Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Association Between Waist Circumference and Dementia in Older Persons: A Nationwide Population-Based Study

Geum Joon Cho[1], Soon Young Hwang[2], Kyu-Min Lee[3], Kyung Mook Choi[4], Sei Hyun Baik[4], Tak Kim[1], Sung Won Han[3], and Hye Jin Yoo[4]

Objective: This study examined whether a positive association exists between waist circumference (WC) and dementia among older persons.

Methods: The study population comprised 872,082 participants aged 65 years and older who participated in a Korean national health screening examination between January 1, 2009, and December 31, 2009. Adjusted hazard ratios and 95% CIs for dementia during follow-up from 2009 to 2015 were calculated according to baseline BMI and WC categories.

Results: After a multivariate adjustment that included BMI, the hazard ratios for dementia showed a stepwise increase according to the increase in WC categories by 5 cm from 85 to 90 cm in men and from 80 to 85 cm in women until ≥110 cm (from 1.06 [95% CI: 1.03-1.09] to 1.64 [95% CI: 1.37-1.94] in men and from 1.04 [95% CI: 1.02-1.07] to 1.58 [95% CI: 1.36-1.84] in women). The influence of the current WC category for abdominal obesity on the risk of dementia was different according to BMI; especially, the normal weight men and women with abdominal obesity had a prominent increased risk of dementia compared with those without abdominal obesity.

Conclusions: Abdominal obesity, as measured by WC, was associated with significantly increased risk of dementia after adjustment for general obesity.

Obesity (2019) **27**, 1883-1891. doi:10.1002/oby.22609

Introduction

Dementia is a critical disease to consider when discussing public health in rapidly aging societies because it affects 6% to 10% of people aged 65 years and older (1). Dementia is regarded as a preventable condition with many possible modifiable risk factors. Current clinical guidelines for dementia prevention consider obesity to be one such modifiable risk factor (2). Obesity likely influences cognition through an indirect impact on vascular risk factors or through direct effects of adipocyte-derived hormones and cytokines on cognitive function (3).

Despite the possible direct and indirect links between obesity and dementia, epidemiological studies focused on the association have reported conflicting results. Many prospective studies have demonstrated that midlife obesity is a risk factor for dementia (4-6), but a 2015 large-scale retrospective cohort study of nearly 2 million people from the UK Clinical Practice Research Datalink showed that the incidence of dementia continued to fall for every increasing BMI category (7), and two Mendelian randomization studies showed no association between obesity and dementia (8,9). The main reason for such divergent outcomes may be the difference in follow-up duration, the age when BMI was measured, and the limitation of BMI in assessing obesity. BMI is not a perfect measure of adiposity because it cannot discriminate between fat and lean body mass. Furthermore, aging is characterized by a loss of lean body mass and an increase in adipose tissue without weight gain. A higher BMI in older individuals can be the result of more lean body mass as well as more fat mass. As a result, the association between high BMI and adverse clinical outcomes was shown to attenuate with age (10).

[1] Department of Obstetrics and Gynecology, Korea University Guro Hospital, College of Medicine, Korea University, Seoul, Republic of Korea [2] Department of Biostatistics, College of Medicine, Korea University, Seoul, Republic of Korea [3] School of Industrial Management Engineering, Korea University, Seoul, Republic of Korea. Correspondence: Sung Won Han (swhan@korea.ac.kr) [4] Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Guro Hospital, College of Medicine, Korea University, Seoul, Republic of Korea. Correspondence: Hye Jin Yoo (deisy21@naver.com)

Funding agencies: HJY was supported by the Basic Science Research Program through the National Research Foundation of Korea, which is funded by the Ministry of Education (2018R1D1A1B07047587), and GJC was also supported by the Basic Science Research Program through the National Research Foundation of Korea, which is funded by the Ministry of Education (2018R1D1A1B07048788).

Disclosure: The authors declared no conflict of interest.

Author contributions: Study concept and design: HJY and GJC; acquisition, analysis, or interpretation of data: K-ML, SYH, and SWH; drafting of the manuscript: HJY and GJC; critical revision of the manuscript for important intellectual content: KMC and SHB; statistical analysis: SYH, K-ML, and SWH; obtained funding: HJY and GJC; study supervision: TK, GJC and SWH are the guarantors of this work and, as such, had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Additional Supporting Information may be found in the online version of this article.

Received: 10 February 2019; **Accepted:** 5 July 2019; **Published online 5 November 2019. doi:10.1002/oby.22609**

Waist circumference (WC) is a more accurate indicator of abdominal visceral fat level than BMI, particularly in older individuals (11), potentially making it a better marker for the assessment of abdominal fat. To date, however, there have been limited studies focused on the relationship between WC and dementia in older persons. Abbatecola et al. (12) showed that central adiposity, represented by WC, predicted an increased risk for cognitive decline during a 2-year follow-up period in older patients with diabetes. Recently, West et al. (13) reported that WC was correlated with lower overall cognition and executive performance in older women with type 2 diabetes. However, there has been no large-scale cohort study to examine the association of late-life WC with the incidence of dementia in an older population.

To help determine a healthy WC related to dementia risk for an older population, we compared relative risk of dementia associated with WC and BMI categories using the large-scale National Health Screening Examination (NHSE) database. Furthermore, to clarify the differential relationship between WC and dementia according to BMI categories, we performed an interaction analysis between WC categories and BMI categories on the risk of dementia.

Methods

Data sources

The Korea National Health Insurance Service (NHIS) program is a mandatory social health insurance program that enrolls about 98% of Koreans who participate in biannual standardized health examinations, the NHSE, provided by the Korean government. The NHIS is a single-payer universal health care system for all residents of Korea. Accordingly, the NHIS database represents the entire Korean population and can be used for nationwide population-based studies of disease. The NHIS database contains an eligibility database (including data such as age, sex, and socioeconomic variables), a health examination database (comprising questionnaires on health-related behavioral variables and results of laboratory measurements), and a medical history database (comprising information on diagnosis, medication, admission, and death). This database was described in detail in previous reports (14,15).

Study population

We identified participants aged 65 years or older who had participated in the NHSE between January 1, 2009, and December 31, 2009. Among these 1,278,060 people, participants with an extreme BMI, defined as <15 kg/m^2 or ≥ 40 kg/m^2 ($N=1{,}575$), participants who were diagnosed with dementia within 1 year ($N=86{,}979$), and people with at least one piece of missing data in the NHSE report ($N=317{,}424$) were excluded. The remaining 872,082 individuals were observed until December 31, 2015, and monitored for a dementia diagnosis using the NHIS claims database. A flowchart of participant enrollment is shown in Supporting Information Figure S1. The median follow-up duration for dementia was 6.46 (interquartile range 6.12-6.75) years. The study population was observed from baseline until the date of development of dementia, death, or December 31, 2015, whichever came first. This study was approved by the Institutional Review Board of Korea University Medical Center (2018GR0024). An exemption from informed consent was granted by the board because all data were analyzed anonymously.

Measurement of baseline characteristics

The NHSE consists of a health interview and health examination. The health interview includes questions regarding demographic, socioeconomic, and lifestyle status. Data for the following covariates were obtained: age, smoking status, alcohol consumption, and exercise level. Smoking status was classified as current smoker, past smoker, or never smoker based on the answers to the following questions: "Have you ever been a smoker?" and "If yes, do you smoke currently?" Alcohol consumption was categorized according to the weekly frequency of alcohol intake: no alcohol consumption, one to two servings per week, or three or more servings per week. Exercise was categorized according to the weekly frequency of full-body, sweat-inducing exercise: no exercise, one to two exercise sessions per week, or three or more exercise sessions per week. Because employee health insurance premiums reflect a worker's salary, the study used health insurance premiums as a substitute variable for income level. Based on insurance premiums, economic status was classified into 20 levels of performance, with the highest status defined as the first level. A history of diabetes, hypertension, and cardiovascular disease (CVD) diagnosed by a physician was also identified as an individualized investigation question.

The health examination included the calculation of BMI as measured weight in kilograms divided by measured height in meters squared. WC was measured at the narrowest point between the lower border of the rib cage and the iliac crest during minimal respiration. Blood pressure (BP) was measured using a standard mercury sphygmomanometer. All blood samples were obtained after a minimum fast of 8 hours. The levels of fasting blood glucose (FBS), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured with a Hitachi 747 Analyzer (Hitachi Instruments Inc., Tokyo, Japan) using enzymatic methods.

Charlson Comorbidity Index

Because late-life BMI can be confounded by comorbid medical conditions and concealed baseline diseases, we calculated a hazard ratio (HR) of dementia after adjusting for the Charlson Comorbidity Index (CCI), a scoring system of underlying comorbidity (16). The CCI was defined based on 19 chronic diseases using *International Classification of Diseases, Tenth Revision* codes, including diabetes with diabetic complications, cerebrovascular diseases, congestive heart failure, chronic pulmonary disease, mild and severe liver disease, hemiplegia, renal disease, leukemia, lymphoma, metastatic tumor, and AIDS (17). In this study, the CCI was classified into two groups, with a score of zero indicating no comorbidity and a score of one meaning at least one or more comorbidities.

Outcomes

The primary study outcome was diagnosis of dementia. Dementia was identified by principal or secondary diagnosis based on *International Classification of Diseases, Tenth Revision* codes (F00, F01, F03, G30, and G318). Participants were classified as having dementia only if they were newly diagnosed. The timing of the initial diagnosis was confirmed by the lack of a medical claim for dementia as a primary or secondary disease before the NHSE.

Statistical analysis

Continuous and categorical variables were expressed as means (SD) and percentages, respectively. Clinical and biochemical characteristics were compared among two groups using independent two-sample t tests for continuous variables and Pearson χ^2 test or Fisher exact test

for categorical variables. Clinical and biochemical characteristics were compared among three or more groups using independent one-way ANOVA for continuous variables and Pearson χ^2 test or Fisher exact test for categorical variables. Contrast tests in ANOVA for continuous variables and Mantel-Haenszel χ^2 tests for categorical variables were used to calculate *P* values for linear trends. Cox proportional hazards models were used to estimate the adjusted HRs and 95% CIs of dementia according to baseline WC categories or BMI categories in older men and women. In this analysis, BMI was divided into six groups according to the obesity guidelines for Asian populations. These categories included underweight (<18.5), normal weight (18.5≤BMI<23), overweight (23≤BMI<25), and obesity (grade 1: 25≤BMI<27.5; grade 2: 27.5≤BMI<30; and grade 3: BMI≥30) (18). WC categories were classified into 5-cm increments: <65, 65 to <70, 70 to <75, 75 to <80, 80 to <85 (reference for women), 85 to <90 (reference for men), 90 to <95, 95 to <100, 100 to <105, 105 to <110, and ≥110 cm. The reference WC for men and women was defined as the WC category just below the Korean criteria for abdominal obesity (18). In the Cox regression analysis, participants were monitored for a dementia diagnosis until December 31, 2015. To document the independent influence of obesity on dementia not mediated by various cardiometabolic risk factors, we adjusted measurements for individuals with medical histories that included diabetes, hypertension, and CVD in the Cox proportional HR analysis as well as various covariates, including baseline age; alcohol, smoking, exercise, and economic status; anthropometric parameters (such as BMI or WC); FBS; HDL-C; LDL-C; AST; ALT; and other comorbidities as assessed by the CCI. All tests were two-sided, and $P<0.05$ was considered statistically significant. Statistical analysis was performed using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics of study population

Among the total 872,082 participants, 397,517 were men and 474,565 were women. The detailed baseline characteristics of study participants

TABLE 1 Baseline characteristics of study participants

	Total participants (*N* = 872,082)	Men (*n* = 397,517)	Women (*n* = 474,565)
Age (y), mean ± SD	70.4 ± 4.7	70.2 ± 4.5	70.6 ± 4.7
BMI, mean ± SD	24.1 ± 3.1	23.6 ± 2.9	24.5 ± 3.3
WC (cm), mean ± SD	83.7 ± 8.4	85.1 ± 8.1	82.5 ± 8.4
Systolic BP (mm Hg), mean ± SD	130.9 ± 16.3	130.7 ± 16.2	131.0 ± 16.5
Diastolic BP (mm Hg), mean ± SD	78.4 ± 10.1	78.4 ± 10.1	78.4 ± 10.1
Fasting glucose (mg/dL), mean ± SD	105.0 ± 29.0	106.3 ± 30.0	103.9 ± 28.2
Total cholesterol (mg/dL), mean ± SD	196.8 ± 43.8	187.6 ± 40.8	204.5 ± 44.8
HDL-C (mg/dL), mean ± SD	55.7 ± 42.9	54.3 ± 43.7	56.8 ± 42.2
LDL-C (mg/dL), mean ± SD	118.2 ± 81.2	111.1 ± 79.6	124.2 ± 82.0
AST (IU), mean ± SD	26.7 ± 23.1	27.9 ± 23.6	25.7 ± 22.7
ALT (IU)	23.2 ± 21.9	24.9 ± 26.3	21.8 ± 17.3
Smoking history, *n* (%)			
Never	632,485 (72.5)	175,339 (44.1)	457,146 (96.3)
Past	132,861 (15.2)	126,875 (31.9)	5,986 (1.3)
Current	106,736 (12.2)	95,303 (24.0)	11,433 (2.4)
Alcohol, *n* (%)			
0 per week	648,330 (74.3)	208,388 (52.4)	439,942 (92.7)
1-2 per week	120,937 (13.9)	92,943 (23.4)	27,994 (5.9)
≥3 per week	102,815 (11.8)	96,186 (24.2)	6,629 (1.4)
Exercise, *n* (%)			
0 per week	590,481 (67.7)	246,956 (62.1)	343,525 (72.4)
1-2 per week	111,776 (12.8)	54,847 (13.8)	56,929 (12.0)
≥3 per week	169,825 (19.5)	95,714 (24.1)	74,111 (15.6)
Diabetes, *n* (%)[a]	158,516 (18.2)	73,039 (18.4)	85,477 (18.0)
Hypertension, *n* (%)[a]	467,992 (53.7)	195,040 (49.1)	272,952 (57.5)
CVD, *n* (%)[a]	74,836 (8.6)	32,613 (8.2)	42,223 (8.9)
CCI score ≥1, *n* (%)[b]	836,170 (95.9)	376,861 (94.8)	459,309 (96.8)
Economic status (grade), mean ± SD[c]	12.7 ± 6.0	12.5 ± 6.0	12.8 ± 6.0

[a]Definitions of diabetes, hypertension, and CVD based on past history of diagnosis by physician.
[b]CCI score ≥1 means participant had any comorbidity.
[c]Based on insurance premiums, economic status classified into 20 levels of performance, with highest status defined as first level.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WC, waist circumference.

are described in Table 1. Increased WC was associated with an increase in BMI; with an increase in systolic BP, diastolic BP, FBS, AST, ALT, LDL-C, and total cholesterol levels; with an increase in the proportion of individuals with diabetes, hypertension, and CVD; and with an increase in CCI scores of more than one. Increased WC was also associated with a significant decrease in HDL-C levels and in the proportion of current smokers (Supporting Information Table S1). These patterns were also observed when BMI was classified into the six categories (Supporting Information Table S2).

Association of WC categories with dementia in older men and women

During the median 6.47 years of follow-up, 114,024 older people were diagnosed with dementia (13.1% of the cohort). The HR of dementia according to WC categories is described in Table 2. The participants with WC ≥ 90 cm for men and WC ≥ 85 cm for women, which is the current cutoff value for the diagnosis of abdominal obesity (18), showed a significantly increased risk of dementia after adjustment for other covariates, including age, BMI, systolic BP, FBS, lipid profile, liver function test, various lifestyle factors (such as alcohol, smoking, and exercise habits), underlying comorbidities (such as history of diabetes, hypertension, and CVD) and CCI values (Table 2). There was an almost linear relationship between WC categories and the risk of dementia in older men, whereas there was a J-shaped association in older women (Figure 1A-1B). In model 5, the older men with WC < 85 cm exhibited a significantly lower risk of developing dementia, whereas the women with WC < 75 cm showed no significantly decreased incidence of dementia compared with reference groups (Table 2). The lowest risk for dementia was observed in older men with WC of 65 to 70 cm (HR 0.84 [95% CI: 0.79-0.90]) and in older women with WC of 75 to 80 cm (HR 0.96 [95% CI: 0.94-0.99]).

Association of BMI categories with dementia in older men and women

The older men and women with underweight (according to BMI) had a significantly increased risk of dementia compared with normal weight individuals after adjustment for other covariates, including WC (men: HR 1.21 [95% CI: 1.15-1.27]; women: HR 1.26 [95% CI: 1.21-1.31];

TABLE 2 HR for dementia according to WC categories

WC, cm	Incidence, *n* (%)	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)	Model 4, HR (95% CI)	Model 5, HR (95% CI)
Men						
<65	306 (13.05)	1.41 (1.26-1.58)	1.13 (1.01-1.26)	0.81 (0.72-0.91)	0.82 (0.73-0.92)	0.85 (0.76-0.96)
65 to < 70	1,113 (12.27)	1.27 (1.20-1.35)	1.08 (1.01-1.15)	0.80 (0.75-0.86)	0.82 (0.76-0.87)	0.84 (0.79-0.90)
70 to < 75	3,264 (11.91)	1.21 (1.16-1.26)	1.08 (1.04-1.12)	0.86 (0.82-0.90)	0.87 (0.83-0.91)	0.90 (0.86-0.94)
75 to < 80	6,112 (11.63)	1.16 (1.12-1.20)	1.08 (1.05-1.11)	0.93 (0.90-0.96)	0.94 (0.91-0.97)	0.96 (0.92-0.99)
80 to < 85	9,814 (10.56)	1.04 (1.01-1.06)	1.01 (0.99-1.04)	0.94 (0.92-0.97)	0.95 (0.92-0.98)	0.96 (0.93-0.99)
85 to < 90	9,895 (10.28)	1	1	1	1	1
90 to < 95	7,205 (10.33)	1.01 (0.98-1.04)	1.00 (0.97-1.03)	1.07 (1.04-1.11)	1.07 (1.03-1.10)	1.06 (1.02-1.09)
95 to < 100	3,418 (10.33)	1.06 (1.02-1.10)	1.04 (1.00-1.08)	1.19 (1.14-1.24)	1.17 (1.13-1.22)	1.16 (1.11-1.21)
100 to < 105	1,255 (10.84)	1.07 (1.01-1.13)	1.04 (0.98-1.10)	1.26 (1.19-1.34)	1.24 (1.17-1.32)	1.21 (1.14-1.29)
105 to < 110	336 (11.14)	1.11 (0.99-1.23)	1.05 (0.94-1.17)	1.37 (1.22-1.53)	1.34 (1.20-1.50)	1.30 (1.16-1.45)
≥110	134 (13.15)	1.34 (1.13-1.59)	1.26 (1.06-1.49)	1.77 (1.48-2.10)	1.70 (1.43-2.03)	1.63 (1.37-1.94)
Women						
<65	1,233 (18.91)	1.38 (1.31-1.47)	1.18 (1.11-1.25)	0.96 (0.90-1.02)	0.97 (0.91-1.03)	0.99 (0.94-1.06)
65 to < 70	3,323 (17.37)	1.23 (1.19-1.28)	1.12 (1.08-1.16)	0.95 (0.92-0.99)	0.97 (0.93-1.01)	0.99 (0.95-1.03)
70 to < 75	8,198 (15.70)	1.10 (1.07-1.13)	1.05 (1.03-1.08)	0.95 (0.92-0.97)	0.96 (0.93-0.98)	0.97 (0.94-1.00)
75 to < 80	13,064 (14.49)	1.01 (0.99-1.03)	1.01 (0.98-1.03)	0.95 (0.93-0.97)	0.96 (0.94-0.98)	0.96 (0.94-0.99)
80 to < 85	17,457 (14.63)	1	1	1	1	1
85 to < 90	13,638 (15.00)	1.01 (0.99-1.03)	1.00 (0.98-1.02)	1.059 (1.03-1.08)	1.05 (1.02-1.07)	1.04 (1.02-1.07)
90 to < 95	8,523 (15.44)	1.04 (1.01-1.07)	1.02 (0.99-1.04)	1.12 (1.09-1.15)	1.11 (1.08-1.14)	1.10 (1.07-1.13)
95 to < 100	3,747 (16.20)	1.08 (1.04-1.11)	1.03 (0.99-1.07)	1.19 (1.15-1.24)	1.18 (1.13-1.22)	1.16 (1.11-1.20)
100 to < 105	1,453 (16.20)	1.14 (1.08-1.20)	1.08 (1.02-1.13)	1.32 (1.25-1.40)	1.29 (1.22-1.37)	1.27 (1.20-1.34)
105 to <110	357 (14.94)	1.04 (0.94-1.16)	1.00 (0.90-1.11)	1.30 (1.17-1.45)	1.26 (1.13-1.41)	1.23 (1.10-1.37)
≥110	179 (18.17)	1.31 (1.13-1.51)	1.24 (1.07-1.43)	1.68 (1.45-1.96)	1.62 (1.40-1.89)	1.58 (1.36-1.84)

HRs (95% CI) calculated using Cox proportional hazards model.
Model 1 was unadjusted.
Model 2 was adjusted for age.
Model 3 was adjusted for age, BMI, alcohol consumption, and smoking and exercise status.
Model 4 was adjusted for age, BMI, alcohol consumption, smoking and exercise status, systolic BP, FBS, HDL-C, LDL-C, AST, and ALT.
Model 5 was adjusted for age; BMI; alcohol consumption; smoking and exercise status; systolic BP; FBS; HDL-C; LDL-C; AST; ALT; economic status; history of diabetes, hypertension, and CVD; and CCI.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; FBS, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; WC, waist circumference.

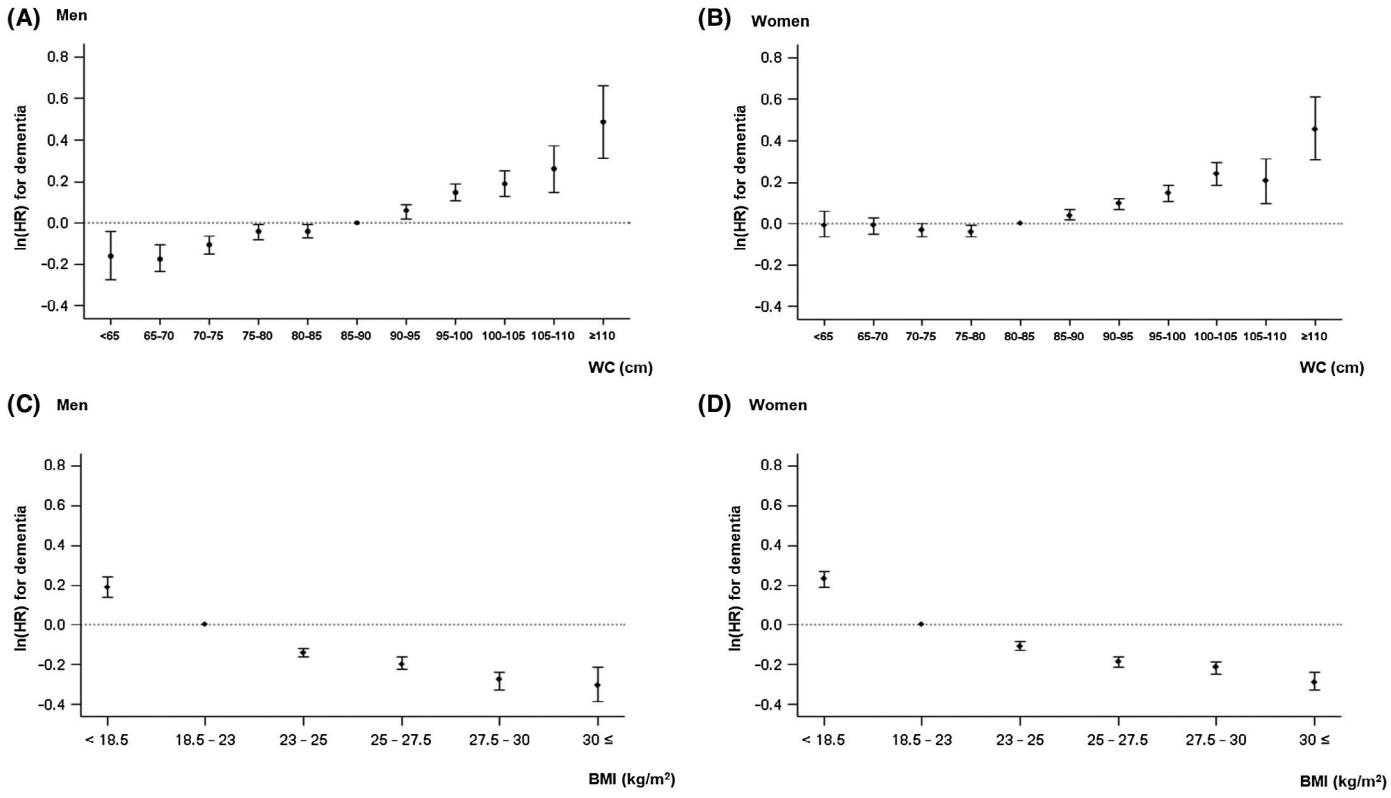

Figure 1 (**A,B**) HRs for dementia according to WC categories in men and women. (**C,D**) HRs for dementia according to BMI categories in men and women in the fully adjusted models.

TABLE 3 HR for dementia according to BMI categories

BMI	Incidence, *n* (%)	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)	Model 4, HR (95% CI)	Model 5, HR (95% CI)
Men						
<18.5	2,138 (14.50)	1.33 (1.28-1.39)	1.15 (1.10-1.20)	1.22 (1.16-1.28)	1.21 (1.15-1.27)	1.21 (1.15-1.27)
18.5 to < 23	17,500 (11.93)	1	1	1	1	1
23 to < 25	11,204 (10.24)	0.83 (0.81-0.85)	0.91 (0.89-0.93)	0.87 (0.85-0.89)	0.87 (0.85-0.90)	0.87 (0.85-0.89)
25 to < 27.5	8,743 (9.64)	0.78 (0.76-0.80)	0.89 (0.86-0.91)	0.82 (0.79-0.84)	0.82 (0.80-0.85)	0.82 (0.80-0.85)
27.5 to < 30	2,598 (9.05)	0.73 (0.70-0.76)	0.85 (0.92-0.89)	0.75 (0.71-0.79)	0.75 (0.72-0.79)	0.76 (0.72-0.79)
≥ 30	669 (9.22)	0.74 (0.69-0.80)	0.88 (0.92-0.96)	0.73 (0.67-0.80)	0.74 (0.68-0.81)	0.74 (0.68-0.81)
Women						
<18.5	2,811 (22.65)	1.46 (1.40-1.51)	1.20 (1.15-1.25)	1.26 (1.21-1.31)	1.25 (1.20-1.30)	1.26 (1.21-1.31)
18.5 to < 23	23,527 (16.75)	1	1	1	1	1
23 to < 25	17,377 (14.60)	0.85 (0.84-0.87)	0.93 (0.91-0.95)	0.90 (0.88-0.92)	0.90 (0.88-0.92)	0.90 (0.88-0.92)
25 to < 27.5	16,613 (13.67)	0.79 (0.78-0.81)	0.89 (0.87-0.91)	0.83 (0.91-0.85)	0.84 (0.82-0.86)	0.83 (0.81-0.85)
27.5 to < 30	7,631 (13.56)	0.79 (0.77-0.81)	0.89 (0.87-0.91)	0.81 (0.78-0.83)	0.81 (0.79-0.84)	0.81 (0.78-0.83)
≥ 30	3,213 (12.94)	0.75 (0.72-0.78)	0.87 (0.83-0.90)	0.75 (0.72-0.78)	0.75 (0.72-0.79)	0.75 (0.72-0.79)

HRs (95% CI) calculated using Cox proportional hazards model.
Model 1 was unadjusted.
Model 2 was adjusted for age.
Model 3 was adjusted for age, WC, alcohol consumption, and smoking and exercise status.
Model 4 was adjusted for age, WC, alcohol consumption, smoking and exercise status, systolic BP, FBS, HDL-C, LDL-C, AST, and ALT.
Model 5 was adjusted for age; WC; alcohol consumption; smoking and exercise status; systolic BP; FBS; HDL-C; LDL-C; AST; ALT; economic status; history of diabetes, hypertension, and CVD; and CCI.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; FBS, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; WC, waist circumference.

Table 3 and Figure 1C-1D). The participants with overweight or obesity showed a significantly and gradual lower risk for dementia than normal weight individuals after adjustment for other confounding factors. After adjustment for WC in model 3, the decrease in the risk of dementia in the participants with overweight or obesity became more prominent (Table 3).

Interactions between abdominal and general obesity with dementia in older men and women

Normal weight participants with abdominal obesity, defined as WC ≥ 90 cm in men and WC ≥ 85 cm in women, had a significantly increased risk of dementia after adjustment for other covariates (HR 1.15 [95% CI: 1.10-1.21] and HR 1.23 [95% CI: 1.18-1.28], respectively), whereas persons with overweight and obesity with abdominal obesity exhibited a significantly reduced risk of dementia (Figure 2), suggesting that the influence of WC on the risk of dementia might be different for different BMI categories. To verify this, we performed an interaction analysis between WC categories and BMI categories on the risk of dementia. There was a significant interaction between WC categories and BMI categories and the incidence of dementia (P for interaction < 0.001), but the overall trend in the risk of dementia with increasing WC was positive in all groups except the groups with underweight and severe obesity (Figure 3 and Supporting Information Table S3).

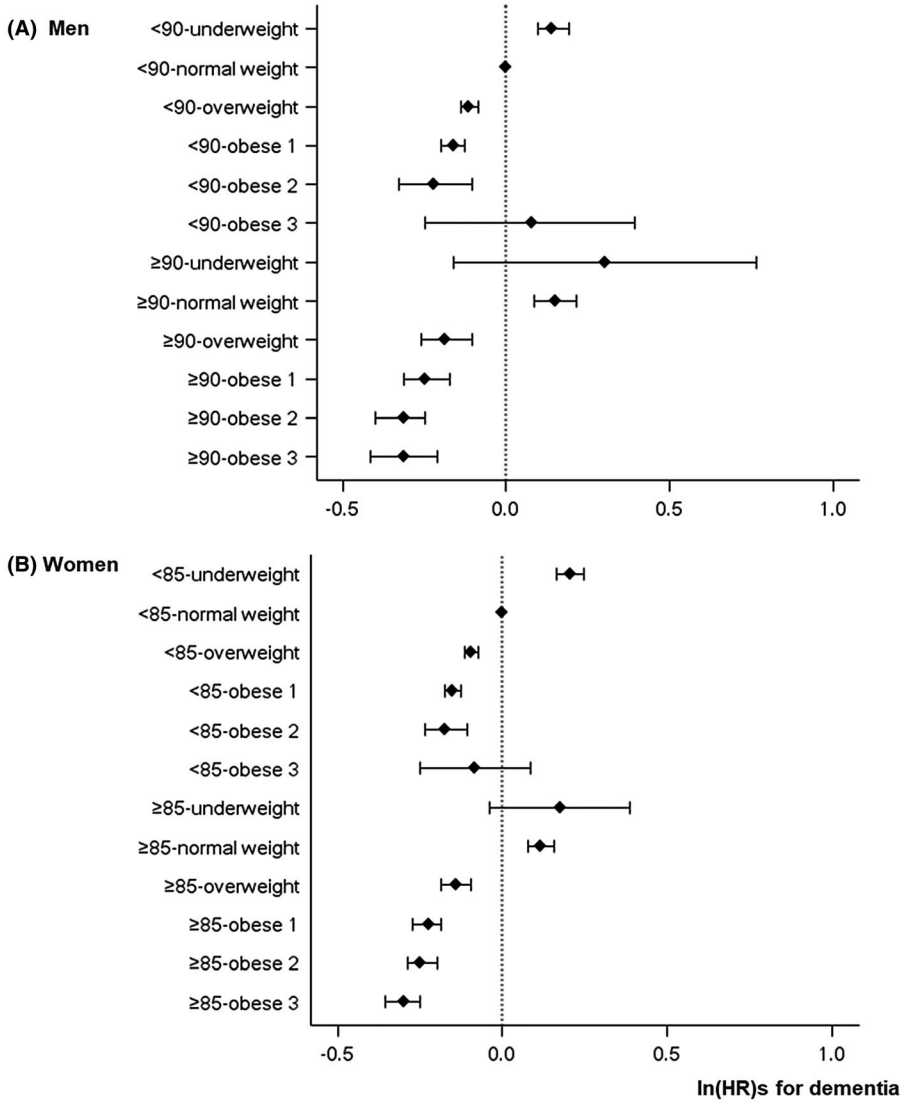

Figure 2 HRs for dementia according to abdominal and general obesity after adjustment for age; alcohol consumption; smoking and exercise status; systolic BP; FBS; HDL-C; LDL-C; AST; ALT; economic status; history of diabetes, hypertension, and CVD; and Charlson comorbidity index in men (A) and women (B). Abdominal obesity was defined as WC ≥ 90 cm in men and WC ≥ 85 cm in women. General obesity was defined by BMI. BMI categories were classified into six groups: underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 23), overweight (23 ≤ BMI < 25), obesity grade 1 (25 ≤ BMI < 27.5), obesity grade 2 (27.5 ≤ BMI < 30), and obesity grade 3: (BMI ≥ 30).

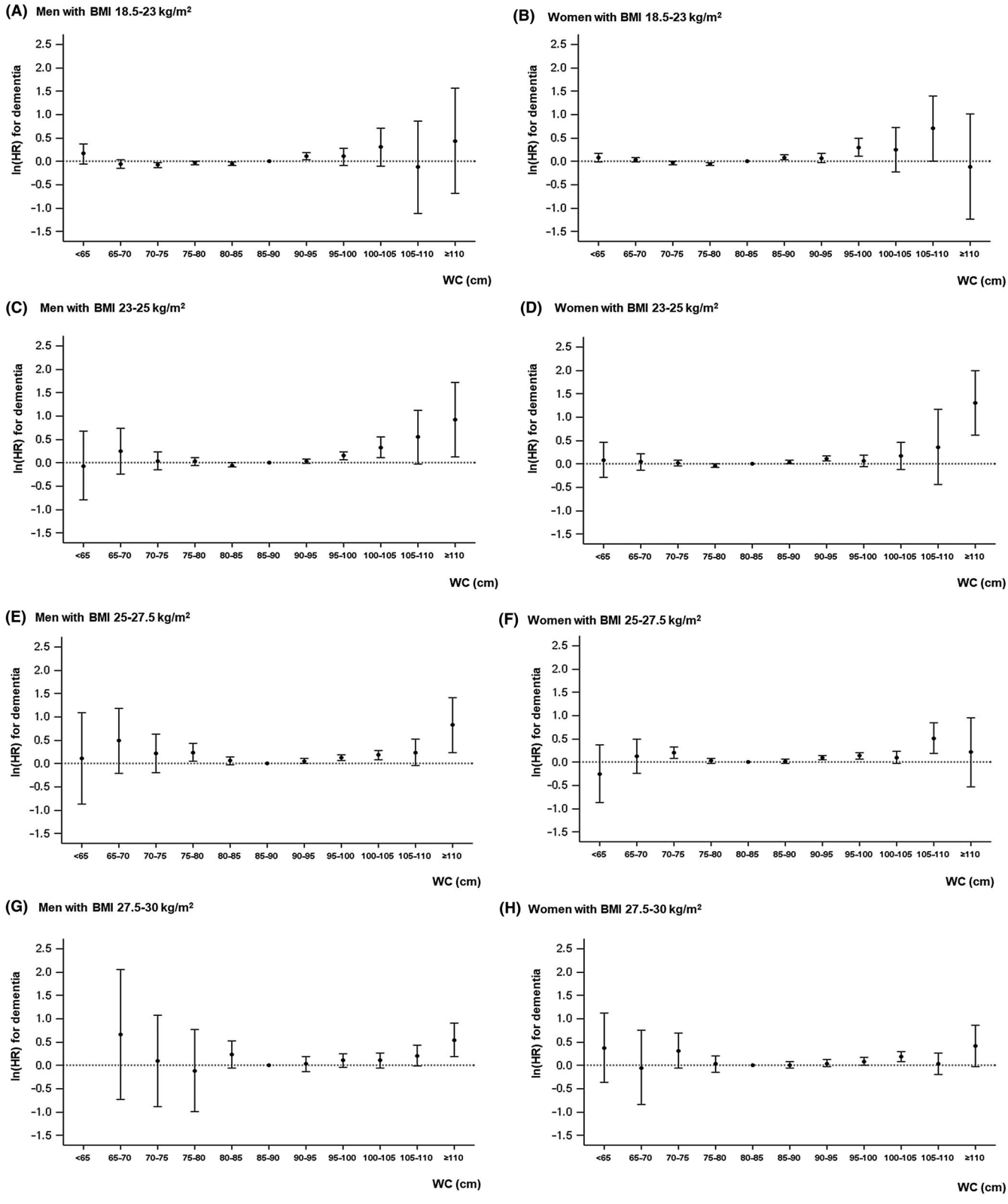

Figure 3 (**A-H**) HRs for dementia according to WC categories interacted by BMI categories in men and women after adjustment for age; alcohol consumption; smoking and exercise status; systolic BP; FBS; HDL-C; LDL-C; AST; ALT; economic status; history of diabetes, hypertension, and CVD; and CCI. *P* values for interactions between WC categories (11 groups) and BMI categories (6 groups) on dementia were <0.001 in both men and women.

Discussion

This is the first study to present evidence that BMI-adjusted late-life WC has a significant positive association with the incidence of dementia, whereas WC-adjusted BMI is negatively correlated with the risk of dementia in older persons. Importantly, older participants with abdominal obesity, defined as WC ≥ 90 cm in men and WC ≥ 85 cm in women, exhibited an increased risk for dementia after adjustment for other covariates, including age, BMI, lifestyle habits, economic status, various CVD risk factors, and other comorbidities.

Adiposity is a well-known risk factor for dementia. Adiposity-related CVD risk factors, such as type 2 diabetes mellitus, hypertension, and dyslipidemia, have been linked to a risk of vascular dementia. Although BMI cannot predict adiposity correctly, BMI has been widely used for the definition of obesity because of its practicality. The Honolulu-Asia Aging Study showed that many CVD risk factors, including BMI, were associated with vascular dementia. In that study, a 1-SD increase in BMI was associated with a 21% higher risk of vascular dementia during a follow-up period of 25 years (19). However, the present study showed that late-life BMI had a negative association with the risk of dementia during a relatively short follow-up period. Similarly, in the Cardiovascular Health Study, having obesity in midlife was associated with a 40% increase in the risk of dementia, with adjustment for other demographics, whereas having obesity later in life was associated with a reduced risk of dementia (HR 0.63 [95% CI: 0.44-0.91]) (20). In a recent systemic review and meta-analysis of longitudinal studies on the relationship between obesity and dementia, having obesity before the age of 65 had a positive association with dementia, with a risk ratio of 1.41 (95% CI: 1.20-1.66); the opposite, however, was seen in those aged 65 years and older, with a risk ratio of 0.83 (95% CI: 0.74-0.94) (21). Measurement of BMI in older individuals may not adequately reflect abdominal fat accumulation because of a potential concurrent decrease in muscle mass. A higher BMI can be the result of either more body fat or more lean mass in older persons. Older women with the highest quartile of fat-free mass had a decreased risk of cognitive impairment compared with those in the lowest quartile group (22). Therefore, in older individuals, the assessment of WC, which is used as a precise indicator for visceral fat, can overcome the potential issues with using only BMI as an adiposity measure in older people.

Besides mediating CVD risk factors, central obesity plays an independent role in the etiology of dementia (23,24). Visceral fat exhibits a detrimental effect on cognitive impairment by increasing the production of proinflammatory cytokines and causing the dysfunction of certain adipokines (25). In the present study, we demonstrated that the WC of older participants had a significant positive association with dementia even when results were adjusted for various CVD risk factors, suggesting that other independent biological factors may be responsible for the association. Some of these biological mechanisms for the effect of adiposity on cognitive function include the fat-brain axis (26) and the hypothalamic-pituitary-adipose axis (27). For example, the direct injection of adipocyte-derived leptin into the hippocampus improved memory processing in mice (28). In the present study, normal weight individuals with abdominal obesity exhibited a significantly increased risk of dementia compared with those without abdominal obesity. Previous studies have shown no association of general obesity with dementia but a positive association of central obesity with dementia (23,29). The Women's Health Initiative Memory Study demonstrated that normal weight women with central obesity (a waist to hip ratio ≥0.8) were at greater risk of cognitive impairment than women with high BMI (30). West et al. (31) reported that individuals with obesity had a 61% decreased rate of dementia after adjusting for WC. In the same study, the dementia rate for individuals in the highest tertile of WC was 90% higher than that for those in the lowest tertile of WC after adjustment for BMI. These results emphasized the importance of measuring WC in combination with BMI in older persons for accurate prediction of dementia risk.

This study stands apart from other previous research on the association between obesity and dementia because of the timing of the measurement of anthropometric parameters and the follow-up period. Measures of BMI late in life are more likely to be confounded by comorbid medical conditions or by perturbations in feeding behavior in the early stages of Alzheimer disease (32,33). Weight loss may be a potential preclinical marker for dementia 6 to 10 years before a clinical diagnosis (34). The brain regulates energy homeostasis through the control of hunger and satiety (35), and individuals with memory impairment may forget to eat, which leads to declining body weight (36). The present study reports that BMI levels within 6.47 years showed a negative association with dementia incidence, whereas WC values within the same period exhibited a positive correlation with the risk of dementia. Similar to our results, Luchsinger et al. (37) showed that dementia risk decreased with higher BMI in people aged 76 years and older, whereas the highest quartile of WC was correlated with an increased dementia risk, suggesting that the association between adiposity and dementia differs depending on the anthropometric parameters used. For older persons, WC might be a more precise anthropometric parameter for the assessment of obesity-related dementia risk than BMI.

The present study has several limitations. First, because of the lack of data, we could not consider the role of apolipoprotein E *(APOE)* e4 (the major susceptibility allele for dementia), family history of dementia, dietary factors, or educational factors. We could not completely exclude survival bias because the participants with high-risk obesity died earlier, mainly caused by CVD; therefore, older individuals who had survived might have had a more favorable obesity phenotype, making the protective effect of BMI on the incidence of dementia more obvious. Another limitation of our study is the lack of analysis on the subtypes of dementia. Chen et al. (38) reported that individuals with obesity or overweight in their 40s had an increased risk of vascular dementia but not Alzheimer disease. The differential relationship between WC and cause-specific dementia will be the focus of future research using this data set. Lastly, only Asian men and women were enrolled in this study. Asians have a higher risk of metabolic disturbances than Caucasians because of a larger amount of metabolically active visceral fat at the same BMI (39); thus, our study results should be revaluated in other ethnic groups. Despite these limitations, this study clarified the association of both WC and BMI with the risk of dementia in older persons using a large-scale nationwide database, which is standardized and validated by the Korean government and represents the entire older Korean population.

Conclusion

This study highlights the critical role of late-life central obesity in the development of dementia in older persons. BMI-adjusted late-life WC had a significant positive association with the incidence of dementia. Clinicians should be aware of the utility of WC for the assessment of obesity-related dementia risk in older persons.

References

1. Hendrie HC. Epidemiology of dementia and Alzheimer's disease. *Am J Geriatr Psychiatry* 1998;6(suppl 1):S3-S18.
2. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol* 2016;15: 455-532.
3. Gustafson D. Adiposity indices and dementia. *Lancet Neurol* 2006;5:713-720.
4. Chuang YF, An Y, Bilgel M, et al. Midlife adiposity predicts earlier onset of Alzheimer's dementia, neuropathology and presymptomatic cerebral amyloid accumulation. *Mol Psychiatry* 2016;21:910-915.
5. Gorospe EC, Dave JK. The risk of dementia with increased body mass index. *Age Ageing* 2007;36:23-29.
6. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* 2005;62:1556-1560.
7. Qizilbash N, Gregson J, Johnson ME, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *Lancet Diabetes Endocrinol* 2015;3:431-436.
8. Ostergaard SD, Mukherjee S, Sharp SJ, et al. Associations between potentially modifiable risk factors and Alzheimer disease: a Mendelian randomization study. *PLoS Med* 2015;12:e1001841. doi:10.1371/journal.pmed.1001841
9. Mukherjee S, Walter S, Kauwe JSK, et al; Adult Changes in Thought Study Investigators; Religious Orders Study/Memory and Aging Project Investigators; Alzheimer's Disease Genetics Consortium. Genetically predicted body mass index and Alzheimer's disease-related phenotypes in three large samples: Mendelian randomization analyses. *Alzheimers Dement* 2015;11:1439-1451.
10. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *N Engl J Med* 1998;338: 1-7.
11. Rankinen T, Kim SY, Perusse L, Després JP, Bouchard C. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. *Int J Obes Relat Metab Disord* 1999;23:801-809.
12. Abbatecola AM, Lattanzio F, Spazzafumo L, et al. Adiposity predicts cognitive decline in older persons with diabetes: a 2-year follow-up. *PLoS One* 2010;5:e10333. doi:10.1371/journal.pone.0010333
13. West RK, Ravona-Springer R, Heymann A, et al. Waist circumference is correlated with poorer cognition in elderly type 2 diabetes women. *Alzheimers Dement* 2016;12:925-929.
14. Seong SC, Kim YY, Park SK, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ Open* 2017;7:e016640. doi:10.1136/bmjopen-2017-016640
15. Kwon S. Thirty years of national health insurance in South Korea: lessons for achieving universal health care coverage. *Health Policy Plan* 2009;24:63-71.
16. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. A critical review of available methods. *J Clin Epidemiol* 2003;56:221-229.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.
18. Kim MK, Lee WY, Kang JH, et al; Committee of Clinical Practice Guidelines; Korean Society for the Study of Obesity. 2014 clinical practice guidelines for overweight and obesity in Korea. *Endocrinol Metab (Seoul)* 2014;29:405-409.
19. Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. *Arterioscler Thromb Vasc Biol* 2000;20:2255-2260.
20. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol* 2009;66:336-342.
21. Pedditizi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. *Age Ageing* 2016;45:14-21.
22. Nourhashemi F, Andrieu S, Gillette-Guyonnet S, et al. Is there a relationship between fat-free soft tissue mass and low cognitive function? Results from a study of 7,105 women. *J Am Geriatr Soc* 2002;50:1796-1801.
23. Luchsinger JA, Cheng D, Tang MX, Schupf N, Mayeux R. Central obesity in the elderly is related to late-onset Alzheimer disease. *Alzheimer Dis Assoc Disord* 2012;26:101-105.
24. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev* 2008;9:204-218.
25. Kiliaan AJ, Arnoldussen IA, Gustafson DR. Adipokines: a link between obesity and dementia? *Lancet Neurol* 2014;13:913-923.
26. Elmquist JK, Flier JS. Neuroscience. The fat-brain axis enters a new dimension. *Science* 2004;304:63-64.
27. Schaffler A, Binart N, Schölmerich J, Büchler C. Hypothesis paper brain talks with fat–evidence for a hypothalamic-pituitary-adipose axis? *Neuropeptides* 2005;39:363-367.
28. Harvey J, Shanley LJ, O'Malley D, Irving AJ. Leptin: a potential cognitive enhancer? *Biochem Soc Trans* 2005;33:1029-1032.
29. Gustafson DR, Bäckman K, Waern M, et al. Adiposity indicators and dementia over 32 years in Sweden. *Neurology* 2009;73:1559-1566.
30. Kerwin DR, Gaussoin SA, Chlebowski RT, et al; Women's Health Initiative Memory Study. Interaction between body mass index and central adiposity and risk of incident cognitive impairment and dementia: results from the Women's Health Initiative Memory Study. *J Am Geriatr Soc* 2011;59:107-112.
31. West NA, Haan MN. Body adiposity in late life and risk of dementia or cognitive impairment in a longitudinal community-based study. *J Gerontol A Biol Sci Med Sci* 2009;64:103-109.
32. Akushevich I, Kravchenko J, Ukraintseva S, Arbeev K, Kulminski A, Yashin AI. Morbidity risks among older adults with pre-existing age-related diseases. *Exp Gerontol* 2013;48:1395-1401.
33. Gillette-Guyonnet S, Nourhashemi F, Andrieu S, et al. Weight loss in Alzheimer disease. *Am J Clin Nutr* 2000;71:637S-642S.
34. Knopman DS, Edland SD, Cha RH, Petersen RC, Rocca WA. Incident dementia in women is preceded by weight loss by at least a decade. *Neurology* 2007;69:739-746.
35. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000;404:661-671.
36. Davidson TL, Kanoski SE, Walls EK, Jarrard LE. Memory inhibition and energy regulation. *Physiol Behav* 2005;86:731-746.
37. Luchsinger JA, Patel B, Tang MX, Schupf N, Mayeux R. Measures of adiposity and dementia risk in elderly persons. *Arch Neurol* 2007;64:392-398.
38. Chen YC, Chen TF, Yip PK, Hu CY, Chu YM, Chen JH. Body mass index (BMI) at an early age and the risk of dementia. *Arch Gerontol Geriatr* 2010;50(suppl 1):S48-S52.
39. Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006;368:1681-1688.