BMI, Weight Change, and Dementia Risk in Patients With New-Onset Type 2 Diabetes: A Nationwide Cohort Study

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OBJECTIVE

This study examined the association between baseline BMI, percentage weight change, and the risk of dementia in patients newly diagnosed with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Using the South Korean National Health Insurance Service-National Health Screening Cohort database, we identified 167,876 subjects aged ≥40 years diagnosed with new-onset type 2 diabetes between 2007 and 2012. Their weight changes were monitored for ∼2 years after diagnosis, with follow-up assessments occurring for an average of 3.5 years. The hazard ratios (HRs) and Bonferroni-adjusted 95% CIs of all-cause dementia, Alzheimer disease (AD), and vascular dementia were estimated using multivariable Cox proportional hazards regression models.

RESULTS

We identified 2,563 incident dementia cases during follow-up. Baseline BMI among patients with new-onset type 2 diabetes was inversely associated with the risk of all-cause dementia and AD, independent of confounding variables (*P* for trend <0.001). The percentage weight change during the 2 years after a diagnosis of type 2 diabetes showed significant U-shaped associations with the risk of all-cause dementia development (*P* < 0.001); the HRs of the disease increased significantly when weight loss or gain was >10% (1.34 [95% CI 1.11–1.63] and 1.38 [1.08–1.76], respectively). Additionally, weight loss >10% was associated with an increased risk of AD (HR 1.26 [95% CI 1.01–1.59]).

CONCLUSIONS

A lower baseline BMI was associated with increased risks of all-cause dementia and AD in patients with new-onset type 2 diabetes. Weight loss or weight gain after the diagnosis of diabetes was associated with an increased risk of all-cause dementia. Weight loss was associated with an increased risk of AD.

Type 2 diabetes and dementia are major chronic diseases with increasing prevalence and are expected to have substantial impacts on the aging population (1,2). Recent evidence implies that type 2 diabetes is associated with an increased risk of cognitive decline and incident dementia (3–8). Although the underlying mechanisms remain unclear, it has been hypothesized that cerebrovascular pathologies are influenced by hyperglycemia and insulin resistance (9,10). Moreover, any specific treatment for dementia in patients with type 2 diabetes has been unknown. It is therefore important

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to identify risk factors for cognitive decline and dementia in patients with type 2 diabetes.

In the general population, there is a growing interest in the role of simple and feasible measures of adiposity in relation to predicting dementia development (11–14). High adiposity can lead to cognitive decline in late life through vascular and dysmetabolic pathways, and accumulation of brain lesions through these pathways may further increase the risk of dementia with their longer duration throughout the life course (15). Thus, the predictive roles of BMI and weight change for the onset of Alzheimer disease (AD) have been extensively investigated. However, methodological differences have resulted in discrepancies among studies regarding the effects of BMI and weight change on cognitive prognoses. Moreover, these studies have predominantly been conducted in Western nations, whereas obesity parameters and the frequency of dementia differ across ethnic groups (16). Although these parameters have clinical implications in the prevention and treatment of type 2 diabetes (17), there are limited data on the association between baseline BMI, weight change, and the risk of incident dementia in patients with type 2 diabetes. We conducted a nationwide population-based cohort study to explore the association of baseline BMI and weight change with the risk of dementia in patients newly diagnosed with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Subjects

We used a database provided by the South Korean National Health Insurance Service (NHIS), which is a single insurer managed by the South Korean government. The NHIS manages a mandatory universal insurance system that covers ~97% of the South Korean population and provides biannual health examinations for all insured Koreans. Hence, the South Korean NHIS retains an extensive data set of 50,000,000 Koreans that includes patient demographics, medical treatments and procedures, and disease diagnoses according to the ICD-10-CM codes. Since 2015, the South Korean NHIS has released a nationally representative data set that includes nearly the entire Korean population and is open to all researchers whose study protocols are approved by an official review committee.

To identify patients with new-onset type 2 diabetes among all individuals (n = 25,315,068) who had undergone health examinations between 1 January 2007 and 31 December 2012, we excluded individuals aged <40 years (n = 6,928,382), those with a fasting plasma glucose (FPG) level <126 mg/dL at the first health examination (n = 17,415,192), and those with a prior history of diabetes (n = 659,776). We then excluded individuals without a follow-up examination within 2 years (n = 136,215), those diagnosed with cancer (n = 5,528), those with a prior diagnosis of dementia between 2002 and enrollment (n = 979), and those with any missing variables (n = 1,120). Finally, 167,876 individuals with new-onset type 2 diabetes (108,025 men and 59,851 women) with 2 years of body weight change measurements were enrolled in this study (Fig. 1). Participants were tracked until 31 December 2015. The mean follow-up duration was 3.5 ± 1.7 years. This study was approved by the The Catholic University of Korea Institutional Review Board (No. SC18ZESI0022).

Definition of Dementia

Dementia was diagnosed based on the relevant ICD-10-CM codes (F00 or G30 for AD; F01 for vascular dementia [VD]; and F02, F03, or G31 for other dementia) and the prescription of one or more medications for dementia (donepezil, rivastigmine, galantamine, or memantine). When there were codes for both AD and VD, the main diagnosis was extracted as the final diagnosis. If both codes for AD and VD were as an additional diagnosis, the main diagnosis at the next visit was extracted as the final diagnosis. If there was neither AD nor VD as a main diagnosis up to the second claim database, the diagnosis was defined as "other dementia."

BMI and Weight Change

Height, weight, and waist circumference (WC) were measured while participants wore lightweight clothing. BMI (kg/m^2) was calculated as weight in kilograms divided by the square of height in meters. The World Health Organization recommendations for Asian populations were used to categorize individuals into five BMI groups: <18.5 kg/m^2

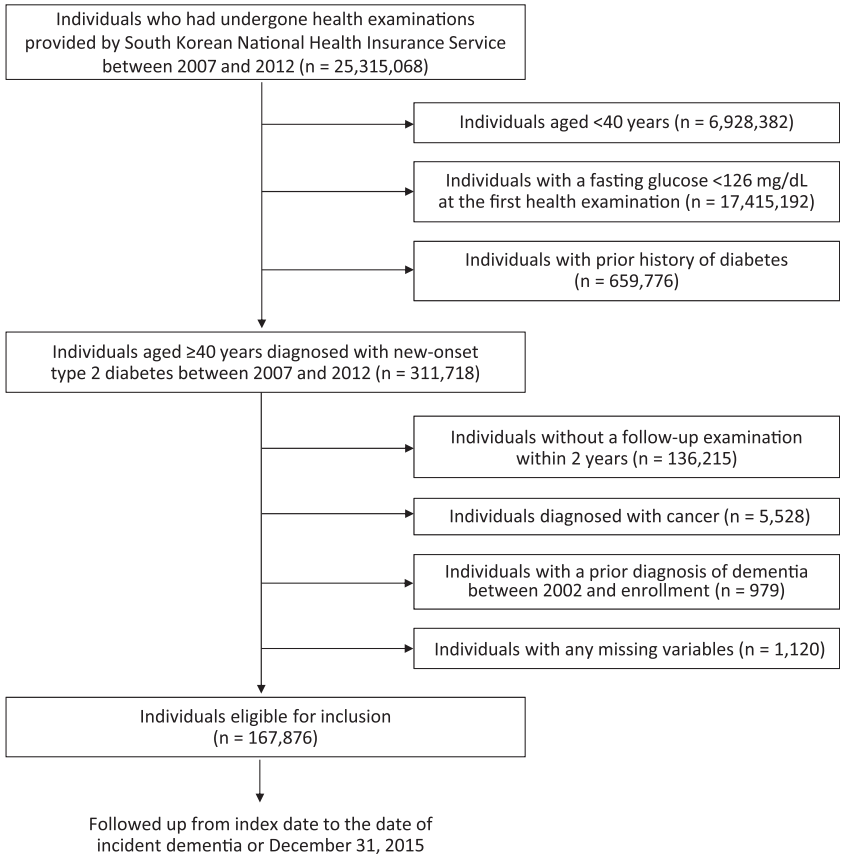

Figure 1—Flowchart of the study population.

(underweight), 18.5–22.9 kg/m^2 (normal), 23.0–24.9 kg/m^2 (overweight), 25.0–29.9 kg/m^2 (class I obese), or ≥30 kg/m^2 (class II obese) (18). Weight change was calculated as the difference in weight from the time of diagnosis of type 2 diabetes until 2 years later. We defined ≤5% weight change as "stable weight" and categorized "weight change" into groups of 5% increments: *1*) ≥10% weight loss, *2*) 5–10% weight loss, *3*) 5–10% weight gain, and *4*) ≥10% weight gain.

Covariates

We assessed subject demographics and lifestyle through standardized self-report questionnaires. Income level was divided into quartile groups. Smoking status was classified as nonsmokers, former smokers, or current smokers. Individuals who consumed ≥30 g/day of alcohol were defined as heavy alcohol drinkers (19). Physical activity was categorized by the frequency of ≥20 min of strenuous exercise (none, ≤4 times per week, or ≥5 times per week).

The health examination provided by the South Korean NHIS included blood pressure (BP) and laboratory measurements. Systolic and diastolic BP was measured with the individual seated after at least 5 min of rest. Blood samples were obtained after overnight fasting to measure serum glucose, total cholesterol, and creatinine levels. Baseline comorbidities, such as hypertension and dyslipidemia, were identified based on combinations of the medical history, health examination results, or ICD-10-CM and prescription codes. Hypertension was defined as BP ≥140/90 mmHg, or at least one claim per year for antihypertensive medication (ICD-10-CM codes I10–I15). Dyslipidemia was defined as a total cholesterol level ≥240 mg/dL or at least one claim per year for lipid-lowering medication (ICD-10-CM code E78). Estimated glomerular filtration rate (eGFR) was calculated using the equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and CKD was defined as an eGFR <60 mL/min/1.73 m^2 (20,21). Ischemic heart disease and stroke were identified based on the answers to the self-report questionnaire for a physician's diagnosis of angina or myocardial infarction, or stroke, respectively. Depressive disorder was defined as at least one claim per year for the ICD-10-CM codes F32 or F33.

Statistical Analyses

Statistical analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC). Clinical and demographic characteristics of the study participants were compared according to weight change (%) status using an ANOVA for continuous variables and a χ^2 test for categorical variables. Data are presented as mean ± SD for continuous variables or as number (percentage) for categorical variables. For each participant, the primary outcome between 1 January 2009 and 31 December 2015 was dementia, and the number of person-years of follow-up was counted. All-cause dementia, AD, and VD were assessed as incident dementia during 3.5 ± 1.7 years after the last recorded weighing. Incidence rates of dementia were calculated by dividing the number of events by 1,000 person-years.

Cox proportional hazards regression models were performed to evaluate the association of baseline BMI and weight change with incident dementia, and hazard ratios (HRs) and Bonferroni-adjusted 95% CIs were calculated. Model 1 was unadjusted and model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, and income. Model 3 was additionally adjusted for hypertension, dyslipidemia, CKD, history of stroke, depressive disorder, FPG level, insulin use, and number of oral antidiabetic agents used. Model 3 was further adjusted for baseline BMI in the analysis regarding the association between weight change and dementia risk. Stratified analyses were performed according to age (<65 vs. ≥65 years), sex (men vs. women), and obesity status (BMI <25 kg/m^2 vs. ≥25 kg/m^2), and interactions between subgroups were tested. In addition, a sensitivity analysis was performed to exclude participants with end points occurring within ≤1 year of the follow-up to account for the possibility of reverse causation. Reported *P* values were two tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of Study Subjects

Our study enrolled 167,876 individuals aged ≥40 years with incident type 2 diabetes. We observed 2,563 events of all-cause dementia (1,846 AD and 381 VD) during an average 3.5 years of follow-up. Table 1 presents the general characteristics of the study participants on the index date after being monitored for ~ 2 years. Weight, BMI, WC, systolic and diastolic BP, and FPG levels were higher in subjects with ≥10% weight gain than in subjects with ≥10% weight loss; individuals in the former group were more likely to be current smokers and heavy alcohol drinkers. The proportion of comorbidities, such as hypertension and dyslipidemia, was higher in subjects with ≥10% weight gain than in those with ≥10% weight loss. Conversely, the proportion of CKD and ischemic heart disease was lower in subjects with ≥10% weight gain than in those with ≥10% weight loss.

Risk of Incident Dementia According to Baseline BMI

Table 2 provides the HRs (95% CIs) of incident dementia according to baseline BMI when subjects were diagnosed with type 2 diabetes. During 5.5 ± 1.7 years of follow-up, after adjusting for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, dyslipidemia, CKD, stroke, depressive disorder, FPG level, insulin use, and number of oral antidiabetic agents used (model 3), the risk of all-cause dementia decreased significantly in those with BMI of 23–25 kg/m^2 (HR 0.80 [95% CI 0.69–0.91]), 25–30 kg/m^2 (HR 0.77 [95% CI 0.68–0.88]), and ≥30 kg/m^2 (HR 0.79 [95% CI 0.63–0.99]), compared with patients with a normal BMI of 18.5–23 kg/m^2. The HRs for all-cause dementia tended to increase as BMI decreased (*P* for trend <0.001). The risk of AD was significantly higher for underweight patients (HR 1.59 [95% CI 1.04–2.43]) and also decreased in those with BMI of 23–25 kg/m^2 (HR 0.79 [95% CI 0.67–0.93]) and 25–30 kg/m^2 (HR 0.76 [95% CI 0.65–0.88]) compared with patients with a normal BMI (*P* for trend <0.001). Baseline BMI was not significantly associated with the risk of VD. The sensitivity analysis showed similar results (Supplementary Table 1).

Risk of Incident Dementia According to Weight Change in the 2 Years After Being Diagnosed With Diabetes

Table 3 reports the HRs (95% CIs) of incident dementia according to the percentage weight change after the diagnosis of type 2 diabetes. After adjusting for all confounding variables, including baseline BMI, the risk of all-cause dementia

Table 1—General characteristics of study subjects according to weight change status

	Weight change (%)					
	≥ −10 (*n* = 6,603)	< −10 to ≥ −5 (*n* = 24,550)	< −5 to <5 (*n* = 115,473)	≥5 to <10 (*n* = 15,539)	≥10 (*n* = 5,711)	*P*
Male sex	3,061 (46.4)	13,684 (55.7)	76,334 (66.1)	10,864 (69.9)	4,082 (71.5)	<0.001
Age (years)	58.9 ± 10.9	58.0 ± 9.9	57.1 ± 9.4	56.2 ± 9.5	55.9 ± 9.8	<0.001
Age (years)						<0.001
40–49	1,405 (3.7)	5,204 (13.5)	26,078 (67.9)	4,119 (10.7)	1,622 (4.2)	
50–59	2,160 (3.4)	8,871 (13.8)	44,986 (70.1)	6,001 (9.3)	2,202 (3.4)	
60–69	1,661 (3.9)	6,498 (15.3)	29,511 (69.4)	3,659 (8.6)	1,188 (2.8)	
≥70	1,377 (6.1)	3,977 (17.5)	14,898 (65.6)	1,760 (7.8)	699 (18.5)	
Height (cm)	160.4 ± 9.4	162.0 ± 9.1	163.6 ± 8.7	164.1 ± 8.7	164.1 ± 8.7	<0.001
Weight (kg)	59.2 ± 10.9	63.7 ± 10.7	68.6 ± 11.0	70.6 ± 11.6	71.3 ± 11.9	<0.001
BMI (kg/m^2)	22.9 ± 3.1	24.2 ± 3.0	25.6 ± 3.1	26.1 ± 3.3	26.4 ± 3.5	<0.001
BMI (kg/m^2)						<0.001
<18.5	363 (5.5)	332 (1.4)	577 (0.5)	52 (0.3)	20 (0.4)	
18.5–23	3,286 (49.8)	8,458 (34.5)	21,843 (18.9)	2,378 (15.3)	838 (14.7)	
23–25	1,516 (23.0)	7,016 (28.6)	30,247 (26.2)	3,468 (22.3)	1,188 (20.8)	
25–30	1,280 (19.4)	7,740 (31.5)	53,349 (46.2)	7,858 (50.6)	2,853 (50.0)	
≥30	159 (2.4)	1,004 (4.1)	9,457 (8.2)	1,783 (11.5)	812 (14.2)	
WC (cm)	80.3 ± 8.6	82.9 ± 8.0	86.4 ± 8.0	87.8 ± 8.3	88.3 ± 8.6	<0.001
BP (mmHg)						
Systolic	123.8 ± 15.1	125.4 ± 14.4	127.7 ± 14.4	129.1 ± 14.5	129.7 ± 14.9	<0.001
Diastolic	76.3 ± 9.8	77.3 ± 9.5	78.9 ± 9.5	79.7 ± 9.5	80.1 ± 9.7	<0.001
Fasting glucose (mg/dL)	125.1 ± 44.5	129.4 ± 39.7	135.9 ± 37.0	138.7 ± 37.7	139.3 ± 41.0	<0.001
Total cholesterol (mg/dL)	182.5 ± 40.7	187.4 ± 40.5	190.2 ± 40.1	188.0 ± 39.4	187.4 ± 39.7	<0.001
Current smoker	1,280 (19.4)	5,560 (22.7)	29,986 (26.0)	4,334 (27.9)	1,637 (28.7)	<0.001
Heavy alcohol drinker	308 (4.7)	1,599 (6.5)	10,392 (9.0)	1,509 (9.7)	582 (10.2)	<0.001
Regular exerciser	3,384 (51.3)	13,366 (54.5)	64,547 (56.0)	8,430 (54.3)	3,020 (52.9)	<0.001
Income quartiles						<0.001
1	1,775 (26.9)	6,076 (24.8)	28,214 (24.4)	4,105 (26.4)	1,592 (27.9)	
2	1,419 (21.5)	5,329 (21.7)	25,193 (21.8)	3,680 (23.7)	1,388 (24.3)	
3	1,599 (24.2)	6,106 (24.9)	28,649 (24.8)	3,927 (25.3)	1,464 (25.6)	
4	1,810 (27.4)	7,039 (28.7)	33,417 (28.9)	3,827 (24.6)	1,267 (22.2)	
Comorbidities						
Hypertension	3,323 (50.4)	12,544 (51.1)	64,927 (56.3)	9,142 (58.9)	3,401 (59.6)	<0.001
Dyslipidemia	3,016 (45.8)	11,760 (48.0)	59,120 (51.3)	8,095 (52.2)	2,992 (52.4)	<0.001
CKD	576 (8.7)	1,680 (6.9)	7,535 (6.5)	1,015 (6.5)	398 (7.0)	<0.001
Ischemic heart disease	321 (6.9)	1,079 (6.1)	4,384 (5.1)	520 (4.4)	189 (4.5)	<0.001
Stroke	155 (3.4)	396 (2.3)	1,526 (1.8)	208 (1.8)	99 (2.4)	<0.001
Depressive disorder	519 (7.9)	1,458 (5.9)	5,012 (4.3)	709 (4.6)	293 (5.1)	<0.001
Insulin use	419 (6.4)	1,164 (4.7)	5,011 (4.3)	891 (5.7)	417 (7.3)	<0.001
≥2 oral antidiabetic agents used	2,587 (39.2)	9,940 (40.5)	61,872 (53.6)	11,399 (73.4)	4,367 (76.5)	<0.001

Values are presented as mean ± SD or *n* (%).

was significantly higher among individuals with ≥10% weight loss (HR 1.34 [95% CI 1.11–1.63]) and ≥10% weight gain (HR 1.38 [95% CI 1.08–1.76]) than among those with <5% weight loss or gain. The correlation between weight change and all-cause dementia among patients with new-onset type 2 diabetes showed a significant U-shaped association ($P < 0.001$). The risk of AD was significantly higher among individuals with ≥10% weight loss (HR 1.26 [95% CI 1.01–1.59]) than among those with <5% weight loss or gain, after correcting for confounding variables. No significant association was found between weight change and risk of VD. The trends of results were not changed largely in the sensitivity analysis (Supplementary Table 2).

Risk of Dementia by Weight Change Status in Subgroups According to Age, Sex, and Baseline BMI

The relationship between weight change and sex in the development of VD was significant, with men with fluctuating weight at greater risk for developing VD than women ($P = 0.020$). Any significant interactions of weight change with age and obesity status were not shown in the development of all types of dementia (Table 4).

CONCLUSIONS

In this population-based longitudinal study, baseline BMI levels among patients with new-onset type 2 diabetes were inversely associated with the risk of all-cause dementia and AD, independent of confounding variables. Weight change during the 2 years after diagnosis showed a significant U-shaped association with the risk of developing all-cause dementia.

Table 2—HR (95% CI) of incident dementia according to baseline BMI among patients with new-onset type 2 diabetes

BMI (kg/m^2)	*N*	Events	Person-years	Incidence rate*	HR (95% CI)† Model 1‡	Model 2§	Model 3¶
All-cause dementia							
<18.5	1,214	49	4,235	11.57	1.97 (1.36–2.85)	1.49 (1.03–2.15)	1.44 (0.99–2.10)
≥18.5–23	33,116	685	116,472	5.88	1 (ref.)	1 (ref.)	1 (ref.)
>23–25	43,071	655	152,611	4.29	0.73 (0.64–0.84)	0.81 (0.70–0.92)	0.80 (0.69–0.91)
>25–30	76,677	1,017	267,897	3.80	0.65 (0.57–0.73)	0.79 (0.69–0.89)	0.77 (0.68–0.88)
>30	13,798	157	45,888	3.42	0.59 (0.47–0.74)	0.79 (0.63–0.99)	0.79 (0.63–0.99)
P for trend					<0.001	<0.001	<0.001
AD							
<18.5	1,214	39	4,235	9.21	2.15 (1.42–3.25)	1.62 (1.07–2.45)	1.59 (1.04–2.43)
≥18.5–23	33,116	500	116,472	4.29	1 (ref.)	1 (ref.)	1 (ref.)
>23–25	43,071	471	152,611	3.09	0.72 (0.61–0.84)	0.79 (0.68–0.93)	0.79 (0.67–0.93)
>25–30	76,677	722	267,897	2.70	0.63 (0.54–0.73)	0.76 (0.66–0.89)	0.76 (0.65–0.88)
>30	13,798	114	45,888	2.48	0.59 (0.46–0.77)	0.77 (0.59–1.01)	0.78 (0.60–1.01)
P for trend					<0.001	<0.001	<0.001
VD							
<18.5	1,214	8	4,235	1.89	2.29 (0.91–5.75)	1.73 (0.69–4.35)	1.71 (0.68–4.31)
≥18.5–23	33,116	96	116,472	0.82	1 (ref.)	1 (ref.)	1 (ref.)
>23–25	43,071	94	152,611	0.62	0.75 (0.52–1.07)	0.82 (0.57–1.18)	0.80 (0.55–1.16)
>25–30	76,677	160	267,897	0.60	0.73 (0.53–1.00)	0.89 (0.64–1.23)	0.86 (0.62–1.20)
>30	13,798	23	45,888	0.50	0.62 (0.34–1.10)	0.89 (0.49–1.60)	0.86 (0.47–1.56)
P for trend					0.001	0.253	0.276

Ref., reference. *Incidence per 1,000 person-years. †Bonferroni correction was used to control the overall significance level 0.05. Actual confidence level was 98.75%. ‡Unadjusted. §Adjusted for age, sex, smoking status, alcohol consumption, physical activity, and income. ¶Adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, dyslipidemia, CKD, stroke, depressive disorder, FPG level, insulin use, and number of oral antidiabetic agents used.

Losing or gaining >10% of body weight was significantly associated with an increased risk of all-cause dementia. In addition, weight loss of >10% was significantly associated with an increased risk of AD. These trends persisted after adjusting for confounding variables, including baseline BMI.

Previous longitudinal studies have reported the impact of type 2 diabetes on cognitive decline, mild cognitive impairment (MCI), and dementia in various

Table 3—HR (95% CI) of incident dementia according to weight change for 2 years after diagnosis for type 2 diabetes

Weight change (%)	*N*	Events	Person-years	Incidence rate*	HR (95% CI)† Model 1‡	Model 2§	Model 3¶
All-cause dementia							
≥ −10	6,603	214	22,208	9.64	2.55 (2.12–3.06)	1.54 (1.28–1.85)	1.34 (1.11–1.63)
< −10 to ≥ −5	24,550	451	83,307	5.41	1.43 (1.25–1.63)	1.13 (0.99–1.30)	1.08 (0.94–1.24)
< −5 to <5	115,473	1,555	404,340	3.85	1 (ref.)	1 (ref.)	1 (ref.)
≥5 to <10	15,539	231	56,695	4.07	1.04 (0.88–1.25)	1.14 (0.95–1.36)	1.11 (0.93–1.33)
≥10	5,711	112	20,552	5.45	1.40 (1.10–1.79)	1.38 (1.08–1.76)	1.38 (1.08–1.76)
P					<0.001	<0.001	<0.001
AD							
≥ −10	6,603	152	22,208	6.84	2.53 (2.04–3.14)	1.47 (1.18–1.83)	1.26 (1.01–1.59)
< −10 to ≥ −5	24,550	349	83,307	4.19	1.54 (1.32–1.80)	1.20 (1.03–1.40)	1.13 (0.97–1.33)
< −5 to <5	115,473	1,116	404,340	2.76	1 (ref.)	1 (ref.)	1 (ref.)
≥5 to <10	15,539	154	56,695	2.72	0.97 (0.78–1.20)	1.06 (0.85–1.31)	1.04 (0.84–1.30)
≥10	5,711	75	20,552	3.65	1.30 (0.97–1.76)	1.27 (0.95–1.72)	1.29 (0.95–1.74)
P					<0.001	<0.001	0.018
VD							
≥ −10	6,603	29	22,208	1.31	2.22 (1.36–3.63)	1.53 (0.93–2.52)	1.38 (0.83–2.31)
< −10 to ≥ −5	24,550	51	83,307	0.61	1.04 (0.71–1.53)	0.88 (0.60–1.31)	0.88 (0.59–1.30)
< −5 to <5	115,473	241	404,340	0.60	1 (ref.)	1 (ref.)	1 (ref.)
≥5 to <10	15,539	39	56,695	0.69	1.14 (0.74–1.76)	1.24 (0.80–1.91)	1.19 (0.76–1.84)
≥10	5,711	21	20,552	1.02	1.70 (0.96–3.00)	1.72 (0.97–3.03)	1.65 (0.93–2.93)
P					<0.001	0.017	0.056

Ref., reference. *Incidence per 1,000 person-years. †Bonferroni correction was used to control the overall significance level 0.05. Actual confidence level was 98.75%. ‡Unadjusted. §Adjusted for age, sex, smoking status, alcohol consumption, physical activity, and income. ¶Adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, dyslipidemia, CKD, stroke, depressive disorder, FPG level, insulin use, number of oral antidiabetic agents used, and baseline BMI.

Table 4—HR (95% CI) of dementia by weight change status in subgroups according to age, sex, and obesity status

		All-cause dementia			AD			VD		
Subgroup	Weight change (%)	Events	IR	HR (95% CI)*	Events	IR	HR (95% CI)*	Events	IR	HR (95% CI)*
Age, years										
<65	≥ −5	103	1.31	1.23 (0.94–1.61)	62	0.79	1.08 (0.76–1.52)	25	0.32	1.67 (0.96–2.92)
	−5 to 5	303	0.95	1 (ref.)	197	0.62	1 (ref.)	60	0.19	1 (ref.)
	≥5	70	1.12	1.22 (0.90–1.65)	37	0.59	1.00 (0.66–1.51)	21	0.34	1.83 (1.02–3.27)
≥65	≥ −5	562	20.86	1.13 (1.00–1.28)	439	16.30	1.18 (1.03–1.36)	55	2.04	0.84 (0.59–1.21)
	−5 to 5	1,252	14.62	1 (ref.)	919	10.73	1 (ref.)	181	2.11	1 (ref.)
	≥5	273	18.64	1.19 (1.02–1.38)	192	13.11	1.14 (0.96–1.37)	39	2.66	1.15 (0.77–1.72)
P for interaction				0.677			0.740			0.030
Sex										
Men	≥ −5	225	3.98	1.03 (0.86–1.24)	165	2.92	1.05 (0.85–1.30)	31	0.55	0.90 (0.57–1.43)
	−5 to 5	722	2.72	1 (ref.)	491	1.85	1 (ref.)	131	0.49	1 (ref.)
	≥5	183	3.37	1.22 (1.01–1.47)	104	1.91	1.02 (0.80–1.30)	47	0.87	1.70 (1.16–2.51)
Women	≥ −5	440	8.98	1.20 (1.05–1.38)	336	6.85	1.22 (1.04–1.43)	49	1.00	1.03 (0.69–1.55)
	−5 to 5	833	6.02	1 (ref.)	625	4.51	1 (ref.)	110	0.79	1 (ref.)
	≥5	160	6.98	1.13 (0.93–1.37)	125	5.45	1.18 (0.94–1.47)	13	0.57	0.73 (0.38–1.41)
P for interaction				0.369			0.574			0.020
BMI, kg/m^2										
<25	≥ −5	488	6.84	1.09 (0.95–1.25)	367	5.15	1.10 (0.94–1.28)	54	0.76	0.88 (0.60–1.29)
	−5 to 5	843	4.56	1 (ref.)	612	3.31	1 (ref.)	127	0.69	1 (ref.)
	≥5	162	5.59	1.17 (0.96–1.42)	109	3.76	1.09 (0.86–1.38)	31	1.07	1.46 (0.93–2.30)
≥25	≥ −5	177	5.18	1.28 (1.05–1.56)	134	3.92	1.34 (1.08–1.66)	26	0.76	1.31 (0.80–2.14)
	−5 to 5	712	3.24	1 (ref.)	504	2.30	1 (ref.)	114	0.52	1 (ref.)
	≥5	181	3.75	1.20 (0.99–1.45)	120	2.49	1.13 (0.89–1.43)	29	0.60	1.20 (0.75–1.93)
P for interaction				0.111			0.101			0.164

IR, incidence rate; ref., reference. *HR (Bonferroni-adjusted 95% CI) was calculated using a multivariable Cox hazard regression analysis after adjusting for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, dyslipidemia, CKD, stroke, depressive disorder, FPG level, insulin use, number of oral antidiabetic agents used, and baseline BMI. The actual confidence level was 97.5%.

populations worldwide. However, the underlying mechanism seems to be complex and remains unclear. Diabetes has been found to increase the risk of cerebral infarction, but whether diabetes lowers the threshold to manifesting dementia through cerebrovascular disease or whether diabetes increases the risk for AD pathophysiology is unclear (9,10). Furthermore, a recent review suggested that the diabetes-related processes may contribute to the development of dementia but not directly to the hallmark pathologies of AD (22).

In this study, we found that the baseline BMI on diagnosis of type 2 diabetes was inversely associated with the risk of developing all-cause dementia or AD but not VD. The relationship between baseline BMI and dementia risk has been poorly studied in patients with diabetes. Several previous cohort studies in Western countries have explored the impact of BMI on the risk of dementia and produced conflicting results: high and low BMIs have both been reported to increase the risk of dementia (11–14). In general, however, low BMIs have been associated with high rates of dementia, such that the optimal BMI for reducing dementia risk is within the overweight range (16). Moreover, a low baseline BMI has been linked with faster cognitive decline in MCI (23,24). Developing countries tend to have lower average BMIs compared with Western countries, and a Nigerian cohort study also reported low BMI was a risk factor for dementia (25).

Although the underlying mechanism is not fully understood, a low BMI may accompany changes in appetite regulation that precede overt dementia (26). Moreover, those with a low BMI have reported feelings of apathy that are a common prodromal sign of early dementia, especially in patients with MCI rapidly progressing to overt dementia (16,27). Our results support a previously demonstrated inverse association between baseline BMI and risk of dementia and include evidence of a similar trend in patients with incident diabetes. Of note, we found that baseline BMI was not associated with VD, suggesting that different pathophysiologic mechanisms are involved.

Our study found significant U-shaped relationships between weight change and all-cause dementia, and weight change >10% increased the risk of all-cause dementia. Furthermore, weight loss >10% was associated with increased risk of AD in patients with incident diabetes. While there is limited evidence regarding the impact of weight change on the risk of dementia in patients with diabetes, several other studies have similar findings. Epidemiologic studies have generally reported the effect of declining BMI and AD risk (28). A U.S. nationwide cohort study of elderly inpatients reported that weight loss increased dementia risk by 1.26 times and that the inpatient population was expected to have more comorbidities and to have diabetes (29). A randomized, controlled lifestyle intervention study of overweight Finnish patients with impaired glucose tolerance reported a decline in cognitive performance with decreasing BMI, although this may have reflected reverse causality (30).

Pathophysiologic pathways linking weight change and dementia may be mediated by cardiovascular risk factors,

insulin resistance, or lifestyle. Recent studies demonstrate a correlation between brain atrophy and rapid loss of lean body mass. Patients with incident diabetes are likely to maintain strict glycemic control and lose weight, which can lead to hypoglycemia and weakness that is associated with dementia (31). Weight loss in developing countries is often a consequence of low caloric intake that is insufficient for the demands of physical activity. Gradual weight loss might precede a diagnosis of dementia while being viewed as forgetting to eat, apathy and loss of initiative, impaired olfactory function, loss of taste, and difficulty in swallowing. Weight loss and the prodromal stages of dementia are likely to affect one another adversely (32,33).

Meanwhile, a 1.6-year follow-up study for individuals with MCI showed that regardless of baseline BMI, significant weight gain or loss increased the risk of progressing to probable AD (34). Also, intentional weight loss by obese and overweight individuals has a positive effect on cognitive function (35). Intentional weight loss has been correlated with cognitive improvement even in obese elderly patients with MCI (36). These studies support our findings that excessive weight gain significantly increases the risk of all-cause dementia in patients with type 2 diabetes. Although our study could not assess whether weight change was intentional, excessive weight gain is expected to have a detrimental effect on the link between type 2 diabetes and cognitive decline. Altered energy homeostasis can affect disease progression in dementia, and neurodegenerative diseases are also related to metabolic changes such as weight gain or loss (37). Of note, our study found that the correlation between weight change and VD risk was stronger in men than in women, implying that weight gain affects cognitive function in men with diabetes; however, further studies are needed to understand this relationship.

Our findings should be interpreted with several limitations in mind. First, the dementia diagnoses based on ICD-10-CM might be under- or overestimated, and we could not determine dementia severity from the medical records. Although we excluded patients with a dementia diagnosis made before the index date, there may have been reverse causality. Second, we could not consider whether weight change was intentional or unintentional. Although the initial glycemic status can affect individual weight, the baseline FPG levels were not high enough to do so. We also corrected for the baseline FPG level in the analysis. Third, the observational duration of weight change after the diagnosis of type 2 diabetes and the follow-up duration for dementia development from the index date might not have been long enough to fully assess relationships. Fourth, the response rate of the self-report questionnaire in the South Korean NHIS was ~70%, and, therefore, there may have been possible selection bias. Fifth, our study included only a Korean population, and thus the findings cannot be generalized to other ethnicities.

Despite these limitations, the strengths of our study include a large sample size, longitudinal design, and abundant data regarding demographics, socioeconomics, biomedical information, comorbidity, and lifestyle variables. To our knowledge, this is the first study to examine the impact of baseline BMI and weight change on the risk of dementia in patients with new-onset type 2 diabetes. Additionally, new-onset diabetes is considered less affected by complications or other comorbidities that further effect weight change.

In conclusion, this large-scale cohort study of the South Korean population demonstrated that baseline BMI was inversely associated with the risk of all-cause dementia and AD among patients with new-onset type 2 diabetes. Furthermore, weight loss and weight gain after diagnosis were associated with increased risks of all-cause dementia. Weight loss was positively correlated with AD risk. In consideration of the risk of dementia, we suggest close monitoring for body weight in patients with diabetes.

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