = 6600$)	Participants with obesity ($n = 3089$)	ASD	Participants without obesity ($n = 2976$)	Participants with obesity ($n = 2976$)	ASD
All-cause dementia	590 (8.9%)	285 (9.2%)	0.010	245 (8.2%)	278 (9.3%)	0.039
AD	315 (4.8%)	138 (4.5%)	0.015	127 (4.3%)	135 (4.5%)	0.013
VaD	98 (1.5%)	53 (1.7%)	0.018	32 (1.1%)	53 (1.8%)	0.060
All-cause mortality	450 (6.8%)	130 (4.2%)	0.115	181 (6.1%)	126 (4.2%)	0.084

Note: Values are presented in mean (standard deviation) for continuous variables or n (%) for categorical variables.
Abbreviations: AD, Alzheimer's disease; ASD, absolute standardized difference; BMI, body mass index; CCI, Charlson Comorbidity Index; cDDD, cumulative defined daily dose; VaD, vascular dementia; WC, waist circumference.

participants stratified by baseline obesity. In participants without obesity, those with BMI loss showed a higher risk of all-cause dementia and AD, but not VaD, compared with those without BMI loss (Figure 1A upper panel). In contrast, BMI loss in participants with obesity was not associated with the risk of all-cause dementia, AD, or VaD (Figure 1A lower panel). Summaries of the cumulative incidence plots including the number at risk are described in Supplementary Table 2. The results of Cox models where the main explanatory variable was the amount of BMI loss (continuous variable) are demonstrated in Figure 1B. The risk of all-cause dementia was significantly increased by 3.3% per 1% BMI loss in participants without obesity ($p = .004$), but not in those with obesity. Likewise, the risk of AD was elevated by 4.8% for every 1% loss in BMI in participants without obesity ($p = .002$), but this association lost significance in those with obesity. Regardless of baseline obesity, BMI loss was not associated with the risk of VaD.

Figure 2 shows the results of the Cox regression analyses where BMI change was divided into five categories with stable BMI (−3% to 3%) as a reference. In participants without obesity, the risk of all-cause dementia increased gradually from participants with stable BMI (adjusted hazard ratio [aHR]: 1.00) to those with small BMI loss (aHR: 1.36, 95% confidence interval [CI]: 0.92 to 2.01, $p = .120$), and with large BMI loss (aHR: 1.45, 95% CI: 1.01 to 2.08, $p = .045$). However, this pattern was not observed in those with obesity. Similarly, only in participants without obesity, the risk of AD consistently increased as the total five categories ordered from large BMI gain (aHR: 0.82, 95% CI: 0.48 to 1.43, $p = .490$) to large BMI loss (aHR: 1.69, 95% CI: 1.05 to 2.72, $p = .030$). Meanwhile, BMI loss or gain was not associated with the risk of VaD regardless of baseline obesity. Supplementary Table 3 shows the details of the five-category analysis.

3.3 | Sensitivity analysis: BMI loss, risk of dementia, and obesity

Supplementary Table 4 presents the three models of sensitivity analyses to assess the relationship between risk of dementia and BMI loss stratified by baseline obesity. In Sensitivity Model 1, we redefined the dementia patients by anti-dementia medication plus ICD codes. Cox regression analyses showed an elevated risk of AD (aHR: 1.60, 95% CI: 1.04 to 2.46, $p = .033$) by BMI loss in participants without obesity, not in those with obesity. Sensitivity Model 2, where we excluded participants with underweight (BMI < 18.5 kg/m^2) or severe obesity (BMI ≥ 30 kg/m^2), also presented the discrepancy between participants with and without baseline obesity; BMI loss in participants without obesity increased the risk of all-cause dementia (aHR: 1.51, 95% CI: 1.17 to 1.98, $p = .002$) and AD (aHR: 1.51, 95% CI: 1.08 to 2.10, $p = .032$), but BMI loss in those with obesity did not. In Sensitivity Model 3, only data on dementia diagnoses made by neurologists or psychiatrists were used. As a result, BMI loss was associated with increased risk of all-cause dementia (aHR: 1.64, 95% CI: 1.15 to 2.34, $p = .006$) and AD (aHR: 1.63, 95% CI: 1.05 to 2.51, $p = .028$) only in participants without obesity.

The same sensitivity analyses were conducted regarding the amount of BMI loss (%) as a continuous variable (Table 2). All three models showed consistent results with the original analyses that risk of all-cause dementia and AD was significantly elevated per 1% loss in BMI in participants without obesity, not in those with obesity. Next, BMI change as a five-category variable with stable BMI (loss or gain ≤ 3%) as a reference level was presented in Supplementary Table 5. In Sensitivity Models 1 and 2, the numerical values of aHR regarding all-cause dementia and AD increased stepwise in the order of conditions with stable BMI, small BMI loss, and large BMI loss in participants without obesity, although statistical significance was only observed in large BMI loss. The Sensitivity Model 3 showed somewhat different results from the original analysis: although the pattern of increasing aHR according to the degree of BMI loss was obvious for AD (in those without obesity), such a pattern was not obvious for all-cause dementia. On the other hand, significant associations disappeared in those with obesity in all sensitivity analysis models, consistent with the results of original analyses.

3.4 | WC loss and risk of dementia: stratified by baseline obesity

In participants without obesity, those with WC loss did not have increased risk of all-cause dementia, AD, or VaD (Figure 3A upper panel and Supplementary Table 6). However, the cumulative incidence of AD,

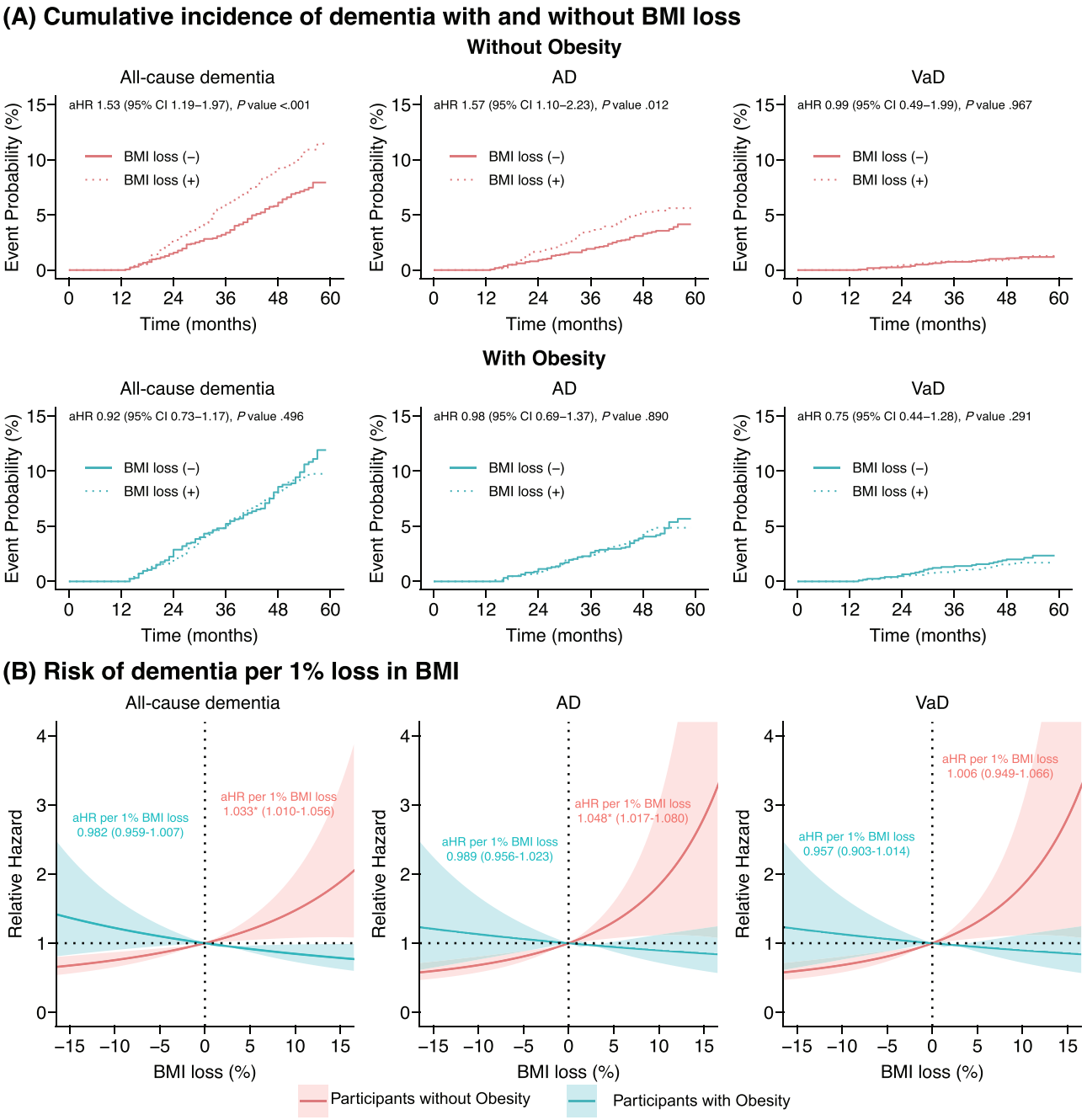

FIGURE 1 Association between BMI loss and risk of dementia stratified by obesity. (A) *P* values and aHRs were calculated from Cox proportional hazard regression models where the presence or absence of BMI loss as a binary variable was the main explanatory variable. Models were adjusted for age, sex, income, region of residence, smoking history, alcohol consumption, exercise frequency, systolic blood pressure, CCI, history of psychiatric and sleep disorders, and cDDD of medications with potential to cause weight gain and loss. BMI loss (+) refers to participants with BMI loss. (B) Cox proportional hazard regression models where BMI loss (%) is a continuous and main explanatory variable with adjustment for same covariates. Relative hazards were calculated with BMI loss of 0% as reference. (–) values in BMI loss mean BMI gain. *P value < .05. Abbreviations: AD, Alzheimer's disease; aHR, adjusted hazard ratio; BMI, body mass index; CCI, Charlson Comorbidity Index; cDDD, cumulative defined daily dose; VaD, vascular dementia.

not all-cause dementia or VaD, was significantly lower in participants with WC loss than those without WC loss among those with obesity (Figure 3A lower panel and Supplementary Table 6). These results were different from those of participants with BMI loss (Figure 1A).

Similarly, the amount of WC loss as a continuous variable was not associated with risk of all-cause dementia in participants both with and without obesity (Figure 3B left panel). Risk of AD was decreased by 1% WC loss in participants with obesity (p = .004), not in those

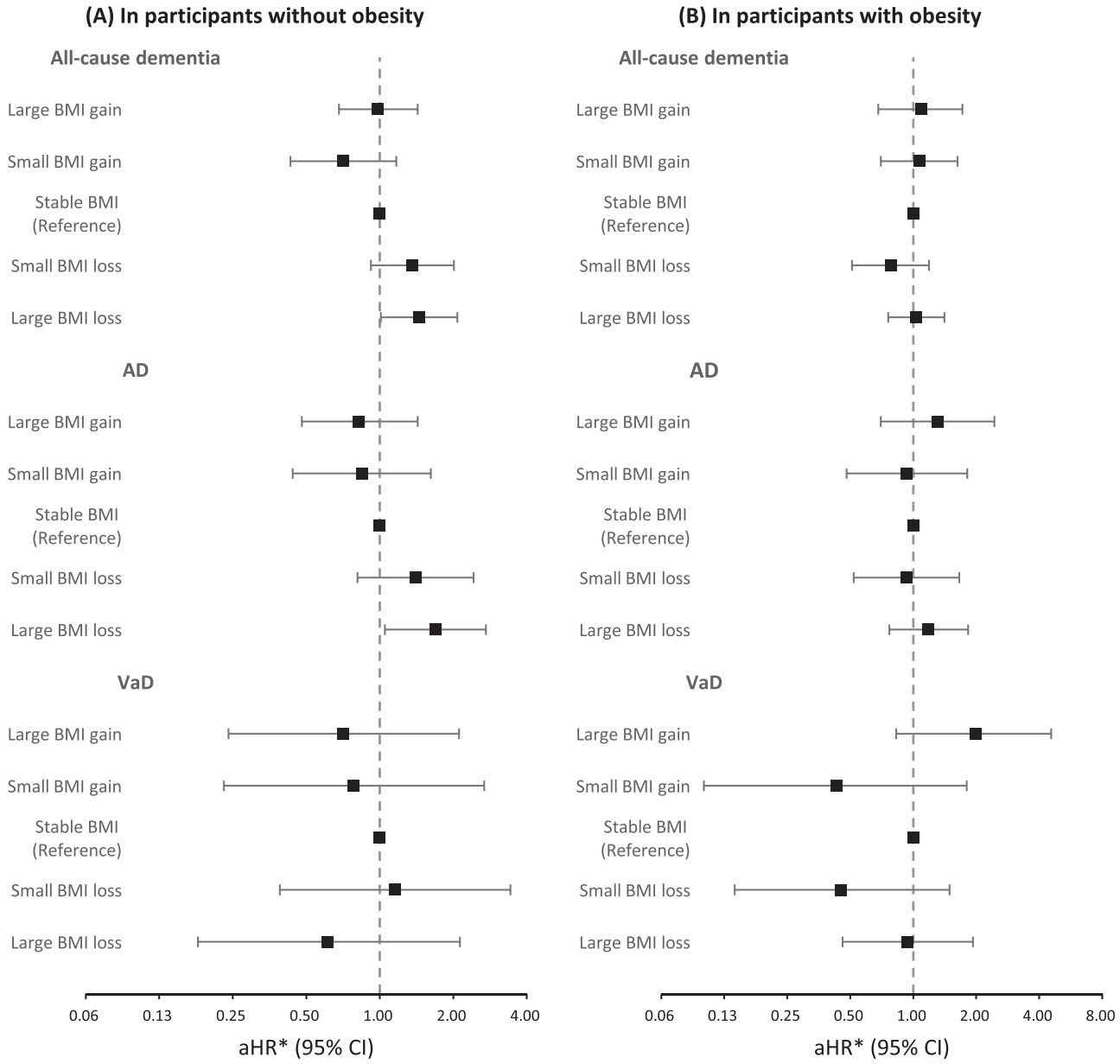

FIGURE 2 Association between BMI change and risk of dementia stratified by obesity – BMI change as a categorical variable. Large BMI loss/gain is defined as a change of > 5%, small BMI loss/gain is a change of > 3% to 5%, and stable BMI loss/gain is a change of ≤ 3%. *Adjusted for age, sex, income, region of residence, smoking history, alcohol consumption, exercise frequency, systolic blood pressure, CCI, history of psychiatric and sleep disorders, and cDDD of medications with potential to cause weight gain and loss. Abbreviations: AD, Alzheimer's disease; aHR, adjusted hazard ratio; BMI, body mass index; CCI, Charlson Comorbidity Index; cDDD, cumulative defined daily dose; CI, confidence interval; VaD, vascular dementia.

without (Figure 3B middle panel). Like BMI, WC loss did not predict VaD in participants both with and without obesity (Figure 3C).

3.5 | WC loss and risk of dementia: stratified by baseline central obesity

The association between WC loss and risk of dementia in participants with and without central obesity is presented in Supplementary Figure 3. After adjusting for covariates, participants with WC loss presented reduced AD risk in central obesity but not in non-central obesity (aHR: 0.66, 95% CI: 0.47 to 0.93, $p = .017$, Supplementary Figure 3A). The amount of WC loss as a continuous variable had no significant association with risk of all-cause dementia, AD, or VaD in participants both with and without central obesity (Supplementary Figure 3B).

4 | DISCUSSION

To date, no study has explored the association between weight loss and subsequent risk of dementia considering the presence or absence of baseline obesity on a nationwide population scale. We found that

TABLE 2 Sensitivity analyses of association between BMI loss and risk of dementia - BMI loss (%) as a continuous variable

	aHR* (95% CI)		
	All-cause dementia	AD	VaD
Sensitivity Model 1			
Without obesity	1.043 (1.010 to 1.076)**	1.056 (1.018 to 1.096)**	1.043 (0.967 to 1.126)
With obesity	0.987 (0.954 to 1.021)	0.977 (0.938 to 1.016)	0.942 (0.875 to 1.015)
Sensitivity Model 2			
Without obesity	1.035 (1.011 to 1.059)**	1.044 (1.012 to 1.077)**	1.02 (0.955 to 1.089)
With obesity	0.980 (0.956 to 1.006)	0.986 (0.951 to 1.023)	0.960 (0.904 to 1.020)
Sensitivity Model 3			
Without obesity	1.035 (1.004 to 1.068)**	1.046 (1.009 to 1.084)**	1.002 (0.921 to 1.090)
With obesity	0.995 (0.962 to 1.029)	0.988 (0.947 to 1.031)	0.975 (0.896 to 1.062)

Model 1: Definition of dementia by ICD-10 codes plus anti-dementia medications (donepezil, rivastigmine, galantamine, and memantine).
Model 2: Exclusion of participants with underweight (BMI < 18.5 kg/m^2) or severe obesity (BMI ≥ 30 kg/m^2).
Model 3: Diagnosis of dementia by psychiatrists or neurologists.
Abbreviations: AD, Alzheimer's disease; aHR, adjusted hazard ratio; BMI, body mass index; CCI, Charlson Comorbidity Index; cDDD, cumulative defined daily dose; CI, confidence interval; ICD, International Classification of Diseases; VaD, vascular dementia.
*Cox regression models where BMI loss is a continuous variable (%). aHR means adjusted risk of outcome by 1% loss in BMI. Adjusted for age, sex, income, region of residence, smoking history, alcohol consumption, exercise frequency, systolic blood pressure, CCI, history of psychiatric and sleep disorders, and cDDD of medications with potential to cause weight gain and loss.
**P value < .05.

BMI loss in the non-obese state, but not in the obese state, was longitudinally associated with increased risk of all-cause dementia and AD during the 4-year observational period. To identify this relationship, three different models of sensitivity analyses were used. The results strongly indicate that the association of weight loss with the risk of dementia is context-dependent: unfavorable weight loss (BMI loss in the non-obese state) versus favorable weight loss (BMI loss in the obese state). Our finding is consistent with that of a recent cohort study, which showed a decreased risk of diabetes with weight loss in individuals with obesity; however, this favorable association was reversed in those without obesity.[33] Unlike BMI loss, WC loss in the non-obese state was not associated with the risk of all-cause dementia or AD, while WC loss in the obese state was associated with a decreased risk of AD.

4.1 | Obesity versus non-obesity: difference in association between BMI loss and risk of dementia

In participants without obesity, BMI loss was associated with increased risk of all-cause dementia and AD. BMI loss before diagnosis of dementia may be due to motivational, olfactory, or hypothalamic dysfunction.[13,20,34] Previous studies demonstrated that cognitively normal older adults with a higher burden of amyloid beta or cerebral vascular disease pathology showed faster BMI decline.[22,34] These findings suggest that BMI loss itself may be linked to pathophysiology of dementia.

However, our results suggest that BMI loss may not predict the development of dementia in individuals with obesity. Our results are consistent with the concept of "obesity paradox" whereby obesity can be a paradoxically protective indicator against dementia[6,7,14] and mortality[35] in older adults. The reason for the attenuated association between BMI loss and the risk of dementia in obesity remains to be elucidated. A possible explanation is that BMI does not accurately measure adiposity.[7] In addition to adipose tissue mass, muscle mass is also captured in the BMI and can be protective against neurodegeneration and dementia.[36] Our results suggest that participants with obesity may have more muscle mass than those without obesity, which may buffer the detrimental effect of BMI loss. Furthermore, adiposity itself may have a role in protection against dementia risk. A recent prospective study showed that high adiposity in older adults predicted a reduced risk of dementia.[15] The neuroprotective role of hormones such as leptin or estrogen could be suggested for this finding.[1,37] Further prospective studies are needed to measure muscle and adipose tissue mass.

4.2 | Risk of dementia according to subtype

Our study showed that BMI loss in the non-obese state predicted an increased risk of all-cause dementia and AD but not VaD. Furthermore, in Sensitivity Model 3 using categorical BMI changes (Supplementary Table 5), significant associations between BMI loss and increased risk were observed only for AD, not for all-cause dementia or VaD. Dementia subtypes, such as AD and VaD, have been included in some studies, which presented mixed results. An analysis of a Japanese-American cohort demonstrated that patients with VaD and AD tended to lose weight in 6 years before diagnosis.[17] Another study of a community-dwelling sample with a follow-up period of 5.4 years showed a high BMI as a predictor of a low incidence of both AD and VaD.[7] However,

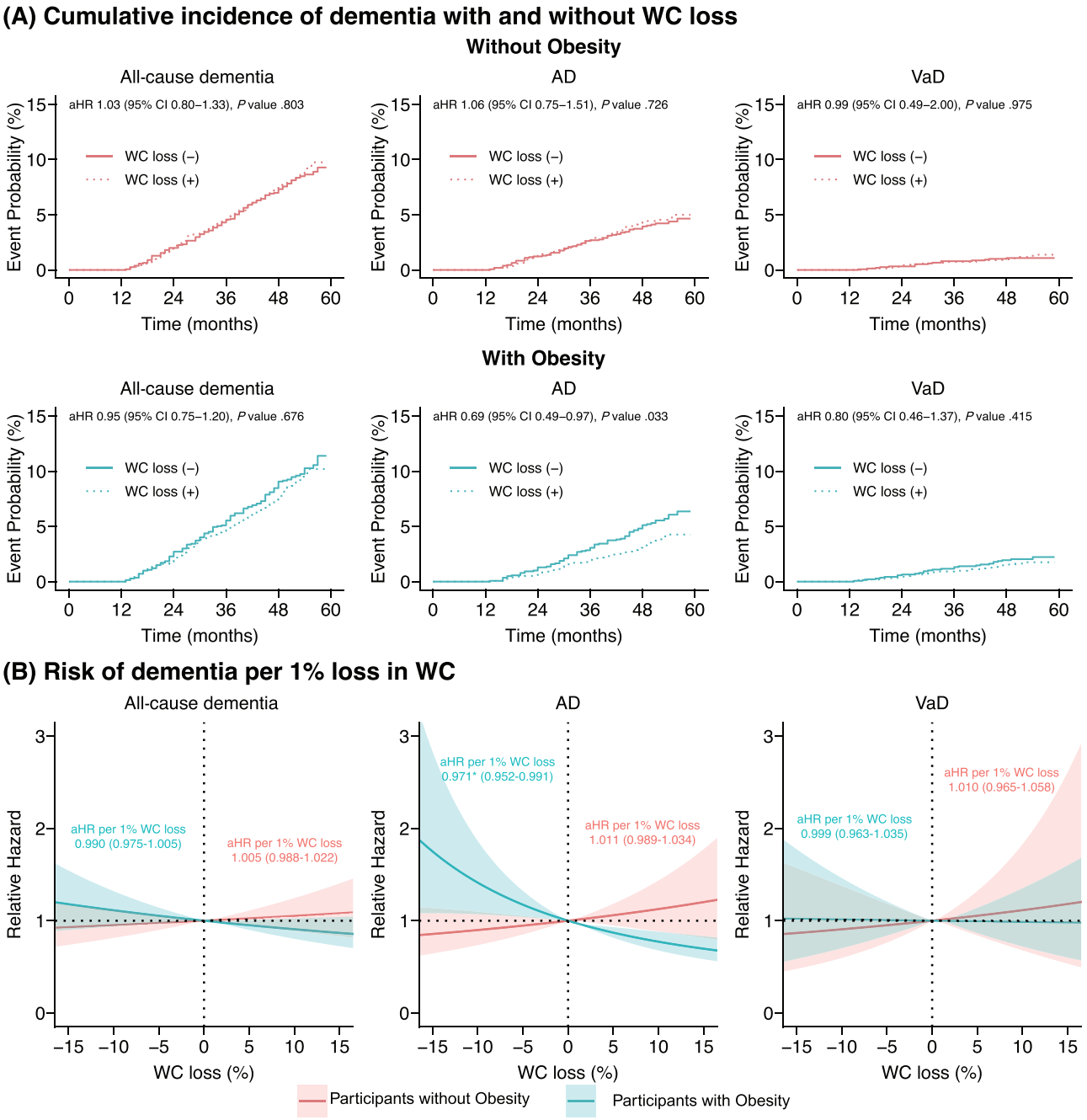

FIGURE 3 Association between WC loss and risk of dementia stratified by obesity. (A) P values and aHRs were calculated from Cox proportional hazard regression models where the presence or absence of WC loss as a binary variable was the main explanatory variable. Models were adjusted for age, sex, income, region of residence, smoking history, alcohol consumption, exercise frequency, systolic blood pressure, CCI, history of psychiatric and sleep disorders, and cDDD of medications with potential to cause weight gain and loss. WC loss (+) refers to participants with WC loss. (B) Cox proportional hazard regression models where WC loss (%) is a continuous and main explanatory variable with adjustment for same covariates. Relative hazards were calculated with WC loss of 0% as reference. (–) values in WC loss mean WC gain. * *P* value < .05. Abbreviations: aHR, adjusted hazard ratio; AD, Alzheimer's disease; aHR, adjusted hazard ratio; CCI, Charlson Comorbidity Index; cDDD, cumulative Defined Daily Dose; VaD, vascular dementia; WC, waist circumference.

studies from the Rochester Epidemiology Project and Kame Project showed that BMI or weight loss was associated with all-cause dementia and AD, but not with VaD,[8,20] consistent with our findings. Furthermore, patients with AD demonstrated more BMI or weight loss as a prodromal symptom in previous studies that did not consider VaD as an outcome.[11,18,19] A recent autopsy study also reported that AD pathologies, such as neuritic plaques and neurofibrillary tangles, are associated with faster BMI decline.[22] In contrast, a study of a cohort of Swedish women showed that high BMI was significantly associated with all-cause dementia, but with neither pure AD nor VaD.[9] Although

our findings indicate that BMI loss may be associated with neurodegeneration rather than vascular injury, further replicative longitudinal studies should be conducted with respect to the observational nature of this study. Moreover, possible inaccuracy in diagnosis using ICD-10 codes is an unavoidable limitation of our study. A future large-scale prospective study with detailed diagnostic assessments, including neuroimaging, will help confirm the relationship between weight loss and AD or VaD.

4.3 | Association between WC loss and risk of dementia: different from BMI loss

Unlike BMI loss, WC loss in the non-obese state was not associated with the risk of all-cause dementia, AD, or VaD. Rather, WC loss decreased AD risk in the obese state after adjustment for covariates. When participants were grouped by central obesity, those with WC loss also showed lower AD risk only in central obesity. Compared with BMI, WC is considered better to explain obesity-related health status, such as metabolic syndrome.[5,25] Previous studies indicated that the development of dementia is associated not only with midlife central obesity[38] but also with late-life central obesity.[39] Our findings suggest that BMI loss may precede the diagnosis of dementia; however, reduced central adiposity, measured by WC, may not be a predictive indicator of the development of dementia in older adults without obesity.

4.4 | Strength of this study

To the best of our knowledge, this is the first study to explore the prospective association between BMI loss and dementia according to baseline obesity, using nationwide cohort data. In addition to BMI loss, WC loss was also simultaneously measured to evaluate the longitudinal association between central adiposity, obesity, and dementia. Loss in BMI or WC was not only classified as presence or absence but also quantified as a continuous variable to illuminate the shape of relationship between loss in BMI or WC and risk of dementia.

4.5 | Limitations

This study has several limitations. First, despite the adjustment for self-reported physical exercise frequency, we could not determine whether BMI loss in this study sample was due to weight reduction strategies, such as physical exercise that reduces cardiovascular risk and neurodegeneration.[2] Second, we could not evaluate and adjust for other important elements related to dementia or adiposity, such as *APOE ε4* status, years of education, and adipokine (adiponectin or leptin) levels, all of which could affect the association between BMI loss and dementia. Third, because this study used claim data using ICD-10 codes, the diagnostic accuracy of dementia was not guaranteed. The prevalence of all-cause dementia and AD in our study sample was 9.0% and 4.7%, respectively, which is comparable to the previously reported epidemiology in South Korea.[40] Moreover, in Sensitivity Model 1, we used a once-validated definition of all-cause dementia, which had a positive predictive value of 94.7%.[32] We tried to further minimize the possible misclassification by selecting participants with dementia whose diagnoses were made by psychiatrists or neurologists and obtained a consistent conclusion (Sensitivity Model 3). Nevertheless, the utilization of unified diagnostic criteria for dementia would have been better. Lastly, a relatively small number of participants with VaD, despite the prevalence being in line with general epidemiology,[40] could not be sufficient to maintain meaningful power. In addition, other types of dementia, such as Parkinson's disease dementia and Lewy body dementia, were not evaluated because of the insufficient sample size.

4.6 | Conclusion

In this longitudinal study of a nationwide cohort of older adults, we found that BMI loss in the non-obese state for 1 year predicted an increased risk of all-cause dementia and AD, but BMI loss in the obese state did not. In contrast to BMI, WC loss in the non-obese state was not associated with an increased risk of dementia, whereas WC loss predicted decreased risk of AD in the obese state. Further longitudinal studies measuring muscle and fat mass are needed to reveal the association between BMI or WC loss and dementia in older adults.

AUTHOR CONTRIBUTIONS

Keun You Kim: conceptualization, methodology, formal analysis, data curation, visualization, writing – original draft preparation. Junghee Ha: resources, investigation. Jun-Young Lee: supervision, writing – reviewing and editing. Eosu Kim: conceptualization, supervision, writing – reviewing and editing, funding acquisition, project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests to report.

CONSENT STATEMENT

Not applicable

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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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