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Effect of late-life weight change on dementia incidence: a 10-year cohort study using claim data in Korea

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ABSTRACT

Background The association between body mass index (BMI) in late-life and dementia risk remains unclear. We investigated the association between BMI changes over a 2-year period and dementia in an elderly Korean population.

Methods We examined 67 219 participants aged 60–79 years who underwent BMI measurement in 2002/2003 and 2004/2005 as part of the National Health Insurance Service-Health Screening Cohort. Baseline characteristics including BMI, socioeconomic status and cardiometabolic risk factors were measured at baseline (2002/2003). The difference between BMI at baseline and at the next health screening (2004/2005) was used to calculate the BMI change. After 2 years, the incidence of dementia was monitored for a mean 5.3 years from 2008 to 2013. Multivariate HRs for dementia incidence were estimated on the basis of baseline BMI and its changes after adjusting for various other risk factors. A subgroup analysis was conducted to determine the effects of baseline BMI and BMI changes.

Results We demonstrated a significant association between late-life BMI changes and dementia in both sexes (men: >−10% HR=1.26, 95% CI 1.08 to 1.46, >+10% HR=1.25, 95% CI 1.08 to 1.45; women: >−10% HR=1.15, 95% CI 1.03 to 1.29, >+10% HR=1.17, 95% CI 1.05 to 1.31). However, the baseline BMI was not associated with dementia, except in underweight men. After stratification based on the baseline BMI, the BMI increase over 2 years was associated with dementia in men with a BMI of <25 kg/m^2 and women with a BMI of 18.5–25 kg/m^2, but not in the obese subgroup in either sex. However, BMI decrease was associated with dementia in those with a BMI of ≥18.5 kg/m^2, but not in the underweight subgroup in either sex.

Conclusion Both weight gain and weight loss may be significant risk factors associated with dementia. Continuous weight control and careful monitoring of weight changes are necessary to prevent dementia development.

Strengths and limitations of this study

- A large cohort data including socioeconomic status, health examination, questionnaires of health behaviours, laboratory data and physician diagnosis.
- Reporting various modifiable risk factors of dementia in late life, such as changes in body mass index, risky health behaviours and uncontrolled diabetes.
- Sensitivity analysis using residual proportional hazard model to check the age effect of age-varying covariates on dementia.
- Some potential confounders, such as educational levels and Apolipoprotein E genotype, could not be adjusted in analysis.
- The accuracy of claim data to identify mild dementia is a known issue.

INTRODUCTION

Dementia is an important health problem with the increase in life expectancy and an ageing population.[1] In 2015, the World Alzheimer Report noted that 46.8 million people had been diagnosed with dementia and the related global cost was estimated to be US$818 billion for that year.[2] Evidence of the association between cardiometabolic risk factors and dementia has been increasingly reported,[3–6] and the worldwide prevalence of obesity, which is closely related to cardiometabolic diseases, has increased by >100% over the past four decades.[7 8] The increasing trend of obesity has recently plateaued in high-income English-speaking countries, while the increasing rate of obesity has accelerated in east and south Asia.[7 8] Reducing the risk of dementia is a fundamental strategy to decrease the dementia-related disease burden, because dementia is an irreversible and progressive age-related brain disorder. Therefore, epidemiological studies have focused on modifiable risk factors including obesity and cardiometabolic risk factors such as diabetes, hyperlipidaemia and hypertension.[9]

Based on several meta-analysis and systematic reviews, mid-life obesity has been closely linked to the risk of dementia, particularly with regard to cognitive decline.[10–14] However, the association between late-life obesity and dementia development has been inconsistent. For example, a preventive effect of being overweight (ie, obesity) on dementia incidence has been reported in several studies,[15–17] but others have indicated

the detrimental effect of obesity on dementia.[18 19] This discrepancy may be due to weight loss that could lead to confounding with regard to the deleterious effect of adiposity. Unintentional weight loss frequently occurs in the older population,[20] and it is related to various morbidities including dementia.[21–23] Thus, a few studies have investigated the effect of later-life body mass index (BMI) and weight change on dementia, but the results were also inconsistent.[22–25] The majority of such studies did not fully consider the lifestyle and cardiometabolic factors that may influence both weight change and dementia, and the sample size was not sufficient to achieve reliable results.

This study aimed to investigate the associations between BMI and weight change in later life and dementia incidence, after adjusting for the various lifestyle and cardiometabolic risk factors, using a large Korean cohort study.

METHODS

Study participants

The National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) is an academic database established by the NHIS, comprising a 10% random sample (n=514 866) of the national health screening programme in 2002 or 2003 and their insurance administrative data for 10 years from 2002 to 2013 (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do).[26] Approximately 97% (Medicaid, approximately 3%) of the Korean population is covered by the NHIS. Health screening is one of the services provided by the NHIS, which involves a biennial medical check-up service for insured people and their dependents aged ≥40 years, and the participation rate of the eligible population in the NHIS health screening programme was 74.8% in 2014.[26] The NHIS-HEALS was constructed using the NHIS claim database and the national health screening databases. The NHIS claim database stores information on participants' insurance eligibility details, including the type of health insurance, household income, residential area and demographics, as well as medical treatments including details of prescriptions and diagnosed diseases based on the International Classification of Diseases, 10th Edition (ICD-10). The national health screening database, as a data source of the NHIS-HEALS, contains the results of biennial health examinations such as anthropometric measurements, laboratory data of blood and urine samples, assessment of health behaviours and family history of specific diseases. The national health screening has included a screening test for cognitive decline using the Korean Dementia Screening Questionnaire-Cognitive (KDSQ-C) for 66-year-old examinees since 2008.[27]

We initially selected 132 680 participants aged 60–79 years who had their BMI measured at least once in either 2002 or 2003. To exclude the possibility of a time lag prior to detecting dementia, we excluded participants who had a medical history of treatment for dementia from baseline (2002/2003) to 2007 (n=11 472), or who died prior to the follow-up for dementia (n=18 446). We also excluded the participants who had not had their BMI measured in 2004 or 2005 for analysis of a 2-year BMI change (n=32 378), or who had missing data regarding the relevant risk factors (n=3165). Finally, 67 219 participants were included in this analysis (figure 1).

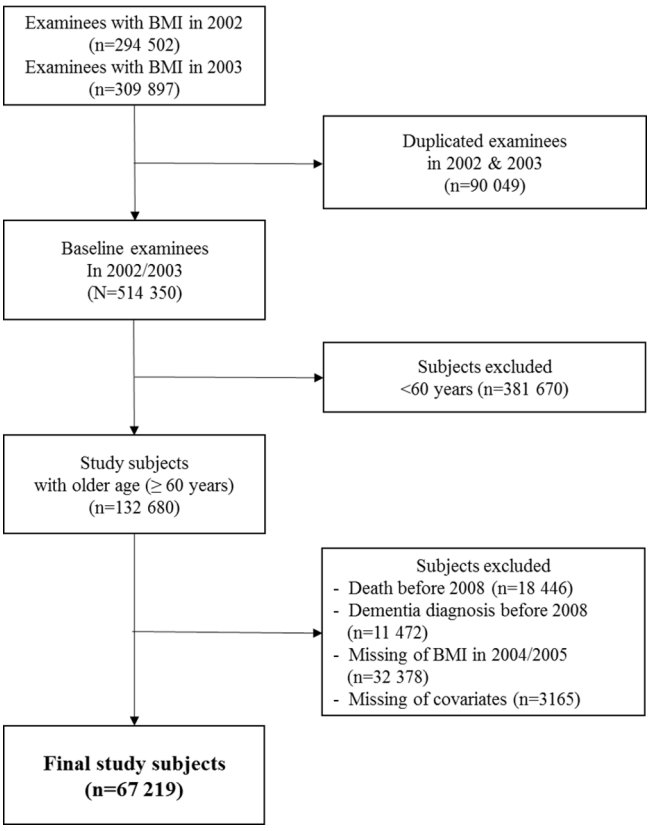

Figure 1 Flow diagram of the subjects included in this study. BMI, body mass index.

In addition, 15 266 subjects who underwent the KDSQ-C in 2009 or 2010 in NHIS-HEALS were used for the subgroup analysis of normal cognitive subjects. After excluding the subjects suspected of cognitive decline (KDSQ-C score of ≤4, n=2165), we analysed 13 101 participants.

Informed consent could not be obtained individually because the NHIS-HEALS was released after anonymisation and deidentification of the data.

Measurements

Physician-diagnosed dementia

Physician-diagnosed dementia was defined as a claim history of the following ICD-10 codes using the insurance administrative data of the NHIS-HEALS: F00 (dementia in Alzheimer's disease), F01 (vascular dementia), F02 (dementia in other diseases classified elsewhere), F03 (unspecified dementia), F051 (delirium superimposed on dementia), G30 (Alzheimer's disease) and G311 (senile degeneration of the brain, not classified elsewhere).

Body mass index

The BMI was calculated as the weight in kilograms divided by the square of the height in metres. Height and weight were measured in a standardised manner by trained nurses in each examination site for the biennial check-up.[28] The baseline BMI was classified into five groups based on the obesity criteria for Asians: <18.5 kg/m^2, 18.5–23 kg/m^2, 23–25 kg/m^2, 25–30 kg/m^2 and ≥30 kg/m^2.[29] A BMI change over a 2-year period was defined as the difference (percentage) between the baseline BMI (2002/2003) and the remeasured BMI after 2 years (2004/2005). The BMI change was categorised into five groups as follows: decrease of >10%, decrease of 5<–10%, stable ±5%, increase of 5<–10% and increase of >10%.

Cardiometabolic risk factors

A patient with a specific chronic disease was defined as a subject with a claim history of specific diagnostic codes. The ICD-10 codes of the relevant chronic diseases were as follows: atrial fibrillation (I48), congestive heart failure (I43, I50, I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429 and P290), diabetes mellitus (DM) (E10-E14) and hypertension (I10). The total cholesterol and fasting plasma glucose levels were categorised into three groups (total cholesterol=optimal <200 mg/dL, intermediate 200–400 mg/dL and high >400 mg/dL; fasting plasma glucose=normal <100 mg/dL, pre-diabetes 100–125 mg/dL, diabetes ≥126 mg/dL) using laboratory measurements from the national health screening programme. To explore the synergistic effect between fasting blood sugar (FBS) and physician-diagnosed DM, combined variable was created and categorised into four levels: (1) no DM diagnosis and normal/pre-diabetic FBS, (2) no DM diagnosis and diabetic FBS, (3) DM diagnosis and normal/pre-diabetic FBS and (4) DM diagnosis and diabetic FBS.

Health-related behaviours and socioeconomic status

Health-related behaviours were assessed using self-reported questionnaires completed during the national health screening. Smoking status was categorised as follows: never smoker, past smoker and current smoker. Frequencies for alcohol consumption and physical activity were grouped as follows: none, less than two times per week and at least three times per week. Household income was divided into three groups (low, middle and high) based on the level of insurance fees in the NHIS insurance eligibility data.

Analysis

Cox-proportional hazard (PH) models were used to estimate the HRs and 95% CIs for the associations between various risk factors and dementia. The analysis considered the induction period before the follow-up of dementia incidence to be from baseline (2002/2003) to 2007 because weight change has been reported as a symptom of dementia in the early stages.[30] Thus, follow-up time (in days) was measured from 01 January 2008 until dementia incidence, death, or 31 December 2013. The time point of dementia incidence was defined as the first date of claim history with the diagnosis codes (figure 2).

We considered BMI (baseline and 2-year change) and socioeconomic status (age and household income), health-related behaviours (smoking, alcohol consumption and physical activity) and cardiometabolic risk factors (total cholesterol, hypertension, atrial fibrillation, congestive heart failure and diagnosis of DM and FBS control) to be potential risk factors of dementia in Cox-models. The PH assumption was checked by the global goodness-of fit test proposed by Schoenfeld,[31] and no violation of the PH assumption was observed.

All analyses were performed separately for men and women, because significant interaction effects of baseline BMI and sex on dementia were observed in our data.[32 33] A stratified analysis using the baseline BMI was conducted to explore the modification of the effect of BMI changes on dementia incidence. In addition, we conducted a subgroup analysis using only the subjects who underwent screening tests for cognitive function to explore the potential effect of mild cognitive impairment on our results.

Statistical analyses were conducted using SAS V.9.4.

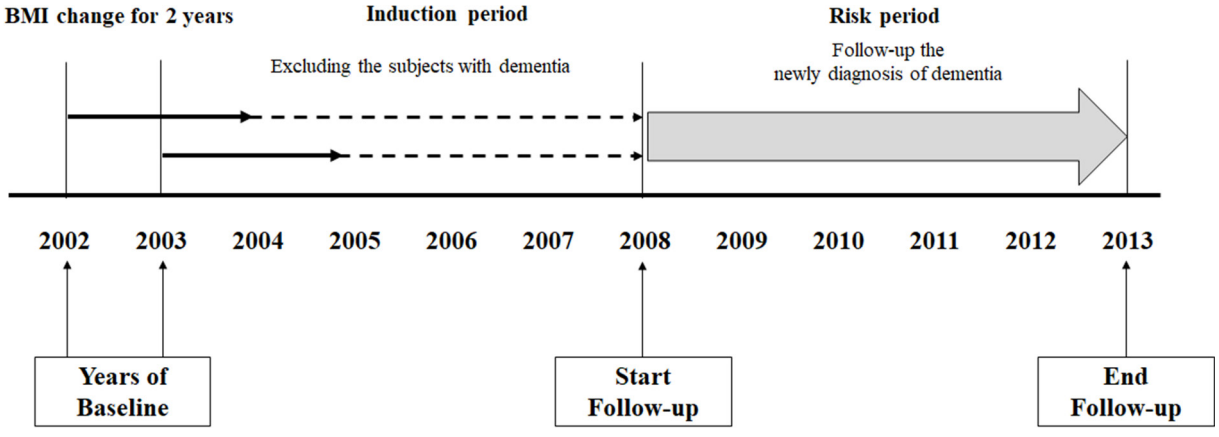

Figure 2 Study timeline for the time point of the dementia follow-up assessment. BMI, body mass index.

Patient and public involvement

No patients were involved in developing the research question, outcome measures and overall design of the study. Due to patient anonymity, we are unable to disseminate the results of the research directly to study participants.

RESULTS

The cohort comprised 67 219 participants (men: 34 205; women: 33 014) and 355 640 person-years (men: 180 013; women: 175 627) of follow-up. During the 5.3 years of mean follow-up time, the numbers of men and women with dementia totalled 4887 and 6685, respectively. The distributions of sex characteristics at baseline are presented in table 1. The mean age at baseline was approximately 65.4 years in both sexes. Men exhibited a higher prevalence of smoking (men: 30.5%; women: 3.1%) and more frequent alcohol consumption (at least three times per week, men: 22.3%; women: 1.4%) than women. The prevalence of high total cholesterol, hypertension and congestive heart failure was higher in women than in men. The proportion of no DM patients with high FBS (≥126 mg/dL) was slightly higher in men (7.0%) than in women (5.3%), whereas, in DM patients, the proportion of high FBS was similar in both sexes (men: 4.0%; women: 4.1%). Patients with atrial fibrillation (men: 1.6%; women: 1.1%) were rare in our cohort.

The prevalence of high BMI (≥25 kg/m^2) was higher in women (40.2%) than in men (28.9%). The distribution of the 2-year BMI change was similar in both sexes (BMI increase of >10%, 3.0% for men, 4.1% for women; BMI decrease of >10%, 2.9% for men, 4.1% for women).

Table 2 presents the univariate and multivariate HRs for dementia incidence according to various risk factors among men. Older age, current smoker, frequent alcohol consumption more than three times a week, hypertension and congestive heart failure were significantly associated with an increased dementia incidence among men. The DM patients with high FBS had an approximately 60% higher risk of developing dementia than did the subjects with non-DM and normal/prehigh FBS (HR=1.59, 95% CI 1.41 to 1.81). Regular physical activity (at least three times per week) was associated with a protective effect against the development of dementia. A U-shaped association between BMI change and dementia incidence was characterised by elevated HRs in a >10% increase or >5% decrease in BMI over 2 years compared with a stable BMI with ±5% change (BMI decrease of >10%, HR=1.26, 95% CI 1.08 to 1.46; BMI decrease of 5 <–10%, HR=1.19, 95% CI 1.09 to 1.29; BMI increase of >10%, HR=1.25, 95% CI 1.08 to 1.45). Low BMI (<18.5 kg/m^2) at baseline was associated with an increased dementia risk (HR=1.23, 95% CI 1.07 to 1.42) compared with that associated with a BMI of 23–25 kg/m^2, whereas high BMI at baseline was not associated with dementia development in men (HR=0.76, 95% CI 0.57 to 1.01).

The association patterns between risk factors and dementia development in women were generally similar

Table 1 General characteristics of study subjects at baseline (2002/2003) by sex

	Men	Women
	n (%)	n (%)
Total	34 205	33 014
Age (years)		
60–69	27 910 (81.6)	26 797 (81.2)
70–79	6295 (18.4)	6217 (18.8)
Income		
Low	6793 (19.9)	6692 (20.3)
Medium	14 229 (41.6)	13 205 (40.0)
High	13 183 (38.5)	13 117 (39.7)
Smoking status		
Never smoked	18 862 (55.1)	31 708 (96.0)
Past smoker	4920 (14.4)	286 (0.9)
Current smoker	10 423 (30.5)	1020 (3.1)
Drinking status		
None	15 852 (46.3)	29 808 (90.3)
<2 times per week	10 733 (31.4)	2749 (8.3)
≥3 times per week	7620 (22.3)	457 (1.4)
Physical activity		
None	19 142 (56.0)	23 894 (72.4)
<2 times per week	6716 (19.6)	3979 (12.1)
≥3 times per week	8347 (24.4)	5141 (15.6)
Total cholesterol		
Optimal	19 659 (57.5)	13 456 (40.8)
Intermediate	10 558 (30.9)	12 693 (38.5)
High	3988 (11.7)	6865 (20.8)
Hypertension		
No	21 465 (62.7)	18 863 (57.1)
Yes	12 747 (37.3)	14 151 (42.9)
Atrial fibrillation		
No	33 657 (98.4)	32 654 (98.9)
Yes	548 (1.6)	360 (1.1)
Congestive heart failure		
No	32 824 (96.0)	30 878 (93.5)
Yes	1381 (4.0)	2136 (6.5)
DM diagnosis and FBS*		
No DM diagnosis and normal/pre-diabetic FBS	28 090 (82.1)	27 200 (82.4)
No DM diagnosis and diabetic FBS	2393 (7.0)	1762 (5.3)
DM diagnosis and normal/pre-diabetic FBS	2354 (6.9)	2696 (8.2)
DM diagnosis and diabetic FBS	1368 (4.0)	1356 (4.1)
BMI		

Continued

Table 1 Continued

	Men	Women
	n (%)	n (%)
<18.5 kg/m^2	1311 (3.8)	874 (2.7)
18.5–23 kg/m^2	13 482 (39.4)	10 403 (31.5)
23–25 kg/m^2	9530 (27.9)	8452 (25.6)
25–30 kg/m^2	9413 (27.5)	11 959 (36.2)
≥30 kg/m^2	476 (1.4)	1326 (4.0)
BMI change over 2 years †		
Decrease of >10%	990 (2.9)	1340 (4.1)
Decrease of 5<–10%	4006 (11.7)	4342 (13.2)
Stable at ±5%	24 934 (72.9)	22 506 (68.2)
Increase of 5<–10%	3252 (9.5)	3490 (10.6)
Increase of >10%	1030 (3.0)	1336 (4.1)

*The combination of the physician's diagnosis of DM using an International Classification of Diseases 10th Edition code (E10-E14) and the laboratory data of FBS of ≥126 mg/dL at baseline.
†The BMI change over 2 years was calculated as follows: (BMI at baseline–BMI in 2004 or 2005)/BMI at baseline.
BMI, body mass index; DM, diabetes mellitus; FBS, fasting blood sugar.

to those in men (table 3). The risk of dementia was elevated in women of older age; current smokers; and those with hypertension, congestive heart failure, and DM with high FBS. High income and regular physical activity were associated with a decreased risk of dementia in women. Unlike men, women exhibited no association between frequent drinking and dementia. The U-shaped association between 2-year BMI changes and dementia was also observed in women, but the effect sizes of a rapid BMI change were smaller than those in men (BMI decrease of >10%, HR=1.15, 95% CI 1.03 to 1.29; BMI increase of >10%, HR=1.17, 95% CI 1.05 to 1.31). Neither low body weight nor obesity at baseline were associated with dementia in women.

Survival plots also exhibited

Table 4 presents the effect of BMI changes on dementia incidence after stratification of the baseline BMI category. The BMI increase over 2 years was associated with dementia risk in men with a BMI of <25 kg/m^2 (BMI increase of >10%, underweight group: HR=1.48, 95% CI 1.04 to 2.10; normal/overwieght: HR=1.24, 95% CI 1.04 to 1.46) and women with a BMI of 18.5–25 kg/m^2 (BMI increase of >10%, HR=1.25 95% CI 1.10 to 1.43), but not in the obese subgroups in both sexes. However, a BMI decrease of >5% was associated with dementia incidence in those with a BMI of ≥18.5 kg/m^2 but not in the underweight subgroups in both sexes.

Survival plots for men and women also exhibited significant separation according to the 2-year BMI changes (online supplementary figure 1). Our cohort data consisted of participants aged 60–79 years, thus the different age at baseline may exaggerate the impact of age-dependent risk factors, including cardiovascular risk factors, on dementia. To check the modification of age in the impact, we have conducted a sensitive analysis using residual PH model, which applied the age-at-follow-up as the time scale and age-varying covariates adjusted for age by taking residuals from a regression on age. The result represents that the estimated HRs were similar to those of the main analysis (online supplementary table 1), which implies that the age effect of age-varying covariates was not large in our data. In the subgroup analysis using only subjects who had undergone screening tests for cognitive function, the similar association patterns of 2-year BMI changes on dementia incidence were confirmed after adjusting the KDSQ score in 2009/2010 during the 3-year follow-up (2010–2013). However, the statistical significance had disappeared due to the small sample size (online supplementary table 2).

DISCUSSION

We demonstrated a U-shaped association between a 2-year BMI change and dementia in both sexes. Rapid weight change (ie, a >10% increase or decrease in BMI) over a 2-year period was associated with an approximately 20% higher risk of dementia compared with a stable BMI. However, baseline BMI was not associated with dementia incidence in either sex, with the exception of low body weight in men. The stratified analysis using BMI at baseline revealed a similar U-shaped association between BMI change and dementia in the normal weight subgroup, but the pattern of this association varied in other BMI ranges. Cardiometabolic risk factors including pre-existing hypertension, congestive heart failure, DM and high FBS were significant risk factors for dementia. In particular, DM patients with high FBS had 1.6-fold higher risk of dementia development. Unhealthy lifestyle habits such as smoking, frequent drinking and less physical activity in late life were also associated with dementia.

Our study demonstrated the detrimental effects of weight gain and loss on dementia in an elderly population. Similar to the findings of our study, Luchsinger *et al* also observed that a weight fluctuation of 1 kg per year was associated with an approximately 10% higher risk of dementia than that associated with a stable weight.[25] Buchman *et al* found that a 1-unit decrease in BMI was associated with a 25% increased risk of dementia compared with no change in BMI.[22] Atti *et al* also reported that a >10% decrease in BMI over a 3-year period was associated with a higher risk of dementia but a BMI increase was not.[23] Although some studies reported that only weight loss was associated with dementia development, the sample sizes of these studies were not sufficient to explore the effect of weight gain (eg, weight gain subjects, n=16).[23]

A BMI increase in the elderly could primarily represent an increase in fat mass.[34] The plasma concentration of inflammatory mediators, such as tumour necrosis factor-α and interleukin 6, is elevated in individuals with adiposity.[35 36] Chronic inflammation could precipitate

Table 2 HRs for dementia during the 6-year follow-up (2008–2013) according to body weight, socioeconomic status, health behaviours and cardiovascular risk factors at baseline among men

	Cases	Univariable model	Multivariable model*
	n	HRs (95% CI)	HRs (95% CI)
Body weight			
BMI change over 2 years †			
Decrease of >10%	177	1.45 (1.25 to 1.68)	1.26 (1.08 to 1.46)
Decrease of 5<–10%	662	1.28 (1.17 to 1.39)	1.19 (1.09 to 1.29)
Stable at ±5%	3375	Ref.	Ref.
Increase of 5<–10%	480	1.11 (1.01 to 1.22)	1.02 (0.92 to 1.12)
Increase of >10%	193	1.47 (1.27 to 1.69)	1.25 (1.08 to 1.45)
BMI			
<18.5 kg/m^2	239	1.54 (1.34 to 1.77)	1.23 (1.07 to 1.42)
18.5–23 kg/m^2	2049	1.16 (1.08 to 1.24)	1.06 (0.99 to 1.14)
23–25 kg/m^2	1293	Ref.	Ref.
25–30 kg/m^2	1257	0.98 (0.91 to 1.06)	1.00 (0.93 to 1.08)
≥30 kg/m^2	49	0.75 (0.56 to 1.00)	0.76 (0.57 to 1.01)
Socioeconomic status			
Age	4887	1.12 (1.11 to 0.00)	1.11 (1.11 to 1.12)
Income			
Low	944	Ref.	Ref.
Medium	2012	1.01 (0.94 to 1.09)	0.99 (0.92 to 1.07)
High	1931	1.04 (0.96 to 1.12)	0.92 (0.85 to 0.99)
Health behaviours			
Smoking status			
Never smoked	2678	Ref.	Ref.
Past smoker	736	1.07 (0.99 to 1.16)	1.07 (0.98 to 1.16)
Current smoker	1473	1.03 (0.96 to 1.09)	1.10 (1.03 to 1.18)
Drinking status			
None	2333	Ref.	Ref.
<2 times per week	1375	0.85 (0.79 to 0.90)	0.97 (0.91 to 1.04)
≥3 times per week	1179	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.19)
Physical activity			
None	2961	Ref.	Ref.
<2 times per week	796	0.73 (0.67 to 0.79)	0.85 (0.78 to 0.92)
≥3 times per week	1130	0.85 (0.79 to 0.91)	0.89 (0.83 to 0.95)
Cardiovascular risk factors			
Total cholesterol			
Optimal	2849	Ref.	Ref.
Intermediate	1515	0.97 (0.91 to 1.03)	1.03 (0.96 to 1.09)
High	523	0.89 (0.81 to 0.97)	0.94 (0.86 to 1.04)
Hypertension			
No	2817	Ref.	Ref.
Yes	2070	1.29 (1.22 to 1.36)	1.16 (1.09 to 1.24)
Atrial fibrillation			
No	4789	Ref.	Ref.
Yes	98	1.36 (1.11 to 1.66)	1.05 (0.86 to 1.29)

Continued

Table 2 Continued

	Cases	Univariable model	Multivariable model*
	n	HRs (95% CI)	HRs (95% CI)
Congestive heart failure			
No	4627	Ref.	Ref.
Yes	260	1.46 (1.29 to 1.65)	1.17 (1.02 to 1.33)
DM diagnosis and FBS ‡			
No DM diagnosis and normal/pre-diabetic FBS	3849	Ref.	Ref.
No DM diagnosis and diabetic FBS	360	1.14 (1.02 to 1.27)	1.14 (1.02 to 1.27)
DM diagnosis and normal/pre-diabetic FBS	407	1.31 (1.19 to 1.45)	1.25 (1.13 to 1.39)
DM diagnosis and diabetic FBS	271	1.56 (1.38 to 1.76)	1.59 (1.41 to 1.81)

*All variables were analysed in one model.
†The BMI change over 2 years was calculated as follows: (BMI at baseline–BMI in 2004 or 2005)/BMI at baseline.
‡The combination of the physician's diagnosis of DM using an International Classification of Diseases 10th Edition code (E10-E14) and the laboratory data of FBS of ≥126 mg/dL at baseline.
BMI, body mass index; DM, diabetes mellitus; FBS, fasting blood sugar.

neurodegenerative changes associated with dementia.[37 38] Thus, increasing fat mass via rapid weight gain might affect dementia development. However, the association between a BMI decrease and dementia might be interpreted as the influence of pre-existing diseases or preclinical symptoms of dementia. Unintentional weight loss is regarded as a symptom of severe disease.[39] Many chronic diseases, including cardiovascular disease, cancer, liver disease and lung disease, are related to a decline in cognitive function or dementia.[40–42] An alternative explanation is that weight loss may be a preclinical symptom of dementia. One previous study identified dementia-related symptoms >6 years prior to a diagnosis of dementia.[43]

The association between high BMI in later life and dementia is not clear. In our results, a higher BMI at baseline (≥25 kg/m^2) was not associated with dementia incidence in either sex. Only a low baseline weight (<18.5 kg/m^2) in men was associated with a significantly increased risk of dementia. These results might be interpreted as a healthy survival effect, as obese people who are vulnerable to many chronic obesity-related diseases are more likely to die before reaching old age. Indeed, obesity is closely related to higher all-cause and cause-specific mortalities in the middle-aged population.[44 45] Therefore, obese elderly people who have survived to the baseline may be more resistant to obesity-related diseases. This pattern was also observed in the results stratified by baseline BMI. In our study, a BMI increase was associated with dementia risk in men of low body weight and women who were of normal weight or who were overweight, but not in the obese subgroup in either sex. Rapid weight gain among non-obese elderly people may place older people at greater risk due to adiposity. An alternative explanation is the limitations associated with BMI measurement. Although BMI is the most commonly used tool to measure obesity in adults, some research has highlighted that BMI alone does not accurately reflect the risk of diseases associated with adiposity.[46 47] In addition, age-associated changes in body weight composition may also have influenced our baseline BMI results.[48]

Our results indicated that cardiometabolic risk factors were independently associated with dementia risk in both sexes, which is in line with the findings of previous studies.[40 49 50] Possible mechanisms that may explain the association include vascular and metabolic processes. Poor vascular condition may lead to brain ischaemia contributing to the development of subcortical white matter lesions, silent infarcts and atrophy.[51] Metabolic processes, such as insulin levels, may be related to cognitive decline and dementia wherein 'cerebral insulin-resistance' may affect neuronal modulation in cognitive-critical brain areas.[52–54] In particular, uncontrolled DM was associated with a higher risk of dementia than was controlled DM in our subjects. This finding suggests that the detrimental effect of DM on dementia might be alleviated by effective control of FBS, and that high FBS may be involved in neuronal degeneration processes.

Our results revealed that healthy lifestyle habits in later life were still influential factors of dementia development. Smoking has been reported to be associated with the risk of dementia risk.[55 56] Regular physical activity, even low-intensity activity, was associated with reduced risk of dementia.[57] However, the effect of alcohol consumption was dependent on sex. Alcohol consumption more than three times a week was significantly associated with dementia risk in men, but not in women. Reviews of studies on the effect of alcohol consumption on dementia risk revealed a protective effect of light-to-moderate alcohol consumption, but no significant effect of heavy alcohol consumption.[58 59] The effect of alcohol depends on the specific alcohol intake in consideration of the beverage type, and frequency and quantity of alcohol consumption. Therefore, future studies should explore the effect of alcohol consumption on dementia based on more detailed calculations in relation to the varieties of alcohol involved in consumption.

Table 3 HRs for dementia during 6-year follow-up (2008–2013) according to body weight, socioeconomic status, health behaviours and cardiovascular risk factors at baseline among women

	Cases	Univariable model	Multivariable model*
	n	HRs (95% CI)	HRs (95% CI)
Body weight			
BMI change over 2 years †			
Decrease of >10%	325	1.33 (1.18 to 1.48)	1.15 (1.03 to 1.29)
Decrease of 5<–10%	943	1.16 (1.08 to 1.24)	1.11 (1.03 to 1.19)
Stable at ±5%	4347	Ref.	Ref.
Increase of 5<–10%	737	1.11 (1.03 to 1.20)	1.07 (0.99 to 1.15)
Increase of >10%	333	1.38 (1.23 to 1.54)	1.17 (1.05 to 1.31)
BMI			
<18.5 kg/m^2	203	1.26 (1.09 to 1.45)	1.07 (0.92 to 1.24)
18.5–23 kg/m^2	2215	1.10 (1.03 to 1.17)	1.05 (0.99 to 1.12)
23–25 kg/m^2	1672	Ref.	Ref.
25–30 kg/m^2	2338	0.98 (0.92 to 1.05)	0.97 (0.91 to 1.03)
≥30 kg/m^2	257	0.99 (0.87 to 1.13)	0.92 (0.81 to 1.05)
Socioeconomic status			
Age	6685	1.10 (1.09 to 0.00)	1.09 (1.08 to 1.10)
Income			
Low	1461	Ref.	Ref.
Medium	2658	0.91 (0.85 to 0.97)	1.00 (0.94 to 1.06)
High	2566	0.87 (0.82 to 0.93)	0.91 (0.85 to 0.97)
Health behaviours			
Smoking status			
Never smoked	6357	Ref.	Ref.
Past smoker	66	1.21 (0.95 to 1.54)	1.06 (0.83 to 1.36)
Current smoker	262	1.38 (1.22 to 1.56)	1.18 (1.04 to 1.34)
Drinking status			
None	6049	Ref.	Ref.
<2 times per week	542	0.96 (0.88 to 1.05)	1.00 (0.92 to 1.10)
≥3 times per week	94	1.04 (0.85 to 1.27)	0.95 (0.77 to 1.16)
Physical activity			
None	5064	Ref.	Ref.
<2 times per week	672	0.77 (0.71 to 0.83)	0.84 (0.77 to 0.91)
≥3 times per week	949	0.85 (0.79 to 0.91)	0.92 (0.86 to 0.99)
Cardiovascular risk factors			
Total cholesterol			
Optimal	2722	Ref.	Ref.
Intermediate	2554	0.99 (0.94 to 1.04)	1.03 (0.97 to 1.08)
High	1409	1.02 (0.95 to 1.08)	1.05 (0.98 to 1.12)
Hypertension			
No	3378	Ref.	Ref.
Yes	3307	1.37 (1.30 to 1.43)	1.22 (1.16 to 1.28)
Atrial fibrillation			
No	6598	Ref.	Ref.
Yes	87	1.28 (1.04 to 1.59)	0.96 (0.78 to 1.19)

Continued

Table 3 Continued

	Cases	Univariable model	Multivariable model*
	n	HRs (95% CI)	HRs (95% CI)
Congestive heart failure			
No	6118	Ref.	Ref.
Yes	567	1.44 (1.33 to 1.57)	1.16 (1.06 to 1.27)
DM diagnosis and FBS ‡			
No DM diagnosis and normal/pre-diabetic FBS	5229	Ref.	Ref.
No DM diagnosis and diabetic FBS	399	1.22 (1.11 to 1.36)	1.13 (1.02 to 1.25)
DM diagnosis and normal/pre-diabetic FBS	681	1.37 (1.27 to 1.49)	1.29 (1.19 to 1.40)
DM diagnosis and diabetic FBS	376	1.55 (1.40 to 1.73)	1.47 (1.32 to 1.63)

*All variables were analysed in one model.
†The BMI change over 2 years was calculated as follows: (BMI at baseline–BMI in 2004 or 2005)/BMI at baseline.
‡The combination of the physician's diagnosis of DM using an International Classification of Diseases 10th Edition code (E10-E14) and the laboratory data of FBS of ≥126 mg/dL at baseline.
BMI, body mass index; DM, diabetes mellitus; FBS, fasting blood sugar.

This study has several limitations. First, there is some uncertainty regarding the accuracy of the definition of dementia using the ICD-10 codes in the NHIS claims database. Taylor *et al* noted that >80% of Alzheimer's disease and related dementias were identified in 3-year Medicare claims data (using the ICD-9-CM codes).[60] We used 10-year follow-up claims data from both Medicare and the NHIS. Therefore, an underestimation of the number of patients with dementia is less likely to affect our study. Second, we selected participants who underwent BMI measurement in both 2002/2003 and 2004/2005, which may have caused a selection bias because many participants who took the examination in other years were excluded. However, the distribution of baseline BMI was similar to that in previous Korean reports.[61] Third, health-related behaviours such as smoking, consuming alcohol and physical activity were defined using self-reported data. The accuracy of self-reported health-related behaviours has been previously explored and has indicated the under-reporting of risky behaviours.[62 63] This limitation could lead to an underestimation of the effect of health-related behaviour on dementia. Fourth, we could not exclude mild cognitive impairment at baseline. However, we considered a long induction time before the dementia follow-up assessment. Further, we confirmed the similar results in the subgroup analysis without cognitive decline before the follow-up assessment of dementia incidence. Fifth, we could not adjust for the apolipoprotein E genotype and educational level, which are well-known risk factors of dementia, due to lack of information.

Table 4 HRs for the association of the change in body mass index (BMI) with dementia incidence by the baseline BMI category

BMI change over 2 years*	Underweight (<18.5 kg/m^2)			Normal/overweight (18.5–25 kg/m^2)			Obesity (≥25 kg/m^2)		
	n	Case	HR (95% CI)	n	Case	HR (95% CI)	n	Case	HR (95% CI)
Men									
Decrease of >10%	26	2	0.40 (0.10 to 1.64)	574	109	1.27 (1.05 to 1.54)	390	66	1.27 (0.99 to 1.63)
Decrease of 5<–10%	122	19	0.89 (0.55 to 1.46)	2486	430	1.20 (1.09 to 1.33)	1396	213	1.19 (1.02 to 1.38)
Stable at ±5%	758	125	Ref	16724	2304	Ref	7447	946	Ref
Increase of 5<–10%	234	51	1.34 (0.97 to 1.87)	2439	357	1.00 (0.89 to 1.11)	579	72	0.99 (0.77 to 1.25)
Increase of >10%	170	42	1.48 (1.04 to 2.10)	785	142	1.24 (1.04 to 1.46)	75	9	0.97 (0.51 to 1.88)
Women									
Decrease of >10%	17	7	1.92 (0.88 to 4.23)	657	164	1.15 (0.98 to 1.35)	666	154	1.13 (0.96 to 1.33)
Decrease of 5<–10%	73	18	1.16 (0.70 to 1.93)	2266	491	1.10 (1.00 to 1.21)	2003	434	1.11 (1.00 to 1.23)
Stable at ±5%	458	98	Ref	12610	2466	Ref	9438	1783	Ref
Increase of 5<–10%	159	32	0.92 (0.61 to 1.39)	2360	521	1.13 (1.03 to 1.24)	971	184	0.97 (0.83 to 1.13)
Increase of >10%	167	48	1.15 (0.80 to 1.64)	962	245	1.25 (1.10 to 1.43)	207	40	0.93 (0.68 to 1.27)

*The BMI change over 2 years was calculated as follows: (BMI at baseline–BMI in 2004 or 2005)/BMI at baseline.
†Adjusted for age, household income, smoking, drinking, physical activity, total cholesterol level, atrial fibrillation, congestive heart failure, diagnosis of diabetes mellitus and fasting blood sugar control and hypertension.

Nonetheless, our findings have important implications. Using a large cohort dataset, this study revealed that severe weight gain, uncontrolled DM, smoking and less physical activity in late-life had a detrimental effect on dementia development. Our results suggest that continuous weight control, disease management and the maintenance of a healthy lifestyle are beneficial in the prevention of dementia, even in later life. Therefore, a health promotion programme is required that focuses on the modifiable risk factors of dementia and accounts for the health status and physical ageing of the elderly. Investigations into the biological mechanisms of the association between weight change and dementia await future research.

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Contributors J-WK took a part in the design of the study. SP and S-MJ analysed the data and wrote the manuscript. S-YJ and JH contributed to revision of manuscript. All authors contributed to interpreting the analyses and to critically revising the article, and approved the final draft.

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