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Weight change in people with depression and the risk of dementia: a nationwide cohort study

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Original Article

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Abstract

Background. Depression is a risk factor for dementia and weight change can appear as a symptom of depression. However, the association between weight change after the diagnosis of depression and the risk of dementia is poorly established. This study aimed to investigate the association between weight change before and after a diagnosis of depression with the subsequent risk of dementia.

Methods. The National Health Insurance Sharing Service database was used. 1 308 730 patients aged ⩾40 years diagnosed with depression were identified to be eligible. Weight changes after their depression diagnosis were categorized and subsequent incidence of dementia was followed up.

Results. During an average follow-up period of 5.2 years (s.d., 2.0 years), 69 373 subjects were newly diagnosed with all-cause dementia (56 351 were Alzheimer's disease and 6877 were vascular dementia). Regarding all outcomes, compared to those with a minimal weight change (−5 to 5%), all groups with weight gain or loss showed increased risks of dementia after adjusting potential risk factors for dementia, in all analysis models with a dose–response relationship, showing a U-shaped association.

Conclusions. Weight change as a symptom of depression could be a predictor for the future development of dementia.

Introduction

Depression is associated with about a 2-fold increased risk of Alzheimer's disease (AD), the most common form of dementia (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Although depression often precedes dementia, there have been debates on whether depression is a modifiable risk factor for dementia or a preclinical/prodromal disease for it. Studies have shown that amyloid β (Aβ) deposition, the initial hallmark pathology of AD, begins decades before the symptom onset of AD (Jack et al., 2013; Villemagne et al., 2013). A large longitudinal cohort study followed the trajectory of depression before dementia over 28 years and revealed that the difference in depressive symptoms between those with and without dementia became apparent 11 years before the diagnosis of dementia, while depressive symptoms in the early phase of the study did not increase the risk of dementia, suggesting depression as a prodromal/preclinical feature of dementia rather than a modifiable risk factor for it (Singh-Manoux et al., 2017). Another longitudinal study showed that even depression was associated with an increased risk of dementia, this was accounted for by people developing dementia within 5 years of depression, and the use of antidepressants did not decrease the risk of dementia (Almeida, Hankey, Yeap, Golledge, & Flicker, 2017). Whereas, a study of people with mild cognitive impairment (MCI) and a history of depression showed that the use of antidepressants was associated with a delayed progression to AD (Bartels, Wagner, Wolfsgruber, Ehrenreich, & Schneider, 2018).

Although the causal relationship between depression and dementia remains questionable, considering that at least 20% of people with dementia experience depression, clinicians should be concerned about the development of subsequent dementia, particularly in people with late-onset depression (Rubin, 2018). The manifestations of symptoms in people with depression are highly heterogeneous. Notably, previous studies have reported that among the depressive symptoms, appetite/weight loss was uniquely associated with an increased risk of neurocognitive deficit and dementia (Potter, McQuoid, & Steffens, 2015; Saha, Hatch, Hayden, Steffens, & Potter, 2016). However, among the general population, obesity is one of the risk factors for dementia; a meta-analysis study reported obesity, which is defined as a body mass index (BMI) ⩾30 kg/m^2, to be associated with late-life dementia (Albanese et al., 2017). Moreover, weight loss of ⩾2 kg in people with BMI ⩾25 was associated with

improvement in attention and memory (Veronese et al., 2017). This suggests that weight changes in patients with depression may have a different effect on the development of dementia compared to the general population.

Meanwhile, the results of previous studies have suggested that the relationship between weight and dementia could be more complex. While obesity in middle age increases the risk of dementia in older age (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005), obesity or overweight in late-life showed a protective effect for dementia (Atti et al., 2008; Natale, Zhang, Hanes, & Clouston, 2023). In addition, there seems a sex difference in the effects of weight on the risk of dementia; the effect of obesity in middle age was more apparent in women (Goble, 2005).

While multiple interaction effects are suggested and the underlying mechanisms are far from being understood, weight change, particularly in middle and old age, seems to be a predictor for future dementia. In addition, considering the increased risk of dementia in patients with depression and the characteristics of depression in that clinical types are distinguishable according to age at onset or cluster of symptoms, the weight change in them could give important information in predicting future dementia. However, data that analyzed the association between weight changes in people with depression and the subsequent development of dementia with consideration of other risk factors for dementia is still lacking. This study aimed to investigate the association between weight change before and after a diagnosis of depression with the subsequent risk of dementia using South Korean national cohort data.

Methods

Data source

We used the National Health Insurance Sharing Service (NHISS) database provided by the National Health Insurance Service (NHIS) of South Korea (Lee, Lee, Park, Shin, & Kim, 2017). NHIS is a government organization in charge of operating a mandatory universal health insurance service covering the South Korean population of over 50 million. The NHISS database involves medical service claims data including admissions, outpatient clinic visits, emergency room visits, pharmaceutical service uses, and health screening programs. The general health screening program of South Korea is one of the world's largest health screening programs and aims at the prevention and early intervention of common chronic diseases (Shin, Cho, Park, & Cho, 2022).

The data of NHISS are anonymized and the Institutional Review Board of Samsung Medical Center exempted this study from review because this study involved retrospective analyses of de-identified data (No. SMC 2022-05-118).

Identification of eligible subjects

Between 2010 and 2016, 4 805 617 were newly diagnosed with depression. The diagnosis of depression was defined as the F32 or F33 code of the International Statistical Classification of Disease and Related Health problems 10th revision (ICD-10). We extracted 1 308 730 eligible subjects ⩾40 years of age who received health screening programs within 2 years before the diagnosis of depression (first health screening) and within 2 years after diagnosis (second health screening), respectively, excluding those who had a previous diagnostic history of dementia between 2002 and the day of second health screening. We followed up on the incidence of dementia from the day of the second health screening program until December 2019 (Fig. 1).

Weight changes

Through the data from two health screening programs, we identified the subjects' weight changes from the first health screening (conducted within 2 years before the diagnosis of depression) to the second health screening (conducted within 2 years after the diagnosis of depression). And, depending on the proportion of weight change, we classified subjects into five groups: <-10%, −10 to −5%, −5 to 5%, 5 to 10%, and ⩾10%.

Outcomes

The main outcome was a new diagnosis of dementia based on the ICD-10 diagnostic code including AD (F00 or G30), VD (F01), and other dementia (F02, F03, or G31) and prescription of one or more dementia medications such as donepezil, galantamine, rivastigmine, and memantine. In South Korea, to file expense claims for the prescription of these medications, physicians need to document evidence of cognitive dysfunction according to National Health Insurance Reimbursement criteria: a Mini Mental State Examination (MMSE) (Baek, Kim, Park, & Kim, 2016) ⩽26 and either a Clinical Dementia Rating (CDR) (Berg, 1984) ⩾1 or a Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982) ⩾3 (Yoo et al., 2020). When a subject had more than one code of dementia, the primary diagnostic code was used. If both AD and VD codes were present in the secondary diagnostic codes, the subject was classified based on the primary diagnostic code at the subsequent hospital visit, and if both codes remained as secondary diagnostic codes at that time, the subject was classified as the other dementias group.

Covariates

We identified subjects' baseline characteristics through the data obtained on the second health screening day. Low income was defined as less than the bottom 20% of the total premium of insurance payment, which is determined by income level. Subjects' body mass index (BMI), waist circumference, smoking status, alcohol drinking, and physical activity were also identified. Those who performed vigorous-intensity physical activity ⩾3 days or moderate-intensity physical activity ⩾5 days per week were considered to engage in regular physical activity (Pescatello, Riebe, & Thompson, 2014). In addition, age, sex, previous medical history of diabetes (ICD-10 code of E11, E12, E13, or E14 and one or more prescriptions of antidiabetic medication or fasting glucose level ⩾126 mg/dl), hypertension (one or more prescriptions of antihypertensive agents under ICD-10 code of I10–13 or I15 or a systolic/diastolic blood pressure ⩾140/90 mmHg), dyslipidemia (one or more prescriptions of antihyperlipidemic agents under ICD-10 code of E78 or total cholesterol ⩾240 mg/dl), hearing loss (a history of disability determination) and traumatic brain injury (ICD-10 code of S06) were identified through medical records.

Statistical analysis

Baseline demographic and clinical characteristics were presented as mean ± standard deviation (S.D.) for continuous variables and

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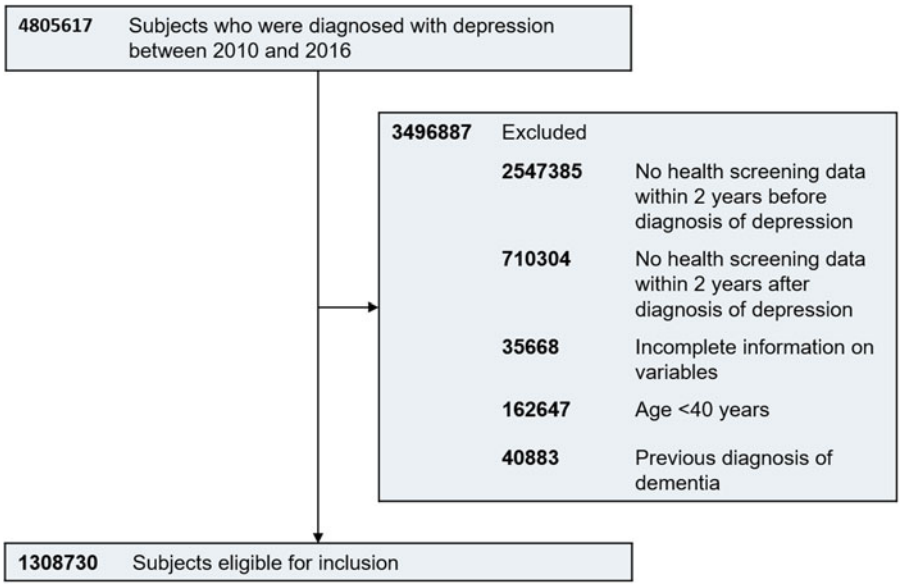

Figure 1. Flow chart showing the identification of subjects.

numbers with percentages for categorical variables. An analysis of variance and a χ^2 test was used to compare the variables according to the weight change group. The incidence rates of all-cause dementia, AD, and VD were calculated and presented per 1000 person-years.

Cox proportional hazard regression analyses were conducted to investigate the association between weight change before and after the diagnosis of depression with the occurrence of outcomes. Hazard ratios and corresponding 95% confidence intervals were presented. Model 1 was non-adjusted, Model 2 was adjusted for age and sex, Model 3 was adjusted for low income, hearing loss, traumatic brain injury, hypertension, diabetes mellitus, dyslipidemia, current alcohol drinking, current smoking, and regular physical activity in addition to Model 2, and Model 4 was adjusted for baseline BMI in addition to Model 3. In addition, subgroup analyses were conducted according to sex and age group, and the interaction effects were examined.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of subjects by weight change group. The mean age of those with weight change of <-10%, −10 to −5%, −5 to 5%, 5 to 10%, and ⩾10% were 62.6 years (S.D., 12.2 years), 61.1 years (S.D., 11.2 years), 59.2 years (S.D., 10.6 years), 58.4 years (S.D., 10.9 years), and 58.8 years (S.D., 11.7 years). The proportion of females was highest in those with a weight change of <-10% (65.6%) and lowest in those with a weight change of −5 to 5% (58.8%). The BMI was lowest in those with a weight change of <-10% and increased as the weight change increased.

Incidence of dementia

The average follow-up period was 5.2 years (S.D., 2.0 years) (online Supplementary Table S1). 69 373 subjects were newly diagnosed with dementia with an incidence rate of 10.2 per 1000 person-years. Among them, 56 351 were diagnosed with AD with an incidence rate of 8.3 per 1000 person-years, and 6877 were diagnosed with VD with an incidence rate of 1.0 per 1000 person-years (online Supplementary Fig. S1).

Risks of dementia according to weight changes

Table 2 shows the HRs and corresponding 95% CIs of weight change groups on the risk of newly diagnosed dementia. Regarding all outcomes, compared to those with a minimal weight change (−5 to 5%), all groups with weight gain or loss showed increased risks of dementia, in all analysis models with a dose–response relationship, showing a U-shaped association.

In the fully adjusted model, compared to those with weight change of −5 to 5%, those with weight loss (adjusted hazard ratio [aHR], 1.49 [95% CI 1.45–1.54] for <−10%; aHR, 1.22 [95% CI 1.20–1.25] for −10 to −5%) and those with weight gain (aHR, 1.17 [95% CI 1.14–1.20] for 5 to 10%; aHR, 1.47 [95% CI 1.42–1.53] for ⩾10%) showed increased risks of all dementia. Likewise, in terms of AD, compared to those with weight change of −5 to 5%, those with weight loss (aHR, 1.47 [95% CI 1.42–1.52] for <−10%; aHR, 1.21 [95% CI 1.18–1.24] for −10 to −5%) and those with weight gain (aHR, 1.15 [95% CI 1.11–1.18] for 5 to 10%; aHR, 1.44 [95% CI 1.39–1.51] for ⩾10%) showed increased risks of AD. And in terms of VD, compared to those with weight change of −5 to 5%, those with weight loss (aHR, 1.66 [95% CI 1.50–1.83] for <−10%; aHR, 1.32 [95% CI 1.24–1.42] for −10 to −5%) and those with weight gain (aHR, 1.24 [95% CI 1.14–1.34] for 5 to 10%; aHR, 1.77 [95% CI 1.58–1.98] for ⩾10%) showed increased risks of VD (Fig. 2 and online Supplementary Fig. S2).

Subgroup analyses

Table 3 shows the subgroup analyses according to sex and age groups. There were significant interaction effects between sex and weight change on the occurrence of all dementias (p-value for interaction = 0.013) and AD (p-value for interaction = 0.017). The increased risks of all dementia and AD by weight loss or gain were prominent in male subjects. There also were significant interaction effects between age groups and weight change on all dementias (p-value for interaction <0.001), AD (p-value

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Table 1. Baseline characteristics of subjects by weight change

	Weight change (%)					
	<−10 (*n* = 39 635)	−10 to −5 (*n* = 141 303)	−5 to 5 (*n* = 947 567)	5 to 10 (*n* = 140 289)	⩾10 (*n* = 39 936)	*p* value
Sex						<0.001
Male	13 649 (34.4)	52 454 (37.1)	390 052 (41.2)	52 477 (37.4)	15 083 (37.8)	
Female	25 986 (65.6)	88 849 (62.9)	557 515 (58.8)	87 812 (62.6)	24 853 (62.2)	
Age group						<0.001
40–49 years	6592 (16.6)	23 572 (16.7)	188, 686 (19.9)	32 889 (23.4)	9990 (25.0)	
50–59 years	9737 (24.6)	40 360 (28.6)	307 883 (32.5)	45 050 (32.1)	11 756 (29.4)	
60–69 years	9600 (24.2)	38 560 (27.3)	260 457 (27.5)	35 599 (25.4)	9285 (23.3)	
70–79 years	10 208 (25.8)	31 459 (22.3)	162 729 (17.2)	22 566 (16.1)	7062 (17.7)	
⩾80 years	3498 (8.8)	7352 (5.2)	27 812 (2.9)	4185 (3.0)	1843 (4.6)	
Age (years)	62.6 ± 12.2	61.1 ± 11.2	59.2 ± 10.6	58.4 ± 10.9	58.8 ± 11.7	<0.001
Low income	8434 (21.3)	28 799 (20.4)	183 716 (19.4)	28 929 (20.6)	9117 (22.8)	<0.001
BMI (kg/m^2)	21.8 ± 3.1	22.9 ± 3.0	24.1 ± 3.1	24.8 ± 3.2	25.3 ± 3.6	<0.001
Waist circumference	77.5 ± 9.1	79.0 ± 8.7	81.5 ± 8.8	82.7 ± 8.9	83.8 ± 9.3	<0.001
Current smoking	4841 (12.2)	19 034 (13.5)	124 843 (13.2)	17 608 (12.6)	5345 (13.4)	<0.001
Current alcohol drinking	8260 (20.8)	37 467 (26.5)	308 208 (32.5)	43 743 (31.2)	11 011 (27.6)	<0.001
Regular physical activity	7454 (18.8)	29 802 (21.1)	206 655 (21.8)	27 411 (19.5)	6914 (17.3)	<0.001
Diabetes mellitus	9296 (23.5)	28 058 (19.9)	142 323 (15.0)	19 678 (14.0)	6874 (17.2)	<0.001
Hypertension	20 200 (51.0)	65 874 (46.6)	406 739 (42.9)	59 598 (42.5)	18 134 (45.4)	<0.001
Dyslipidemia	14 498 (36.6)	51 704 (36.6)	341 399 (36.0)	52 270 (37.3)	15 418 (38.6)	<0.001
Hearing loss	620 (1.6)	1883 (1.3)	10 301(1.1)	1593 (1.1)	497 (1.2)	<0.001
Traumatic brain injury	2557 (6.5)	8071 (5.7)	48 241 (5.1)	7965 (5.7)	2686 (6.7)	<0.001

BMI, body mass index.

for interaction <0.001), and VD (*p*-value for interaction = 0.003). The increased risks of all dementias, AD, and VD by weight loss or gain were greater when subjects were younger.

Online Supplementary Tables S2–S4 show the results according to age at onset of depression and the presence of recurrent depression. Overall, the pattern of outcome in each subgroup was similar to the main outcome. However, the risk of dementia according to weight change was more prominent in those who developed depression before the age of 60 compared to those with late onset (⩾60 years) (*p*-value for interaction <0.001).

Sensitivity analyses

Online Supplementary Tables S5 and S6 show the results among those with ages <55 years and ⩾55 years based on the index date, respectively. The occurrence of dementia was lower in those with age <55 years (4%) compared to those over 55 years old (26.6%). However, the pattern of dementia risks according to weight change was similar to the main outcome.

Discussion

In this population-based cohort study, we found a U-shaped association between weight change before and after the diagnosis of depression and the subsequent occurrence of dementia. Compared to those whose weight change was within 5%, those who gained or lost more than 5% had increased risks of all-cause dementia, AD, and VD, with a dose-response relationship. In addition, the lower the age at the onset of depression, the stronger the association between weight change and the risk of dementia.

To our knowledge, this study is the first to examine the association between weight changes after the diagnosis of depression and the risk of dementia, and it is difficult to directly compare the results with those of previous studies using the same methodology. However, a study that looked at the risk of dementia according to weight change in type 2 diabetes patients from the same data source showed that weight loss or weight gain of more than 10% increased the risk of dementia (34–38%), while the weight changes within 5–10% did not increase the risk of dementia (Nam et al., 2019). In comparison, in our study, the risk of dementia increased even with a smaller weight change, and the range of increases in risks was also larger.

While the underlying explanations for the association between weight change and the increased risk of dementia in patients with depression remain poorly understood, the severity of depression might affect the results. The severity of depression is known to be related to the subsequent risk of dementia (Chen et al.,

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Table 2. Hazard ratios and 95% confidence intervals of weight change on the occurrence of dementia

					Hazard ratio (95% confidence intervals)			
Weight change (%)	*N*	Events	Duration (person-year)	Incidence rate (per 1000 person-years)	Model 1	Model 2	Model 3	Model 4
All dementias								
<−10	39 635	4790	195 920	24.5	2.79 (2.71– 2.88)	1.65 (1.60–1.70)	1.58 (1.54–1.63)	1.49 (1.45–1.54)
−10 to −5	141 303	11 157	742 723	15.0	1.71 (1.67–1.74)	1.29 (1.26–1.31)	1.26 (1.23–1.28)	1.22 (1.20–1.25)
−5 to 5	947 567	43 658	4 972 495	8.8	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
5 to 10	140 289	6855	705 690	9.7	1.12 (1.09–1.14)	1.16 (1.14–1.19)	1.15 (1.12–1.18)	1.17 (1.14–1.20)
⩾10	39 936	2913	193 901	15.0	1.74 (1.67–1.80)	1.49 (1.43–1.54)	1.45 (1.40–1.51)	1.47 (1.42–1.53)
Alzheimer's disease								
<−10	39 635	3918	195 920	20.0	2.81 (2.72–2.90)	1.62 (1.57–1.68)	1.56 (1.51–1.61)	1.47 (1.42–1.52)
−10 to −5	141 303	9078	742 723	12.2	1.70 (1.67–1.74)	1.27 (1.24–1.30)	1.24 (1.21–1.27)	1.21 (1.18–1.24)
−5 to 5	947 567	35 547	4 972 495	7.2	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
5 to 10	140 289	5478	705 690	7.8	1.10 (1.07–1.13)	1.14 (1.11–1.18)	1.13 (1.10–1.17)	1.15 (1.11–1.18)
⩾10	39 936	2340	193 901	12.1	1.72 (1.65–1.79)	1.45 (1.39–1.52)	1.42 (1.36–1.48)	1.44 (1.39–1.51)
Vascular dementia								
<−10	39 635	462	195 920	2.4	2.75 (2.50–3.03)	1.82 (1.65–2.00)	1.72 (1.56–1.89)	1.66 (1.50–1.83)
−10 to −5	141 303	1107	742 723	1.5	1.74 (1.63–1.86)	1.39 (1.30–1.48)	1.35 (1.26–1.44)	1.32 (1.24–1.42)
−5 to 5	947 567	4260	4 972 495	0.9	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
5 to 10	140 289	717	705 690	1.0	1.19 (1.10–1.28)	1.24 (1.15–1.35)	1.23 (1.13–1.33)	1.24 (1.14–1.34)
⩾10	39 936	331	193 901	1.7	1.99 (1.78–2.23)	1.81 (1.62–2.03)	1.75 (1.56–1.96)	1.77 (1.58–1.98)

Model 1, non-adjusted; Model 2, adjusted for age and sex; Model 3, adjusted for age, sex, low income, hearing loss, traumatic brain injury, hypertension, diabetes mellitus, dyslipidemia, current alcohol drinking, current smoking, and regular physical activity; Model 4, adjusted for age, sex, low income, hearing loss, traumatic brain injury, hypertension, diabetes mellitus, dyslipidemia, current alcohol drinking, current smoking, regular physical activity, and baseline body mass index.

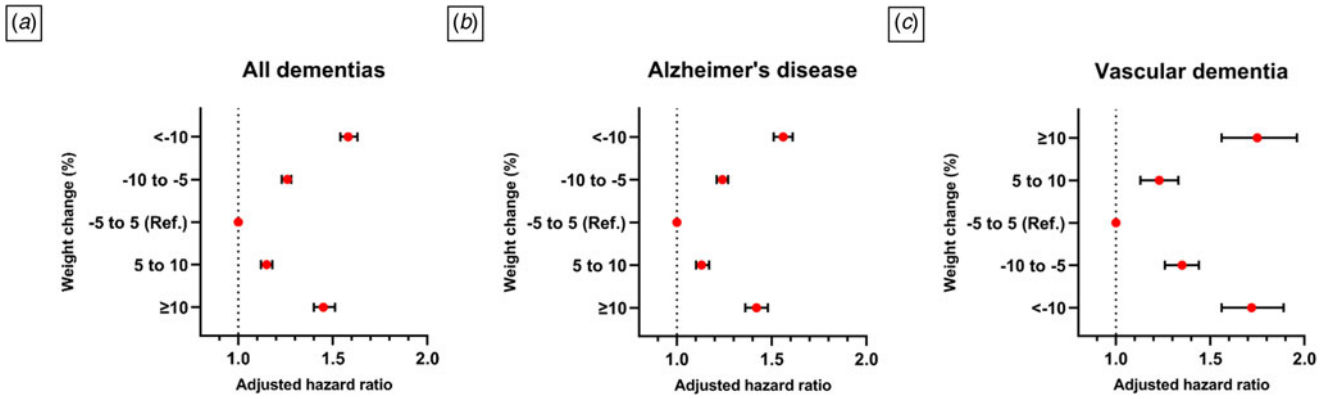

Figure 2. Forest plots showing the hazard ratios and corresponding 95% confidence intervals of weight changes on the risk of the occurrence of dementia. Adjusted for age, sex, low income, hearing loss, traumatic brain injury, hypertension, diabetes mellitus, dyslipidemia, current alcohol drinking, current smoking, regular physical activity, and baseline body mass index.

2008), and since a change in appetite or weight is a symptom of depression, more severe depression could cause larger changes in weight. Often, many patients experience decreased appetite and weight loss, but some patients, especially those with atypical features, experience weight/appetite gain as a reversed neurovegetative symptom (American Psychiatric Association, 2013). In the present study, both weight loss and gain were in a dose–response relationship with dementia, which may be mediated by the severity of depression. In addition, factors that can be induced by symptoms of depression and are risk factors for dementia, such as alcohol consumption, smoking, social isolation, and physical inactivity (Livingston et al., 2020), might affect the results.

Regarding weight gain, obesity due to weight gain might increase the risk of dementia. Previous studies have consistently shown the result that obesity increases the risk of dementia (Albanese et al., 2017; Kivimäki et al., 2018). Obesity contributes to incident cardiovascular risk factors (Powell-Wiley et al., 2021), which can be a possible mechanism that increases the risk of VD. However, in the present study, the risk of dementia in Model 3 (in which baseline BMI was not adjusted) was similar to that in Model 4 (in which baseline BMI was adjusted), bolstering evidence that the weight change *per se* could be a risk factor for dementia independent of BMI. Regarding weight loss, our results are consistent with the results of a study conducted among elderly patients with depression, where the appetite and weight loss symptoms were associated with an increased risk of AD (HR of 1.69) and non-AD (HR of 2.10) (Saha et al., 2016). Dementia has been known as an important cause of weight loss (Shatenstein, Kergoat, & Nadon, 2001), and previous studies suggest that weight loss may have appeared as a preclinical symptom of dementia through analysis of trajectory before the diagnosis of MCI or dementia (Guo et al., 2022; Stewart et al., 2005). The volume changes in the mesial temporal cortex (Grundman, Corey-Bloom, Jernigan, Archibald, & Thal, 1996) and *Apolipoprotein E* (*APOE*) ϵ4 allele (Jefferson et al., 2001; Vanhanen et al., 2001) have been suggested as possible mechanisms of the weight loss in dementia. Considering the maximum duration of the follow-up period of dementia from the index date in our study was less than 10 years, weight loss could be a preclinical symptom of dementia since the initial pathologic change of AD, the accumulation of Aβ is generally known to precede symptoms by 10–15 years (Drew, 2018).

Several methodological issues limit interpretations of our findings. First, the diagnosis of depression was based only on diagnostic codes but not structured evaluation. Second, only those who had participated in consecutive health screening programs before and after the initial diagnosis of depression were included. Therefore, those included in the analyses were more likely to engage in health-promoting behavior or might have already experienced some physical or mental discomfort or symptoms than those excluded from the analyses due to a lack of health screening data. Third, the temporal relationship between the diagnosis of depression and weight change is not determined. Previous studies have suggested the bidirectional relationships between weight and depression (Emery, Finkel, Gatz, & Dahl Aslan, 2020) and between weight and cognitive change (Karlsson, Zhan, Gatz, Reynolds, & Dahl Aslan, 2021). Therefore, weight could have changed first, leading to subsequent depression, and then to increased risk of dementia, or depression could have occurred first, leading to subsequent weight change. Also, the results of our study do not provide information about weight changes over a longer period after diagnosis of depression. Fourth, although we excluded those who developed dementia before the diagnosis of depression, the pathology of dementia might have started earlier, which could have resulted in a reversed causal inference. Fifth, the treatment factors for depression were not included in the analysis. In particular, it is known that antidepressants have different profiles for weight gain depending on the drug (M et al., 2011), but an analysis considering these characteristics has not been performed. Sixth, the analyses did not include the severity of depression, which, as mentioned above, is likely to mediate the association between weight change and dementia. Finally, the follow-up time was relatively short, which might be insufficient to observe the occurrence of dementia, especially at younger ages.

Despite these limitations, our study has strengths in that dementia was followed longitudinally in a large sample with depression, and its relevance was analyzed by comprehensively correcting for potential risk factors for dementia. In addition, we defined the occurrence of dementia through both the diagnostic codes and the prescription of dementia drugs. For the prescription of these drugs, evaluation through MMSE and CDR (or GDS) must be performed and the criteria must be met. Therefore, this definition could have reduced the overdiagnosis or misdiagnosis of dementia and reflected the occurrence of the

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Table 3. Adjusted hazard ratios and 95% confidence intervals by weight change in subgroups according to sex and age group

	All-cause dementia			Alzheimer's disease			Vascular dementia		
Weight change (%)	Events	IR*	aHR (95% CIs)[b]	Events	IR[a]	aHR (95% CIs)[†]	Events	IR[a]	aHR (95% CIs)[b]
Sex									
Males									
<−10	1522	24.0	1.50 (1.42–1.58)	1201	18.9	1.48 (1.40–1.57)	180	2.8	1.73 (1.48–2.02)
−10 to −5	3979	15.0	1.24 (1.19–1.28)	3140	11.8	1.24 (1.18–1.27)	459	1.7	1.34 (1.21–1.49)
−5 to 5	17 098	8.5	1 (Ref.)	13 471	6.7	1 (Ref.)	1911	1.0	1 (Ref.)
5 to 10	2761	10.7	1.22 (1.18–1.27)	2145	8.3	1.22 (1.15–1.26)	320	1.2	1.26 (1.12–1.42)
⩾10	1124	15.7	1.55 (1.46–1.65)	881	12.3	1.54 (1.44–1.65)	149	2.1	1.87 (1.58–2.21)
Females									
<−10	3268	24.7	1.49 (1.43–1.54)	2717	20.5	1.46 (1.40–1.52)	282	2.1	1.61 (1.42–1.83)
−10 to −5	7178	15.1	1.22 (1.18–1.25)	5938	12.5	1.20 (1.16–1.23)	648	1.4	1.31 (1.20–1.43)
−5 to 5	26 560	9.0	1 (Ref.)	22 076	7.5	1 (Ref.)	2349	0.8	1 (Ref.)
5 to 10	4094	9.1	1.13 (1.09–1.17)	3333	7.4	1.11 (1.07–1.15)	397	0.9	1.22 (1.09–1.35)
⩾10	1789	14.6	1.43 (1.36–1.50)	1459	11.9	1.39 (1.32–1.47)	182	1.5	1.69(1.45–1.96)
p for interaction			0.013			0.017			0.854
Age group									
40–49									
<−10	23	0.7	2.47 (1.61–3.78)	12	0.3	2.22 (1.23–4.00)	6	0.2	2.21 (0.96–5.07)
−10 to −5	41	0.3	1.19 (0.85–1.65)	25	0.2	1.25 (0.82–1.90)	14	0.1	1.39 (0.79–2.45)
−5 to 5	263	0.3	1 (Ref.)	152	0.2	1 (Ref.)	78	0.1	1 (Ref.)
5 to 10	55	0.3	1.30 (0.97–1.74)	34	0.2	1.39 (0.96–2.02)	13	0.1	1.03 (0.57–1.86)
⩾10	43	0.9	3.62 (2.62–5.00)	25	0.5	3.67 (2.40–5.60)	13	0.3	3.54 (1.97–6.37)
50–59									
<−10	174	3.3	2.37 (2.03–2.77)	123	2.3	2.33 (1.94–2.80)	26	0.5	2.29 (1.54–3.42)
−10 to −5	421	1.9	1.39 (1.25–1.54)	303	1.4	1.39(1.23–1.58)	75	0.3	1.60 (1.25–2.06)
−5 to 5	2130	1.3	1 (Ref.)	1526	0.9	1 (Ref.)	335	0.2	1 (Ref.)
5 to 10	391	1.7	1.35 (1.21–1.51)	266	1.1	1.29 (1.13–1.47)	67	0.3	1.46 (1.12–1.89)
⩾10	156	2.6	2.11 (1.80–2.49)	99	1.7	1.89 (1.54–2.31)	33	0.6	2.71 (1.89–3.87)
60–69									
<−10	777	15.7	1.83 (1.70–1.97)	601	12.2	1.79 (1.64–1.94)	102	2.1	2.18 (1.78–2.70)
−10 to −5	2202	10.7	1.34 (1.28–1.40)	1741	8.4	1.34 (1.27–1.41)	247	1.2	1.35 (1.18–1.55)
−5 to 5	9965	7.3	1 (Ref.)	7834	5.8	1 (Ref.)	1126	0.8	1 (Ref.)

5 to 10	1600	9.0	1.26 (1.19–1.33)	1210	6.8	1.21 (1.14–1.29)	188	1.1	1.28 (1.10–1.50)
⩾10	614	13.6	1.86 (1.72–2.02)	477	10.6	1.85 (1.69–2.03)	89	2.0	2.29 (1.85–2.84)
70–79									
<−10	2513	53.8	1.52 (1.46–1.58)	2083	44.6	1.51 (1.45–1.59)	225	4.8	1.56 (1.35–1.79)
−10 to −5	6111	39.8	1.22 (1.19–1.25)	5020	32.7	1.21 (1.17–1.25)	585	3.8	1.32 (1.20–1.45)
−5 to 5	23 462	29.6	1 (Ref.)	19 366	24.4	1 (Ref.)	2132	2.7	1 (Ref.)
5 to 10	3566	33.9	1.15 (1.11–1.19)	2909	27.6	1.14 (1.10–1.18)	352	3.3	1.23 (1.10–1.38)
⩾10	1450	44.9	1.46 (1.38–1.53)	1182	36.6	1.44 (1.36–1.53)	148	4.6	1.62 (1.37–1.92)
⩾80									
<−10	1303	106.4	1.27 (1.20–1.35)	1099	89.7	1.25 (1.17–1.33)	103	8.4	1.41 (1.14–1.74)
−10 to −5	2382	83.3	1.10 (1.05–1.15)	1989	69.5	1.07 (1.02–1.13)	186	6.5	1.17 (1.00–1.39)
−5 to 5	7838	70.3	1 (Ref.)	6669	59.8	1 (Ref.)	589	5.3	1 (Ref.)
5 to 10	1243	77.0	1.10 (1.03–1.17)	1059	65.6	1.10 (1.03–1.18)	97	6.0	1.13 (0.91–1.40)
⩾10	650	94.2	1.25 (1.15–1.35)	557	80.7	1.25 (1.15–1.37)	48	7.0	1.24 (0.92–1.66)
p for interaction			<0.001			<0.001			0.003

IR, incidence rate; aHR, adjusted hazard ratio; CI, confidence interval.
*Per 1000 person-years.
†Adjusted for age, sex, low income, hearing loss, traumatic brain injury, hypertension, diabetes mellitus, dyslipidemia, current alcohol drinking, current smoking, regular physical activity, and baseline body mass index.

outcome more accurately. Moreover, the association was consistent across all age groups. In particular, the risk of dementia according to weight change increased prominently at the young age group. While previous studies have focused on the association between late-onset depression and dementia (Almeida et al., 2017; Vilalta-Franch et al., 2013), our study showed that weight change increased the risk of dementia in all age groups ⩾40 years. These suggest that weight change, which appears as a symptom of depression, can be a strong predictor of dementia.

In conclusion, both weight loss and gain after the diagnosis of depression were associated with an increased risk of all-cause dementia, AD, and VD with a dose-response relationship. Our findings suggest that weight change as a symptom of depression could be a predictor for the future development of dementia.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003124

Data availability statement. Publicly available datasets were analyzed in this study. This data can be found here: https://nhiss.nhis.or.kr/.

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References

Albanese, E., Launer, L. J., Egger, M., Prince, M. J., Giannakopoulos, P., Wolters, F. J., & Egan, K. (2017). Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589649 men and women followed in longitudinal studies. *Alzheimer's & Dementia*, *8*, 165–178. doi: 10.1016/j.dadm.2017.05.007

Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J., & Flicker, L. (2017). Depression as a modifiable factor to decrease the risk of dementia. *Translational Psychiatry*, *7*(5), e1117. doi: 10.1038/tp.2017.90

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders : DSM-5* (5th ed.). Washington, DC: American Psychiatric Association.

Atti, A. R., Palmer, K., Volpato, S., Winblad, B., De Ronchi, D., & Fratiglioni, L. (2008). Late-life body mass index and dementia incidence: Nine-year follow-up data from the kungsholmen project. *Journal of the American Geriatrics Society*, *56*(1), 111–116. doi: 10.1111/j.1532-5415.2007.01458.x

Baek, M. J., Kim, K., Park, Y. H., & Kim, S. (2016). The validity and reliability of the mini-mental state examination-2 for detecting mild cognitive impairment and Alzheimer's disease in a Korean population. *PLoS One*, *11*(9), e0163792. doi: 10.1371/journal.pone.0163792

Bartels, C., Wagner, M., Wolfsgruber, S., Ehrenreich, H., & Schneider, A. (2018). Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression. *American Journal of Psychiatry*, *175*(3), 232–241. doi: 10.1176/appi.ajp.2017.17040404

Berg, L. (1984). Clinical dementia rating. *The British Journal of Psychiatry*, *145*(3), 339–339. doi: 10.1192/S0007125000118082

Chen, R., Hu, Z., Wei, L., Qin, X., McCracken, C., & Copeland, J. R. (2008). Severity of depression and risk for subsequent dementia: Cohort studies in China and the UK. *The British Journal of Psychiatry*, *193*(5), 373–377. doi: 10.1192/bjp.bp.107.044974

Drew, L. (2018). An age-old story of dementia. *Nature*, *559*(7715), S2–S3.

Emery, C. F., Finkel, D., Gatz, M., & Dahl Aslan, A. K. (2020). Evidence of bidirectional associations between depressive symptoms and body mass among older adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *75*(8), 1689–1698. doi: 10.1093/geronb/gbz022

Goble, A. J. (2005). Obesity in middle age and future risk of dementia: Problem is probably greater for women. *Bmj*, *331*(7514), 454, author reply 455. doi: 10.1136/bmj.331.7514.454-a

Grundman, M., Corey-Bloom, J., Jernigan, T., Archibald, S., & Thal, L. J. (1996). Low body weight in Alzheimer's disease is associated with mesial temporal cortex atrophy. *Neurology*, *46*(6), 1585–1591. doi: 10.1212/wnl.46.6.1585

Guo, J., Wang, J., Dove, A., Chen, H., Yuan, C., Bennett, D. A., & Xu, W. (2022). Body mass index trajectories preceding incident mild cognitive impairment and dementia. *JAMA Psychiatry*, *79*(12), 1180–1187. doi: 10.1001/jamapsychiatry.2022.3446

Gustafson, D., Rothenberg, E., Blennow, K., Steen, B., & Skoog, I. (2003). An 18-year follow-up of overweight and risk of Alzheimer disease. *Archives of Internal Medicine*, *163*(13), 1524–1528. doi: 10.1001/archinte.163.13.1524

Jack, Jr. C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., … Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurology*, *12*(2), 207–216. doi: 10.1016/s1474-4422(12)70291-0

Jefferson, M. F., Burlinson, S., Burns, A., Mann, D., Pickering-Brown, S., Owen, F., … Horan, M. A. (2001). Clinical features of dementia associated with apolipoprotein epsilon4: Discrimination with a neural network genetic algorithm. *International Journal of Geriatric Psychiatry*, *16*(1), 77–81. doi: 10.1002/1099-1166(200101)16:1 < 77::aid-gps279>3.0.co;2-g

Karlsson, I. K., Zhan, Y., Gatz, M., Reynolds, C. A., & Dahl Aslan, A. K. (2021). Change in cognition and body mass index in relation to preclinical dementia. *Alzheimer's & Dementia*, *7*(1), e12176. doi: 10.1002/trc2.12176

Kivimäki, M., Luukkonen, R., Batty, G. D., Ferrie, J. E., Pentti, J., Nyberg, S. T., … Jokela, M. (2018). Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimer's & Dementia*, *14*(5), 601–609. doi: 10.1016/j.jalz.2017.09.016

Lee, J., Lee, J. S., Park, S. H., Shin, S. A., & Kim, K. (2017). Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *International Journal of Epidemiology*, *46*(2), e15. doi: 10.1093/ije/dyv319

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet (London, England)*, *396*(10248), 413–446. doi: 10.1016/s0140-6736(20)30367-6

M, D. E. H., Correll, C. U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., … Leucht, S. (2011). Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry*, *10*(1), 52–77. doi: 10.1002/j.2051-5545.2011.tb00014.x

Nam, G. E., Park, Y. G., Han, K., Kim, M. K., Koh, E. S., Kim, E. S., … Kwon, H. S. (2019). BMI, weight change, and dementia risk in patients with new-onset type 2 diabetes: A nationwide cohort study. *Diabetes Care*, *42*(7), 1217–1224. doi: 10.2337/dc18-1667

Natale, G., Zhang, Y., Hanes, D. W., & Clouston, S. A. P. (2023). Obesity in late-life as a protective factor against dementia and dementia-related mortality. *American Journal of Alzheimer's Disease & Other Dementias®*, *38*, 15333175221111658. doi: 10.1177/15333175221111658

Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. *Archives Of General Psychiatry*, *63*(5), 530–538. doi: 10.1001/archpsyc.63.5.530

Pescatello, L. S., Riebe, D., & Thompson, P. D. (2014). *ACSM's guidelines for exercise testing and prescription*. Philadelphia, PA: Lippincott Williams & Wilkins.

Potter, G. G., McQuoid, D. R., & Steffens, D. C. (2015). Appetite loss and neurocognitive deficits in late-life depression. *International Journal of Geriatric Psychiatry*, *30*(6), 647–654. doi: 10.1002/gps.4196

Powell-Wiley, T. M., Poirier, P., Burke, L. E., Després, J. P., Gordon-Larsen, P., Lavie, C. J., … St-Onge, M. P. (2021). Obesity and cardiovascular disease:

A scientific statement from the American heart association. *Circulation*, *143* (21), e984–e1010. doi: 10.1161/cir.0000000000000973

Reisberg, B., Ferris, S. H., de Leon, M. J., & Crook, T. (1982). The global deterioration scale for assessment of primary degenerative dementia. *American Journal of Psychiatry*, *139*(9), 1136–1139. doi: 10.1176/ajp.139.9.1136

Rubin, R. (2018). Exploring the relationship between depression and dementia. *Jama*, *320*(10), 961–962. doi: 10.1001/jama.2018.11154

Saha, S., Hatch, D. J., Hayden, K. M., Steffens, D. C., & Potter, G. G. (2016). Appetite and weight loss symptoms in late-life depression predict dementia outcomes. *American Journal of Geriatric Psychiatry*, *24*(10), 870–878. doi: 10.1016/j.jagp.2016.05.004

Shatenstein, B., Kergoat, M. J., & Nadon, S. (2001). Anthropometric changes over 5 years in elderly Canadians by age, gender, and cognitive status. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(8), M483–M488. doi: 10.1093/gerona/56.8.m483

Shin, D. W., Cho, J., Park, J. H., & Cho, B. (2022). National general health screening program in Korea: History, current status, and future direction. *Precision and Future Medicine*, *6*(1), 9–31. doi: 10.23838/pfm.2021.00135

Singh-Manoux, A., Dugravot, A., Fournier, A., Abell, J., Ebmeier, K., Kivimäki, M., & Sabia, S. (2017). Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. *JAMA Psychiatry*, *74*(7), 712–718. doi: 10.1001/jamapsychiatry.2017.0660

Stewart, R., Masaki, K., Xue, Q. L., Peila, R., Petrovitch, H., White, L. R., & Launer, L. J. (2005). A 32-year prospective study of change in body weight and incident dementia: The honolulu-Asia aging study. *Archives of Neurology*, *62*(1), 55–60. doi: 10.1001/archneur.62.1.55

Vanhanen, M., Kivipelto, M., Koivisto, K., Kuusisto, J., Mykkänen, L., Helkala, E. L., … Laakso, M. (2001). APOE-epsilon4 is associated with weight loss in women with AD: A population-based study. *Neurology*, *56*(5), 655–659. doi: 10.1212/wnl.56.5.655

Veronese, N., Facchini, S., Stubbs, B., Luchini, C., Solmi, M., Manzato, E., … Fontana, L. (2017). Weight loss is associated with improvements in cognitive function among overweight and obese people: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *72*, 87–94. doi: 10.1016/j.neubiorev.2016.11.017

Vilalta-Franch, J., López-Pousa, S., Llinàs-Reglà, J., Calvó-Perxas, L., Merino-Aguado, J., & Garre-Olmo, J. (2013). Depression subtypes and 5-year risk of dementia and Alzheimer disease in patients aged 70 years. *International Journal of Geriatric Psychiatry*, *28*(4), 341–350. doi: 10.1002/gps.3826

Villemagne, V. L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., … Masters, C. L. (2013). Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *Lancet Neurology*, *12*(4), 357–367. doi: 10.1016/s1474-4422(13)70044-9

Whitmer, R. A., Gunderson, E. P., Barrett-Connor, E., Quesenberry, Jr. C. P., & Yaffe, K. (2005). Obesity in middle age and future risk of dementia: A 27 year longitudinal population based study. *Bmj*, *330*(7504), 1360. doi: 10.1136/bmj.38446.466238.E0

Yoo, J. E., Shin, D. W., Han, K., Kim, D., Lee, S. P., Jeong, S. M., … Kim, S. (2020). Blood pressure variability and the risk of dementia: A nationwide cohort study. *Hypertension*, *75*(4), 982–990. doi: 10.1161/hypertensionaha.119.14033

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