ORIGINAL RESEARCH

Higher Adiposity Is Associated With Slower Cognitive Decline in Hypertensive Patients: Secondary Analysis of the China Stroke Primary Prevention Trial

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***Background*—**Obesity is a risk factor for many diseases. However, the potential association between adiposity and cognitive decline in hypertensive patients is inconclusive. We performed a secondary data analysis of the CSPPT (China Stroke Primary Prevention Trial) to examine whether adiposity is correlated with longitudinal cognitive performance in hypertensive adults.

***Methods and Results*—**The analysis included 16 791 patients in the CSPPT who received at least 2 cognitive assessments by the Mini-Mental State Examination (MMSE) during the follow-up (median, 4.5 years; interquartile range, 4.2–4.8 years). Outcomes included changes in MMSE scores and cognitive impairment (defined as MMSE score less than education-specific cutoff point). A marked reduction in MMSE scores at the final (compared with at the 1-year) follow-up was apparent in both men (n=4838; mean [SD] score, 0.41 [3.62]) and women (n=7190; mean [SD] score, 1.07 [4.61]; both $P<0.001$). Analysis using a mixed-effects model revealed an association between higher body mass index with less MMSE decline, even after controlling for demographics and comorbidities (men, β=0.0134 [SE, 0.0036]; women, β=0.0133 [SE, 0.0034]; both $P<0.001$). A total of 1037 men (15.3%) and 3317 women (33.1%) developed cognitive impairment. In multivariable Cox regression analyses, being obese in men (11.3% versus 18.0%; hazard ratio, 0.75; 95% confidence interval, 0.60–0.94) and women (30.1% versus 36.5%; hazard ratio, 0.82; 95% confidence interval, 0.74–0.91) was a protective factor against cognitive impairment compared with normal body mass index.

***Conclusions*—**Higher adiposity is independently associated with slower cognitive decline in Chinese hypertensive adults.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00794885 CSPPT. **(*J Am Heart Assoc.* 2017;6:e005561. DOI: 10.1161/JAHA.117.005561.)**

Key Words: adiposity • body mass index • cognitive decline • hypertension • waist circumference

In recent decades, the prevalence of obesity has reached epidemic proportions worldwide.[1] In 2014, >1.9 billion adults were overweight (body mass index [BMI], ≥25 kg/m^2), and >600 million of them were obese (BMI, ≥30 kg/m^2). In the general population, it has been well established that obesity, especially its abdominal form, is a modifiable risk factor for cardiovascular disease (CVD)–related morbidity and mortality. Higher BMI is also an independent predictor of progression from normal cognition to cognitive dysfunction. Dementia, an irreversible deterioration of cognitive function, is one of the most common causes of cognitive impairment in the elderly. Similar to obesity, dementia has been increasing. The 2015 World Alzheimer Report predicted that the number of people living with dementia worldwide is expected to increase from

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Accompanying Data S1, Tables S1 through S10, and Figures S1 through S8 are available at http://jaha.ahajournals.org/content/6/10/e005561/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Most previous studies have focused on the association between obesity and survival, but not cognitive abilities, in individuals with established cardiovascular diseases. This study explores the prospective relationship between adiposity and cognitive decline among hypertensive patients.
- There was a high prevalence of increased body mass index and waist circumference in patients with hypertension, present in approximately one fifth and one half of the patients, respectively.
- Both higher body mass index and waist circumference were related to a decreased risk of subsequent cognitive decline independent of established cardiovascular risk factors, and patients who were underweight showed a substantial acceleration of cognitive decline.

What Are the Clinical Implications?

- Given the increased epidemic of obesity in hypertensive patients, the characterization of trajectories of cognitive change associated with higher adiposity is important in clinical settings.
- Although the reasons for the inverse association of adiposity with cognitive decline cannot be determined in this study, the findings identified groups of patients with hypertension who are at increased risk of accelerated cognitive decline who may benefit from possible strategies to prevent or attenuate cognitive deterioration.

46.8 million in 2015 to 131.5 million in 2050.[2] Growing evidence supports the notion that midlife obesity confers dementia risk in late life.[3,4] Furthermore, considering that accelerated cognitive decline at an early stage is an important predictor of high risk for dementia, the relationship between adiposity and cognitive decline has also garnered considerable interests of clinical investigators. Less compelling, but consistent, evidence links obesity exposure at younger age to a steeper subsequent cognitive decline, even among people without dementia.[5,6]

Paradoxically, obesity also has been shown to confer a survival benefit once CVD is established.[7–9] Emerging evidence has demonstrated that obese patients with CVD may have a more favorable prognosis than their normal-weight counterparts, a phenomenon often termed "obesity paradox." The obesity paradox has also been confirmed in non-CVDs, including type 2 diabetes mellitus, hemodialysis, cancer, and pulmonary disease.[10–13]

Hypertension is a major public health challenge, especially in developing countries. Successive population surveys in China have indicated that increases in the prevalence of hypertension have been substantial during the past 30 years, with the most recent national survey reporting at least 325 million Chinese adults (29.6%) have hypertension.[14] Obesity is often associated with hypertension, as either a causative factor or a concomitant disease. Understanding the prognostic impact of obesity on clinical outcomes among hypertensive patients is a public health priority. In a previous study from our research group, a post hoc analysis using data of 20 694 middle-aged and older subjects from the CSPPT (China Stroke Primary Prevention Trial) demonstrated that obesity could reduce the risk of all-cause mortality by ≈36%. This study strengthened the existing evidence of the obesity paradox in hypertensive patients.[15] Cognitive decline significantly affects daily functioning and, thus, quality of life, especially among patients with CVD. Identifying modifiable risk factors associated with cognitive decline is important, given possible strategies for preventing or attenuating cognitive deterioration early. Although prior studies have documented an association between adiposity and cognitive abilities in the general population, it remains unelucidated how obesity affects cognitive function of hypertensive patients. The CSPPT provided an opportunity to address these questions by including a large and well-defined cohort of hypertensive adults with follow-up measurements of cognitive function. In the current study, we conducted a secondary data analysis to examine whether obesity confers benefit in cognitive status in hypertensive subjects. Specifically, we examined the potential association between cognitive decline in this study sample over a 4.5-year period and both BMI and waist circumference (WC).

Methods

Study Design and Participants

A detailed description of the protocol and primary results of the CSPPT has been presented in Data S1 and published previously.[16] Briefly, the CSPPT is a community-based, randomized, multicenter, double-blind controlled trial conducted from May 19 2008 to August 24 2013 in 32 communities in the Anhui and Jiangsu provinces of China. The study enrolled a total of 20 702 hypertensive adults, aged 45 to 75 years, who were free from other major CVDs. Participants were randomly assigned to receive treatment with either a combination of enalapril and folic acid or enalapril alone and were followed-up every 3 months for a median of 4.5 years. Detailed inclusion and exclusion criteria for the CSPPT have been described elsewhere.[16] This secondary analysis of cognitive outcomes was conducted to determine the effects of adiposity on trajectories of cognitive decline. The analysis included CSPPT participants who received at least 2 cognitive assessments during the follow-up and had available measures of adiposity at the baseline. The CSPPT was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University (Hefei,

China) (FWA assurance number FWA00001263). All patients provided written informed consent before the enrollment.

Definition of Adiposity

Height, weight, and WC were collected at the baseline visit. BMI, the primary measure of adiposity, was calculated as weight in kilograms divided by the square of height in meters. We analyzed BMI as a continuous variable and divided it into Chinese categories for underweight (<18.5 kg/m^2), normal weight (18.5–<24 kg/m^2), overweight (24–<28 kg/m^2), and obese (≥28 kg/m^2).[17] Abdominal adiposity was assessed using WC and defined as high if WC ≥90 cm for men and ≥80 cm for women.[18]

Assessment of Cognitive Performance

Cognitive assessment was completed using the Chinese version of the Mini-Mental State Examination (MMSE) at the 1- and 3-year follow-ups and the final follow-up visit. The Chinese version of the MMSE, as a reliable and standardized tool, has been validated for use in the Chinese population and has been widely used to screen cognitive impairment and dementia.[19] The tests were performed by trained interviewers in a standardized manner during each follow-up visit. Specifically, the MMSE includes a broad set of cognitive domains that measure the following: orientation to time (5 points), orientation to place (5 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language (9 points). The total score ranges from 0 to 30 points, with higher scores indicating better cognitive performance. The test was considered invalid if a subject refused to answer a question or there was a missing item in the test.

Outcome Measures

The primary outcome was change in MMSE score. The secondary outcome was time to cognitive impairment. Cognitive impairment was determined according to the education-specific cutoff points of MMSE in China: ≤17 for illiterate people, ≤20 for people with 1 to 6 years of education (primary school), and ≤24 for people with >6 years of education (middle school or higher).[20] We included 2 additional composite outcomes[21]: (1) cognitive impairment with stroke (defined as the diagnosis of cognitive impairment after a new-onset stroke during the follow-up) and (2) other cases of cognitive impairment.

Covariate Variables

Detailed data on sociodemographic status, lifestyle, and medical history as well as seated blood pressure (BP) measurements were obtained by trained investigators using standard procedures. Systolic BP and diastolic BP for analyses were calculated as the mean of 3 consecutive measurements on the right arm. We categorized marriage status as married, never, or other (divorced, widowed, or separated) and cigarette and alcohol consumption as never, former, and current. Living conditions were determined by self-report (low, moderate, and high). Physical activity was categorized as low, moderate, or high, according to self-reported exercise frequency. Depressive symptoms were evaluated using the Patient Health Questionnaire-9.[22] The CSPPT collected overnight fasting venous blood samples at the baseline visit. Methods for collecting laboratory assays have been described before.[16] Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the equation according to the Chronic Kidney Disease Epidemiology Collaboration.[23] We defined normal kidney function as eGFR ≥90 mL/min per 1.73 m^2 and chronic kidney disease as eGFR <60 mL/min per 1.73 m^2. Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/L (to convert mmol/L to mg/dL, divide by 0.0555), self-reported diagnosis of diabetes mellitus, or use of hypoglycemic agents. New-onset stroke during follow-up was determined by an End Point Adjudication Committee.

Statistical Analysis

Baseline demographic and clinical characteristics are expressed as mean (SD) or percentage and compared using Student *t* test, 1-way ANOVA test, or χ^2 test, where appropriate. Data for marital status (n=81), smoking status (n=2), alcohol consumption (n=5), and physical activity (n=15) were missing for <1% of the patients. Data for serum eGFR (n=326) and diabetes mellitus at baseline (n=310) were missing for 1% to 2% of patients, and data for new-onset diabetes mellitus (n=1832) during the follow-up were missing for 11% of the cohort. Missing values of continuous and categorical covariates in outcome analysis were handled using multiple imputation with 10 imputed data sets and a chained equation approach. Because all adiposity measures differed significantly by sex, all subsequent analyses were conducted separately for men and women.

Generalized linear mixed models using unstructured correlation matrices and maximum likelihood method were applied to evaluate whether baseline adiposity measures predicted trajectories of MMSE change during the follow-up. Intersubject variability was the random effect (random intercepts and slopes), and baseline adiposity measures were the fixed effect. We included adiposity measures, the time in the study (years after randomization), and potential covariates and their interactions with time in the mixed-effects model. The term for time was modeled as a continuous variable or categorical variable to reflect change in MMSE score per year or per cognitive assessment in the reference group, respectively.

We applied Cox proportional hazards models to estimate the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for cognitive impairment related to categories of adiposity measures. Follow-up duration was calculated from the date of randomization to first diagnosis of cognitive impairment or the end of CSPPT. For patients who were unavailable for follow-up, data were censored at the last follow-up visit with cognitive assessment. Tests for linear trend in the HRs of cognitive impairment were based on medians across categories of BMI and WC. Multivariable models (model 1-2) adjusted for baseline age, study center, educational level, smoking and alcohol consumption, marital status, living conditions, physical activity, depressive symptoms, systolic BP (SBP), mean SBP during treatment period, eGFR, medical diseases (diabetes mellitus and stroke), and treatment allocation. We combined several strategies to select covariates for multivariable adjustment. First, we included variables producing >10% change in the regression coefficient of BMI (or WC) after they were introduced into the basic model and removed from the full model. In addition, we selected variables that were associated with cognitive function at a level of $P<0.1$ in the univariate analysis. Moreover, we also included appropriate covariates based on evidence from published literature and our clinical perspective. We applied the same modeling strategy in the covariate selection for change in MMSE score in the generalized linear mixed models. In the Cox models, we tested the proportional hazard assumption for each covariate by examining the log-minus-log plots against log follow-up time, and the likelihood-ratio test was also conducted after introducing an interaction term between time and each covariate into the main effects model.

We further investigated the nonlinear relationship between BMI and WC as continuous variables and the risk of cognitive impairment by smooth curve fitting using penalized thin plate regression splines within general additive models. Threshold analysis was conducted using the segmented regression model, likelihood ratio test, and bootstrap resampling method if tests for nonlinear trend were significant.

In subgroup analyses, we used stratified Cox proportional hazards models to examine the robustness of our primary results on the basis of prespecified baseline variables. Among men, we performed additional analysis to explore if the relationship varied by smoking status (never versus former versus current). Effect modification by above individual covariates was estimated from the likelihood-ratio test of models with and without interaction terms, where BMI was regarded as a continuous variable.

Several sensitivity analyses were implemented to address reverse causation by excluding patients with chronic kidney disease at baseline, those with new stroke during the follow-up, and those with cognitive impairment at the 1-year follow-up. In additional sensitivity analyses, we divided BMI into World Health Organization categories for underweight (<18.5 kg/m^2), normal weight (18.5–<25 kg/m^2), overweight (25–30 kg/m^2), and obese (≥30 kg/m^2). We also defined high WC using ≥94 cm for men and ≥80 cm for women (recommended for whites) and ≥90 cm for men and ≥80 cm for women (recommended in the United States).

A 2-tailed $P<0.05$ was considered statistically significant. All analyses were performed using EmpowerStats (http://www.empowerstats.com) and R (http://www.R-project.org) software.

Results

Demographic and Baseline Characteristics of the Study Participants

Of the 20 702 participants enrolled in the CSPPT study, 7 had no information on weight or height at baseline; 13 had missing important covariates, including age and education level, at baseline; 78 died before the first follow-up; and 3813 had no available cognitive assessments at all follow-up visits (n=928) or had only 1 cognitive measure (n=2885). A total of 16 791 participants (81.1%) were included in data analysis in the current study (Figure 1). Patient characteristics of the subjects included in the study in comparison with those excluded are reported in Table S1. Excluded participants were slightly younger, more likely to smoke, less likely to be married and diabetic (women only), had higher stroke incidence, and had lower baseline SBP. The demographic data and baseline characteristics of the study participants are summarized in Table 1. Of the 16 791 patients (mean [SD] baseline age, 60.1 [7.4] years; 10 033 [59.8%] were women) in our study, 6370 (37.9%) had normal BMI, 6610 (39.4%) were overweight, and 3411 (20.3%) were obese. In addition, 11.5% of the patients had diabetes mellitus at baseline, 11.3% had de novo diabetes mellitus during the follow-up, and 2.7% had new-onset stroke. Table S2 provides demographic and clinical characteristics stratified by BMI categories.

Changes in MMSE Scores

The patients in CSPPT were followed-up for a median duration of 4.5 years (interquartile range, 4.2–4.8 years). The total MMSE score and subscores for each domain of the study participants at each follow-up visit are shown in Table 2. The mean (SD) MMSE scores were 26.2 (4.0) in men and 22.3 (4.5) in women at the 1-year follow-up visit and 25.8 (4.6) in men and 21.2 (5.2) in women at the final follow-up visit. A significant mean (SD) reduction of 0.41 (3.62) points in total MMSE score was observed in men at the final follow-up versus the 1-year follow-up, and a marked 1.07 (4.61) point reduction was observed in women at the final follow-up versus

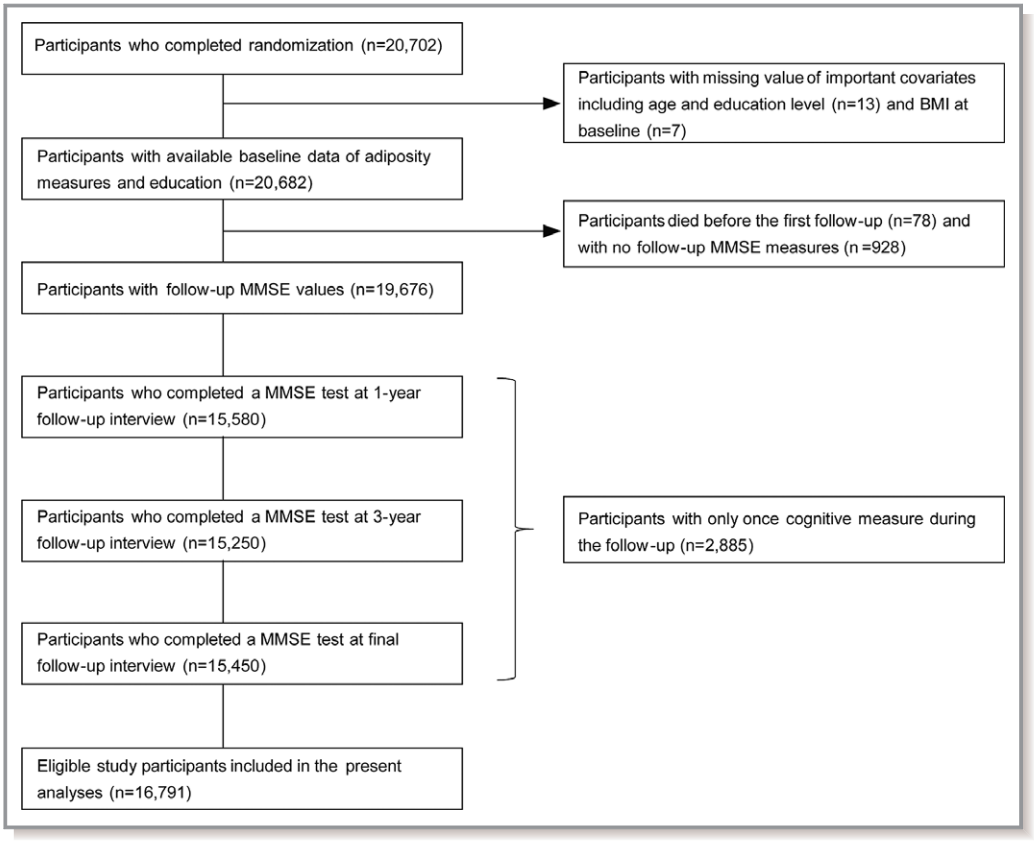

Figure 1. The study flow chart for post hoc cognition analysis of the CSPPT (China Stroke Primary Prevention Trial). BMI indicates body mass index; and MMSE, Mini-Mental State Examination.

the 1-year follow-up. Consistently, a significant reduction was also noticed in the MMSE subscores, especially orientation to time and attention/calculation, at the final follow-up visit versus the 1-year follow-up visit (Table 2). Figure 2 also shows the unadjusted mean changes in total MMSE score and their corresponding 95% CIs and sample size of participants with available data by BMI category across follow-up visits.

Baseline Adiposity Measures and Trajectories of Cognitive Decline in MMSE Scores

When BMI was analyzed as a continuous variable, analysis using the mixed-effects regression model showed a 1-U increase in BMI was associated with significantly slower rates of decline in total MMSE score during the follow-up ($P<0.001$; Table 3). The mean (SEM) rate of MMSE decline for a participant at a normal BMI level of 24 kg/m^2 was 0.4785 (0.0856) points per year among men ($P<0.001$) and 0.6430 (0.0841) points per year among women ($P<0.001$). The decline in total MMSE score per year is 0.0153 points less with each additional unit increase in BMI >24 kg/m^2 among men and 0.0142 points less with each additional unit increase in BMI >24 kg/m^2 among women. When BMI was analyzed as a categorical variable, a more rapid decrease in MMSE score over time was observed in patients who were underweight compared with normal-weight individuals, although this association was significant only among men ($\beta=-0.1669$ [SE, 0.0704]; $P=0.018$; Table 4). Furthermore, rates of MMSE decline were significantly slower in obese patients than those of normal-weight patients (men: $\beta=0.1104$ [SE, 0.0359] [$P=0.002$]; women: $\beta=0.1176$ [SE, 0.0328] [$P<0.001$]). In particular, obese individuals experienced a 0.0250-point decrease per year in men and a 0.2213-point decrease per year in women, whereas those with a normal BMI experienced a 0.1354-point decrease per year in men and a 0.3389-point decrease per year in women. These associations remained significant after further adjustment for cardiovascular risks and other factors (Table 5). Similar associations were also found between WC and MMSE decline (Table S3 through S5).

We further explored the relationship between BMI and changes in multifactorial MMSE subscores (Table 6). Higher BMI was significantly associated with a decelerated decline in MMSE subscores in both men and women ($P<0.05$ for both), especially in the domains of orientation to time, attention/calculation, and recall. Further adjustment for cardiovascular risk factors also did not substantially change these results (Table 7). A similar pattern was found in the effect of WC in men, but not in women (Tables S6 and S7).

Table 1. Demographic and Clinical Characteristics of Study Participants by Sex

Characteristics	Total (N=16 791)	Men (n=6758)	Women (n=10 033)	*P* Value
Age, mean (SD), y	60.1 (7.4)	61.3 (7.4)	59.3 (7.4)	<0.001
Marital status, n (%)				
Married	14 435 (86.4)	5880 (87.5)	8555 (85.6)	<0.001
Never married	151 (0.9)	103 (1.5)	48 (0.5)	
Other (divorced, widowed, or separated)	2124 (12.7)	734 (10.9)	1390 (13.9)	
Educational level, n (%)				
Illiteracy	10 853 (64.6)	2549 (37.7)	8304 (82.8)	<0.001
Primary school	2759 (16.4)	1749 (25.9)	1010 (10.1)	
Middle school and higher	3179 (18.9)	2460 (36.4)	719 (7.2)	
Living conditions, n (%)				
Low	1963 (11.7)	942 (13.9)	1021 (10.2)	<0.001
Moderate	12 909 (76.9)	5147 (76.2)	7762 (77.4)	
High	1919 (11.4)	669 (9.9)	1250 (12.5)	
BMI, mean (SD), kg/m^2	25.1 (3.7)	24.3 (3.4)	25.5 (3.8)	<0.001
BMI category, n (%)				
Underweight	400 (2.4)	209 (3.1)	191 (1.9)	<0.001
Normal weight	6370 (37.9)	3018 (44.7)	3352 (33.4)	
Overweight	6610 (39.4)	2528 (37.4)	4082 (40.7)	
Obese	3411 (20.3)	1003 (14.8)	2408 (24.0)	
WC, mean (SD), cm	84.5 (9.9)	84.4 (10.1)	84.5 (9.8)	0.460
SBP, mean (SD), mm Hg				
Baseline	167.3 (20.5)	165.7 (20.6)	168.4 (20.4)	<0.001
Follow-up	138.9 (10.5)	138.7 (10.2)	139.0 (10.7)	0.127
eGFR, mean (SD), mL/min per 1.73 m^2	93.5 (13.0)	91.9 (13.4)	94.6 (12.7)	<0.001
Current smoking, n (%)	3819 (22.7)	3498 (51.8)	321 (3.2)	<0.001
Current alcohol drinking, n (%)	3918 (23.3)	3528 (52.2)	390 (3.9)	<0.001
Low physical activity, n (%)	6170 (36.8)	2421 (35.9)	3749 (37.4)	0.093
Treatment allocation, n (%)				
Enalapril	8446 (50.3)	3393 (50.2)	5053 (50.4)	0.842
Enalapril–folic acid	8345 (49.7)	3365 (49.8)	4980 (49.6)	
Medical comorbidities, n (%)				
Diabetes mellitus at baseline	1889 (11.5)	677 (10.3)	1212 (12.3)	<0.001
New diabetes mellitus*	1694 (11.3)	677 (11.3)	1017 (11.3)	0.973
Stroke	447 (2.7)	210 (3.1)	237 (2.4)	0.003

BMI indicates body mass index; WC, waist circumference; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
*New diabetes mellitus is defined as having no diabetes mellitus at baseline and being diabetic at final follow-up visit.

Baseline Adiposity Measures and Cognitive Impairment

A total of 25.9% of the patients developed cognitive impairment, including 1037 men (15.3%) and 3317 women (33.1%). Among them, 159 (3.7%) had "cognitive impairment with stroke," and the remaining 4195 had "other cognitive impairment." Analysis using the multivariable Cox proportional hazards model showed a decline in relative risk for every increasing BMI category after adjustment for study center, age, and education only (P<0.001; Table 8). The highest risk was seen in the underweight group (men: HR, 1.37; 95% CI, 1.02–1.85; women: HR, 1.24; 95% CI, 1.00–1.54). After

Table 2. Total MMSE Score and Subscores of the Study Participants at Each Follow-Up Visit

Measures	Men					Women				
	1 Year	3 Years	Final	Change*	Change†	1 Year	3 Years	Final	Change*	Change†
No. of participants with available data	5707	5786	5889	4735	4838	8550	8790	8673	7307	7190
MMSE score	26.2 (4.0)	26.0 (4.0)	25.8 (4.6)	0.04 (3.32)	0.41 (3.62)‡	22.3 (4.5)	22.1 (4.4)	21.2 (5.2)	0.06 (4.02)	1.07 (4.61)‡
MMSE subscores										
Orientation to time	4.4 (1.0)	4.4 (1.0)	4.2 (1.2)	−0.0042 (1.1198)	0.2377 (1.2373)‡	3.9 (1.3)	3.8 (1.3)	3.3 (1.6)	−0.0053 (1.5089)	0.5764 (1.7400)‡
Orientation to place	5.0 (0.2)	5.0 (0.2)	4.9 (0.4)	−0.0004 (0.2986)	0.0593 (0.4738)‡	4.8 (0.7)	4.8 (0.6)	4.6 (1.0)	−0.0365 (0.8764)	0.1982 (1.0803)‡
Registration	2.9 (0.5)	2.9 (0.5)	2.8 (0.6)	−0.0068 (0.6142)	0.0562 (0.7007)‡	2.8 (0.6)	2.8 (0.6)	2.7 (0.8)	−0.0140 (0.7989)	0.1462 (0.9591)‡
Attention/calculation	4.0 (1.6)	4.0 (1.7)	4.0 (1.7)	0.0707 (1.6683)§	0.0978 (1.7462)‡	2.3 (2.1)	2.2 (2.0)	2.2 (2.1)	0.1384 (1.9928)‡	0.0979 (2.0968)‡
Recall	2.3 (1.0)	2.4 (1.0)	2.4 (1.0)	−0.0967 (1.2382)	−0.1114 (1.2531)	2.1 (1.1)	2.2 (1.1)	2.1 (1.2)	−0.1403 (1.3502)	−0.0501 (1.4019)‡
Language	7.5 (1.4)	7.5 (1.4)	7.5 (1.5)	0.0788 (1.1532)‡	0.0699 (1.1575)‡	6.3 (1.0)	6.2 (1.1)	6.2 (1.1)	0.1222 (1.0637)‡	0.1053 (1.0478)‡

For continuous variables, data are presented in mean (SD). MMSE indicates Mini-Mental State Examination.
*Changes in total MMSE score and subscores (scores at 1-year follow-up visit–scores at 3-year follow-up visit).
†Changes in total MMSE score and subscores (scores at 1-year follow-up visit–scores at final follow-up visit).
‡$P<0.001$.
§$P<0.01$.

controlling for known cardiovascular risk factors, there was a nonsignificant trend for increasing risk in patients who were underweight (men: HR, 1.25; 95% CI, 0.90–1.76; women: HR, 1.21; 95% CI, 0.96–1.53). Being overweight or obese was significantly associated with reduced risk of cognitive impairment relative to normal weight among both men (overweight: HR, 0.78; 95% CI, 0.67–0.91; obese: HR, 0.75; 95% CI, 0.60–0.94) and women (overweight: HR, 0.87; 95% CI, 0.80–0.95; obese: HR, 0.82; 95% CI, 0.74–0.91). The reduction in risk was exclusively observed in patients with "other cognitive impairment" ($P<0.001$). Adiposity did not alter the risk of cognitive impairment with stroke (men: HR, 0.95; 95% CI, 0.87–1.04; women: HR, 0.97; 95% CI, 0.91–1.04). When BMI was modeled as a continuous variable, the penalized spline plots showed an approximately linear pattern in the effect of BMI on cognitive impairment in men, with a 4% decrease in risk for a 1-U increase in BMI (HR, 0.96; 95% CI, 0.94–0.98). The association was seemingly weaker, but statistically significant, in women, and a threshold effect was observed at a BMI >28.7 kg/m^2 (Figure 3). Similar findings were observed for the association between WC and cognitive impairment (Table S8 and Figure S1). Threshold analysis revealed a clear cutoff for WC in relation to cognitive impairment in women, with the association between increasing WC levels and an ever-decreasing risk reaching a plateau at >92 cm.

Effect Modification by Important Covariates

Stratified analyses showed that the inverse relations between BMI and the risk of cognitive impairment are consistent for all strata (Figure S2). There was no significant interaction between BMI (as a continuous variable) and important covariates stratified by sex ($P>0.05$ for interaction for all), except that the diabetes mellitus status had a moderate effect modification in women ($P=0.041$ for interaction). Furthermore, we observed no apparent heterogeneity in the effect of BMI between the men with or without smoking ($P=0.487$ for interaction; data not shown).

Sensitivity Analyses

The imputation of missing variables did not affect the results (Table S9). The results were virtually unchanged after excluding patients with chronic kidney disease at baseline, those with new stroke during the follow-up, or those with cognitive impairment at the 1-year follow-up (Figure S3). When using ethnic-specific cut points for adiposity categories, the effect on cognitive impairment remained statistically significant (Figure S4).

Discussion

Despite overwhelming evidence linking obesity to a higher incidence of cognitive dysfunction in the general population,

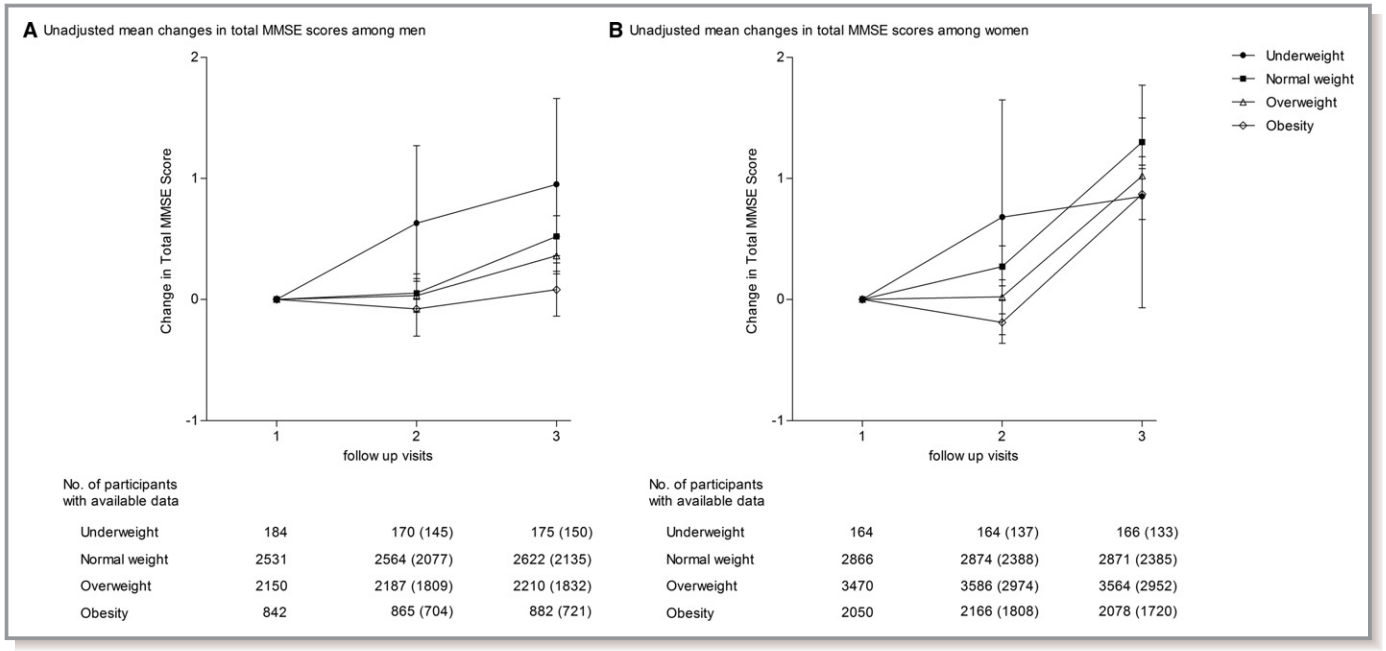

Figure 2. Unadjusted mean change in total Mini-Mental State Examination (MMSE) score by body mass index (BMI) categories at baseline. Changes of MMSE scores at the 3-year follow-up visit and final follow-up visit vs the 1-year follow-up visit are presented in men (A) and women (B). A, After adjusting for covariates, the changes in total MMSE score between all other BMI groups and normal-weight group are not statistically significant at 3-year follow-up visit vs 1-year follow-up visit; the change in total MMSE score between obesity group and normal-weight group is P=0.004 at final follow-up visit vs 1-year follow-up visit. B, After adjusting for covariates, the change in total MMSE score between obesity group and normal-weight group is P=0.004 at 3-year follow-up visit vs 1-year follow-up visit; the changes in total MMSE score between overweight group and normal-weight group and between obesity group and normal-weight group are P=0.027 and P<0.027, respectively, at final follow-up visit vs 1-year follow-up visit. Error bars indicate 95% confidence intervals. Numbers outside parentheses represent number of participants with available data at each follow-up visit, and numbers in parentheses represent number of participants with available data on the changes of MMSE between 3-year follow-up (or final follow-up) and 1-year follow-up.

there is a particular paucity of data in hypertensive patients. Using the cohort of the CSPPT, we examined the hypothesis that obesity may confer protection against cognitive decline in hypertensive patients. Approximately one quarter of the study participants (25.9%) developed cognitive impairment during a median follow-up duration of 4.5 years. The study has demonstrated that higher adiposity is associated with a decelerated decline in MMSE score in Chinese hypertensive adults. Notably, we observed a reduction in risk exclusively in patients with cognitive impairment attributable to causes other than stroke. We also report novel information regarding the effect of adiposity on several cognitive subdomains. These findings are generally supported by analysis using WC as a measure for adiposity, which is more accurate in evaluating the fat distribution and considered by some investigators to be superior in reflecting metabolic characteristics.[24–26]

Although our previous analysis from CSPPT and other prior studies have already described the survival advantage in obese patients with hypertension, it remains to be established whether obesity confers a benefit in neurocognitive abilities of hypertensive adults. The present study represents the first attempt to evaluate the issue using a longitudinal design in a large cohort of middle-aged and elderly patients. The strengths of our study include large sample size and comprehensive adjustments for major demographic and vascular risk factors. Moreover, mixed models can account for the correlation of the repeated MMSE assessments appropriately and use all available data without the imputation of any missing values, compared with traditional methods. An early cross-sectional study of 184 Japanese hypertensive patients (aged 61–94 years) revealed that lower BMI (14.5–20.3 kg/m^2) was a risk for cognitive impairment (odds ratio, 2.54; 95% CI, 1.13–5.73; P=0.02).[27] Our analysis using the mixed-effects regression models also uncovered a more rapid decline in MMSE score in men with a BMI <18.5 kg/m^2. We further showed that overweight status and obesity were associated with smaller cognitive decline and a decreased risk of cognitive impairment. In addition, this benefit in cognitive function was independent of comorbidities, treatment allocation, and other factors. Our results lend further support to the obesity paradox that patients with established CVDs benefit from increased BMI. Previous studies reporting the obesity paradox are limited by relying predominantly on BMI assessment. Thus, our study goes 1 step further by demonstrating that consistent results extend beyond BMI to a marker of abdominal adiposity.

Table 3. Effects of Continuous BMI Levels on Longitudinal Change in Cognitive Function Represented by MMSE Score

Model*		Men		Women	
		Coefficient β (SE)†	*P* Value	Coefficient β (SE)†	*P* Value
Effect of time on change in MMSE score (per year/test)					
Model 1‡	Time	−0.4785 (0.0856)	<0.001	−0.6430 (0.0841)	<0.001
Model 2§	Time (2)	−1.1359 (0.3448)	0.001	−1.0952 (0.3326)	0.001
	Time (3)	−1.9174 (0.3421)	<0.001	−2.5749 (0.3351)	<0.001
Additional effect of BMI on change in MMSE score (per year/test)					
Model 1	BMI×time	0.0153 (0.0035)	<0.001	0.0142 (0.0033)	<0.001
Model 2	BMI×time (2)	0.0431 (0.0140)	0.002	0.0386 (0.0129)	0.003
	BMI×time (3)	0.0614 (0.0139)	<0.001	0.0570 (0.0130)	<0.001

BMI indicates body mass index; and MMSE, Mini-Mental State Examination.
*The mixed model is adjusted for study center, age, and education.
†Coefficient β (SE) represents mean change over time for an individual in the reference group (with a BMI level of 18.5 kg/m^2, which is the lower bound of the normal-weight group) and the additional effect of a 1-U increase in BMI on change in MMSE score per year (or per test).
‡In model 1, time is modeled as a continuous variable to reflect change in MMSE score per year for an individual in the reference group.
§In model 2, time is modeled as a categorical variable to reflect change in MMSE score per test for an individual in the reference group, time (2) represents comparison of MMSE score at the 3-year follow-up visit vs the 1-year follow-up visit, and time (3) represents comparison of MMSE score at the final follow-up visit and the 1-year follow-up visit.

Our results provide statistically reliable evidence for true cognitive change. The magnitude of the effect of obesity status on MMSE changes in the current study was similar to the time effect during follow-up. Moreover, we also applied a more rigorous definition of cognitive impairment to exclude small changes (eg, measurement error, practice effect, and normal aging) in MMSE score (Data S1 and Figure S5). The relationship between adiposity and specific subtypes of

Table 4. Effects of Categorical BMI Status on Longitudinal Change in Cognitive Function Represented by MMSE Score

Model*		Men		Women	
		Coefficient β (SE)†	*P* Value	Coefficient β (SE)†	*P* Value
Effect of time on change in MMSE score (per year/test)					
Model 1‡	Time	−0.1354 (0.0180)	<0.001	−0.3389 (0.0212)	<0.001
Model 2§	Time (2)	−0.1222 (0.0725)	0.092	−0.2888 (0.0845)	<0.001
	Time (3)	−0.5390 (0.0719)	<0.001	−1.3554 (0.0845)	<0.001
Additional effect of BMI categories on change in MMSE score (per year/test)					
Model 1	Underweight×time	−0.1669 (0.0704)	0.018	0.0488 (0.0918)	0.595
	Overweight×time	0.0481 (0.0265)	0.070	0.0724 (0.0286)	0.011
	Obese×time	0.1104 (0.0359)	0.002	0.1176 (0.0328)	<0.001
Model 2	Underweight×time (2)	−0.5846 (0.2844)	0.040	−0.4850 (0.3631)	0.182
	Overweight×time (2)	0.0688 (0.1067)	0.519	0.2457 (0.1137)	0.031
	Obese×time (2)	0.1872 (0.1446)	0.195	0.3661 (0.1295)	0.005
	Underweight×time (3)	−0.6676 (0.2816)	0.018	0.1976 (0.3660)	0.589
	Overweight×time (3)	0.1914 (0.1061)	0.071	0.2953 (0.1138)	0.009
	Obese×time (3)	0.4414 (0.1436)	0.002	0.4735 (0.1306)	<0.001

BMI indicates body mass index; and MMSE, Mini-Mental State Examination.
*The mixed model is adjusted for study center, age, and education.
†Coefficient β (SE) represents mean change over time for an individual with a BMI level in the reference group of the normal-weight category and the additional effect of being underweight, overweight, or obese on change in MMSE score per year (or per MMSE test).
‡In model 1, time is modeled as a continuous variable to reflect change in MMSE score per year for an individual in the reference group.
§In model 2, time is modeled as a category variable to reflect change in MMSE score per test for an individual in the reference group, time (2) represents the comparison of MMSE score at the 3-year follow-up visit vs the 1-year follow-up visit, and time (3) represents comparison of MMSE score between the final follow-up visit and the 1-year follow-up visit.

Table 5. Multivariate-Adjusted Associations Between BMI at Baseline and Change in Cognitive Function Represented by MMSE Score

Model*		Men		Women	
		Coefficient β (SE)†	*P* Value	Coefficient β (SE)†	*P* Value
Effect of time on change in MMSE score (per year/test)					
Model 1‡	Time	−0.4293 (0.0897)	<0.001	−0.6179 (0.0885)	<0.001
Model 2§	Time (2)	−0.9189 (0.3727)	0.014	−1.0277 (0.3596)	0.004
	Time (3)	−1.7163 (0.3588)	<0.001	−2.4590 (0.3524)	<0.001
Additional effect of BMI on change in MMSE score (per year/test)					
Model 1	BMI×time	0.0134 (0.0036)	<0.001	0.0133 (0.0034)	<0.001
Model 2	BMI×time (2)	0.0356 (0.0151)	0.019	0.0389 (0.0139)	0.005
	BMI×time (3)	0.0538 (0.0146)	<0.001	0.0534 (0.0136)	<0.001
Effect of time on change in MMSE score (per year/test)					
Model 1‡	Time	−0.1297 (0.0189)	<0.001	−0.3345 (0.0223)	<0.001
Model 2§	Time (2)	−0.0798 (0.0788)	0.311	−0.2169 (0.0917)	0.018
	Time (3)	−0.5078 (0.0756)	<0.001	−1.3192 (0.0889)	<0.001
Additional effect of BMI categories on change in MMSE score (per year/test)					
Model 1	Underweight×time	−0.1335 (0.0746)	0.073	0.0717 (0.0965)	0.457
	Overweight×time	0.0375 (0.0278)	0.178	0.0648 (0.0299)	0.030
	Obese×time	0.1091 (0.0374)	0.004	0.1146 (0.0344)	<0.001
Model 2	Underweight×time (2)	−0.3114 (0.3127)	0.319	−0.2637 (0.3917)	0.501
	Overweight×time (2)	0.0325 (0.1152)	0.778	0.2236 (0.1223)	0.067
	Obese×time (2)	0.1751 (0.1547)	0.258	0.3976 (0.1396)	0.004
	Underweight×time (3)	−0.5421 (0.2983)	0.069	0.2695 (0.3843)	0.483
	Overweight×time (3)	0.1453 (0.1113)	0.192	0.2625 (0.1193)	0.028
	Obese×time (3)	0.4324 (0.1498)	0.004	0.4623 (0.1372)	<0.001

BMI indicates body mass index; and MMSE, Mini-Mental State Examination.

*The mixed model is adjusted for study center, age, education, smoking, alcohol drinking, marital status, living conditions, physical activity, Patient Health Questionnaire-9 scores, systolic blood pressure at baseline, mean systolic blood pressure during the follow-up, estimated glomerular filtration rate, new stroke, diabetes mellitus, and treatment allocation.

†Coefficient β (SE) represents mean change over time for an individual in the reference group (with a BMI level of 18.5 kg/m^2, which is the lower bound of the normal-weight group) and the additional effect of a 1-U increase in BMI on changes in MMSE score per year (or per test) or mean change over time for an individual with a BMI level in the reference group of the normal-weight category and the additional effect of being underweight, overweight, or obese on change in MMSE score per year (or per MMSE test).

‡In model 1, time is modeled as a continuous variable to reflect change in MMSE score per year for an individual in the reference group.

§In model 2, time is modeled as a categorical variable to reflect change in MMSE score per test for an individual in the reference group, time (2) represents comparison of MMSE score at the 3-year follow-up visit vs the 1-year follow-up visit, and time (3) represents comparison of MMSE score between the final follow-up visit and the 1-year follow-up visit.

cognitive impairment identified in the current study was similar to the findings from the Kame Project study.[28] However, the outcome definition herein may insufficiently reflect the actual subtypes of vascular cognitive impairment. The relatively few events also have limited power to confirm that the absence of the effect on "cognitive impairment with stroke" is a true consequence.

Nevertheless, the interpretation of our results presented herein requires caution. There has been previous evidence of a *U*-shaped or curvilinear association between BMI and dementia and cardiovascular events.[29–31] Although we observed a threshold effect (>28.7 kg/m^2) in female patients, we failed to observe an increased risk caused by further higher degree of obesity (eg, grade 2 or 3 obesity; BMI, ≥35 kg/m^2) because of the limited numbers of patients in the extreme groups. Our results still could be the benefit effects of the active BP control in the CSPPT treatment period. The obese people in our study received a higher number of concomitant antihypertensive drugs, which may attenuate the deleterious effects of obesity; however, the proportion was relatively small (Figure S6). Moreover, the mean reduction of BP was comparable across different BMI groups, and obese men and overweight women even had a significantly lower reduction in SBP when compared with normal-weight patients (Figure S7). Meanwhile, covariate adjustment was made for both baseline and timed-average SBP.

Table 6. Associations Between Baseline BMI and Longitudinal Changes in Cognitive Domains Represented by MMSE Subscores

	Men				Women			
	Time†		BMI×Time‡		Time†		BMI×Time‡	
MMSE Subscores*	Coefficient β (SE)	*P* Value	Coefficient β (SE)	*P* Value	Coefficient β (SE)	*P* Value	Coefficient β (SE)	*P* Value
Orientation to time (0–5 points)	−0.1882 (0.0292)	<0.001	0.0053 (0.0012)	<0.001	−0.2220 (0.0313)	<0.001	0.0029 (0.0012)	0.018
Orientation to place (0–5 points)	−0.0176 (0.0101)	0.082	0.0001 (0.0004)	0.772	−0.1001 (0.0192)	<0.001	0.0020 (0.0007)	0.009
Registration (0–3 points)	−0.0428 (0.0160)	0.008	0.0012 (0.0007)	0.073	−0.0477 (0.0170)	0.005	0.0003 (0.0007)	0.621
Attention/calculation (0–5 points)	−0.1272 (0.0417)	0.002	0.0040 (0.0017)	0.015	−0.1170 (0.0390)	0.003	0.0036 (0.0015)	0.016
Recall (0–3 points)	−0.0546 (0.0295)	0.064	0.0034 (0.0012)	0.005	−0.0731 (0.0258)	0.005	0.0032 (0.0010)	0.001
Language (0–9 points)	−0.0406 (0.0280)	0.146	0.0009 (0.0011)	0.413	−0.0763 (0.0205)	<0.001	0.0019 (0.0008)	0.019

BMI indicates body mass index; and MMSE, Mini-Mental State Examination.
*The mixed model is adjusted for study center, age, and education.
†Time is modeled as a continuous variable to reflect changes in MMSE subscores per year for an individual in the reference group (with a BMI level of 18.5 kg/m^2).
‡The term of BMI×time represents the additional effect of a 1-U increase in BMI on annual changes in MMSE subscores for an individual in the reference group.

The finding that underweight was associated with an accelerated rate of cognitive decline is consistent with the observations of the CPRD (Clinical Practice Research Datalink) study, which identified a 34% excess risk of dementia in underweight people.[32] Literature available reveals that higher risks of cognitive dysfunction associated with underweight pertain to elderly people in the general population and have been attributed to preclinical dementia and other preexisting illnesses.[33,34] Several perspectives from our study could, to some extent, limit this bias because of reverse causality: (1) the detrimental effect of low body weight existed in younger patients (aged <65 years) but not in elderly patients and (2) excluding patients with cognitive impairment at 1 year of follow-up and other existing diseases at baseline did not affect the results. Nevertheless, a long-term follow-up study with a series of adiposity measures before disease onset and with dementia as the primary end point is needed to eliminate this bias. The recently reported results from the ARIC (Atherosclerosis Risk in Communities) study already demonstrate that premorbid obesity still offers a significant survival advantage in patients with incident heart failure, and weight loss attributable to disease progression may not completely explain the protective effect of higher BMI.[10]

The age of people at which obesity status is assessed may significantly modify the relationship between adiposity and cognition.[28,35,36] Several studies report that being overweight in later life may be associated with reduced risk of dementia. These studies enrolled the general population >65 years, whereas our study cohort was a mean age of 60.1±7.4 years (range, 45–75 years). Our Cox regression analysis of

Table 7. Multivariate-Adjusted Associations Between Baseline BMI and Longitudinal Changes in Cognitive Domains Represented by MMSE Subscores

	Men				Women			
	Time†		BMI×Time‡		Time†		BMI×Time‡	
MMSE Subscores*	Coefficient β (SE)	*P* Value	Coefficient β (SE)	*P* Value	Coefficient β (SE)	*P* Value	Coefficient β (SE)	*P* Value
Orientation to time (0–5 points)	−0.1854 (0.0306)	<0.001	0.0051 (0.0012)	<0.001	−0.2149 (0.0332)	<0.001	0.0025 (0.0013)	0.047
Orientation to place (0–5 points)	−0.0160 (0.0110)	0.145	0.0001 (0.0004)	0.950	−0.1015 (0.0204)	<0.001	0.0020 (0.0008)	0.014
Registration (0–3 points)	−0.0375 (0.0167)	0.025	0.0009 (0.0007)	0.177	−0.0497 (0.0175)	0.005	0.0004 (0.0007)	0.561
Attention/calculation (0–5 points)	−0.1063 (0.0437)	0.015	0.0034 (0.0018)	0.059	−0.1081 (0.0402)	0.007	0.0033 (0.0016)	0.033
Recall (0–3 points)	−0.0535 (0.0310)	0.084	0.0034 (0.0013)	0.008	−0.0694 (0.0265)	0.009	0.0031 (0.0010)	0.003
Language (0–9 points)	−0.0344 (0.0292)	0.239	0.0007 (0.0012)	0.544	−0.0747 (0.0210)	<0.001	0.0018 (0.0008)	0.025

BMI indicates body mass index; and MMSE, Mini-Mental State Examination.
*The mixed model is adjusted for study center, age, education, smoking, alcohol drinking, marital status, living conditions, physical activity, Patient Health Questionnaire-9 scores, systolic blood pressure at baseline, mean systolic blood pressure during the follow-up, estimated glomerular filtration rate, new stroke, diabetes mellitus, and treatment allocation.
†Time is modeled as a continuous variable to reflect changes in MMSE subscores per year for an individual in the reference group (with a BMI level of 18.5 kg/m^2).
‡The term of BMI×time represents the additional effect of a 1-U increase in BMI on annual changes in MMSE subscores for an individual in the reference group.

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Table 8. Multivariable Cox Proportional Hazards Model for Cognitive Impairment According to BMI Categories at Baseline

	Cognitive Impairment			Cognitive Impairment With Stroke			Other Cognitive Impairment		
Variables	Events, %	Model 1	Model 2	Events, %	Model 1	Model 2	Events, %	Model 1	Model 2
Men									
BMI, kg/m^2	1037 (15.3)	0.96 (0.94–0.97)	0.96 (0.94–0.98)	66 (1.0)	0.96 (0.88–1.04)	0.95 (0.87–1.04)	971 (14.4)	0.96 (0.94–0.98)	0.96 (0.94–0.99)
BMI category, kg/m^2									
<18.5	49 (23.4)	1.37 (1.02–1.85)	1.25 (0.90–1.76)	3 (1.4)	2.06 (0.61–6.98)	2.66 (0.74–9.58)	46 (22.0)	1.34 (0.99–1.82)	1.23 (0.87–1.74)
18.5–23.9	544 (18.0)	1.00 (Ref)	1.00 (Ref)	28 (0.9)	1.00 (Ref)	1.00 (Ref)	516 (17.1)	1.00 (Ref)	1.00 (Ref)
24–27.9	331 (13.1)	0.75 (0.65–0.86)	0.78 (0.67–0.91)	29 (1.1)	1.11 (0.65–1.89)	1.01 (0.55–1.87)	302 (11.9)	0.73 (0.63–0.84)	0.76 (0.65–0.89)
≥28	113 (11.3)	0.75 (0.61–0.93)	0.75 (0.60–0.94)	6 (0.6)	0.65 (0.26–1.59)	0.55 (0.20–1.54)	107 (10.7)	0.76 (0.61–0.94)	0.78 (0.62–0.98)
P value for trend		<0.001	<0.001		0.333	0.171		<0.001	<0.001
Women									
BMI, kg/m^2	3317 (33.1)	0.98 (0.97–0.99)	0.98 (0.97–0.99)	93 (0.9)	1.03 (0.97–1.08)	0.97 (0.91–1.04)	3224 (32.1)	0.98 (0.97–0.99)	0.98 (0.97–0.99)
BMI category, kg/m^2									
<18.5	89 (46.6)	1.24 (1.00–1.54)	1.21 (0.96–1.53)	3 (1.6)	2.24 (0.67–7.46)	2.63 (0.78–8.91)	86 (45.0)	1.22 (0.98–1.52)	1.18 (0.93–1.50)
18.5–23.9	1224 (36.5)	1.00 (Ref)	1.00 (Ref)	28 (0.8)	1.00 (Ref)	1.00 (Ref)	1196 (35.7)	1.00 (Ref)	1.00 (Ref)
24–27.9	1279 (31.3)	0.87 (0.80–0.94)	0.87 (0.80–0.95)	38 (0.9)	1.02 (0.62–1.67)	0.83 (0.48–1.44)	1241 (30.4)	0.86 (0.80–0.94)	0.87 (0.80–0.95)
≥28	725 (30.1)	0.87 (0.79–0.95)	0.82 (0.74–0.91)	24 (1.0)	1.08 (0.62–1.89)	0.81 (0.43–1.50)	701 (29.1)	0.86 (0.78–0.95)	0.83 (0.74–0.92)
P value for trend		<0.001	<0.001		0.897	0.238		<0.001	<0.001

For the multivariate-adjusted hazard ratios, data are adjusted for study center, age (continuous variable), and education (illiteracy vs primary school vs middle school and higher) in model 1; and additional adjustment for smoking (never smoking vs ever smoking vs current smoking), alcohol drinking (never drinking vs ever drinking vs current drinking), marital status (married vs never married vs other), living conditions (low vs moderate vs high), physical activity (low vs moderate vs high), Patient Health Questionnaire-9 scores (continuous variable), systolic blood pressure at baseline (continuous variable), mean systolic blood pressure during the follow-up (continuous variable), estimated glomerular filtration rate (continuous variable), new stroke (yes vs no, adjusted for all cognitive impairment only), diabetes mellitus (yes vs no), and treatment allocation (enalapril–folic acid vs enalapril) in model 2. BMI indicates body mass index.

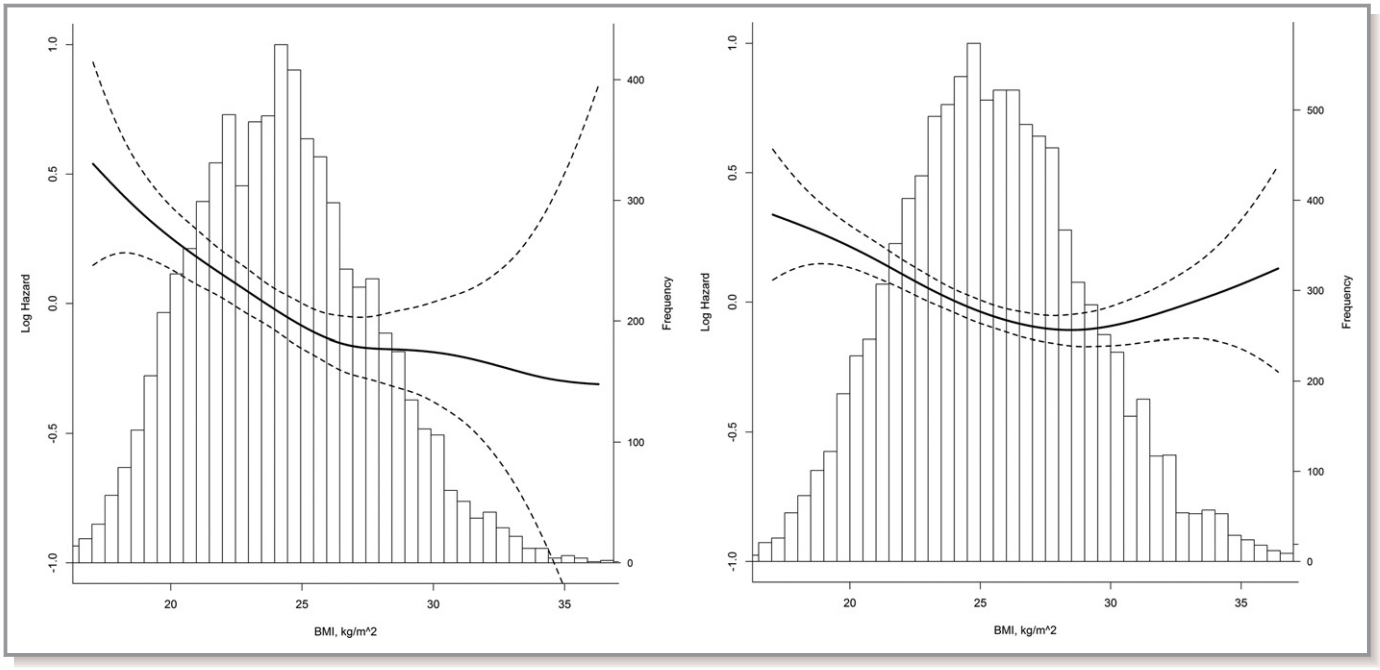

Figure 3. Relationship between body mass index (BMI) at baseline and risk of cognitive impairment by penalized splines. The relative risk of cognitive impairment in association with BMI is shown in men (A) and women (B). Solid lines represent the log hazard ratios for BMI as a continuous variable, and dashed lines represent the 95% confidence intervals. The graphs are truncated at the 1st and 99th percentiles of BMI. Analyses are adjusted for study center, age, education, smoking status, alcohol drinking, marital status, living conditions, physical activity, Patient Health Questionnaire-9 scores, systolic blood pressure (SBP) at baseline, mean SBP during the follow-up, estimated glomerular filtration rate, new stroke, diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation.

sex-specific risk of cognitive impairment related to baseline BMI and WC categories, according to age tertiles, demonstrated the same pattern in the oldest (aged ≥65 years) and the middle tertile (aged 55–64 years) of patients (Figure S8). Among patients in the youngest tertile (aged <55 years), the effect was consistently smaller; we found age does not significantly modify the relationship between adiposity and cognitive impairment, with no evidence of heterogeneity (P>0.05 for interaction). However, we observed a more prominent effect in older women (P<0.05 for interaction) when age was stratified by 60 years (Table S10). Given a rapid decline in estrogen production in postmenopausal women, estrone secreted by adipose tissues becomes a primary source of endogenous estrogen, which increases in obesity status and may mediate potentially beneficial effects.[37] Our results, mainly from the subgroup analyses, may not be as reliable because of the effect of sample size. Future studies having obesity measures at different ages in the same people are needed to validate the possible difference across age spectrums.

Whether the obesity paradox is a product of true biological processes or simply originates from methodological biases has been intensely debated in the clinical and epidemiologic literature. The obesity status of hypertensive patients in our cohort may reflect a specific disease subtype and a metabolic reserve to protect against hypertension and age-related cognitive decline.[10,38] Although the precise mechanisms underlying the obesity paradox are not elucidated, adipokines, including leptin and insulin-like growth factor, are neuroprotective; obesity may even protect structural brain integrity.[39–41] Furthermore, abdominal and peripheral subcutaneous adipose tissues were regarded as the nonpathogenic and benign fat depots, and may prevent excessive release of free fatty acids and subsequent ectopic fat deposition, including visceral fat accumulation.[42–44] The imaging technologies used to assess the metabolic properties of fat depositions (eg, abdominal computed tomography/magnetic resonance imaging and dual-energy x-ray absorptiometry) are necessary for future studies. On the other hand, selection of patients based on the CVD status from an unbiased general population may generate selection bias. For instance, previous evidence suggested that obese patients receive more optimal treatment for comorbidities at an earlier stage of the disease before enrollment.[45] The CSPPT participants were recruited mainly from the rural areas in China, where patients have inadequate resources to receive optimal therapy. Our recent study has confirmed a low use rate of lipid-lowering drugs (0.8%), glucose-lowering drugs (1.6%), and antiplatelet drugs (3%) in the CSPPT population.[16] Besides, nonobese patients who develop a chronic disease may be more likely than their obese counterparts to have other unmeasured harmful risk factors related to cognitive impairment.[46] Our current

analyses with a high incidence of cognitive impairment allow us to conduct various subgroup analyses with sufficient adjustment for potentially confounding variables; yet, we cannot completely rule out the possibility of residual confounders (eg, inflammatory biomarkers).

Several limitations of the current study should be mentioned. First, our study is a post hoc analysis in which the cognition end point was not prespecified. However, this should not change the reliability of our results because MMSE measurements coincided with study visits over the trial and were conducted by trainers who were blinded to the present objective. Second, the study cohort lacked baseline cognitive measurement. However, when we used available MMSE scores at the 1-year follow-up as the surrogate in a subsample, the observed results persisted. Third, the MMSE test is mainly used as a limited screening tool and may have a poor sensitivity in the detection of mild cognitive impairment. However, acknowledging that our study population came mainly from the rural areas in China, where resources are limited and people have limited or no formal education, the MMSE test may be more appropriate and clinically convenient for the target population than comprehensive neuropsychological assessments.[47] Furthermore, several previous studies have provided the support for the use of this test for cognitive assessment and definition according to MMSE scores.[21,48] Finally, our study was limited to relatively homogeneous patients with hypertension in China, and the generalizability of our findings requires confirmation in more cohort studies of ethnically diverse adults.

Conclusion

We report that higher adiposity is independently associated with slower cognitive decline in Chinese hypertensive adults, especially in elderly people. The link between underweight and the unfavorable prognosis of cognition is particularly relevant to routine medical management of hypertension and may deserve more attention.

Author Contributions

K. Wang and Xu had full access to all study data and had final responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: K. Wang, B. Wang, Xu, and Huo. Acquisition, analysis, or interpretation of data: All authors. Drafting of the article: K. Wang and J. Zhang. Critical revision of the article for important intellectual content: All authors. Statistical analysis: K. Wang and J. Zhang. Obtained funding: K. Wang, B. Wang, Xu, and Huo. Administrative, technical, or material support: K. Wang and Huo. Study supervision: K. Wang and Xu.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Detailed inclusion and exclusion criteria

Participants were eligible for recruitment into CSPPT if they were aged 45-75 years old with hypertension, defined as seated resting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or taking an anti-hypertensive medication. The major exclusion criteria included a history of physician- diagnosed stroke, myocardial infarction (MI) and other cardiovascular diseases (e.g., physician-diagnosed heart failure, post-coronary revascularization, and congenital heart disease).

Intervention and Follow-Up

Eligible participants who were tolerant and adhered to enalapril therapy during the 3-week run-in treatment period were randomly assigned to one of two treatment groups in a 1:1 ratio. The treatment allocation here included a daily oral dose of one tablet containing 10mg enalapril and 0.8mg folic acid (the enalapril-folic acid group) and a daily oral dose of one tablet containing 10mg enalapril only (the enalapril group). Other classes of antihypertensive medications, mostly dihydropyridine calcium channel blockers and hydrochlorothiazide, could be prescribed concomitantly if necessary. All patients were scheduled for follow-up every 3 months after randomization. At each visit, trained study staff measured blood pressures and pulses for all participants, and recorded the number of pills that were taken between visits, concomitant medication use, and any adverse events.

Additional analyses

To account for potential differences in baseline MMSE scores and fluctuations in MMSE changes, we conducted additional analyses by involving the definition for cognitive impairment in ONTARGET/TRANSCEND studies into the present definition. Cognitive impairment was then defined as a decrease of MMSE scores of 3 or more and to a level of less than education-specific cut-off points at any time during the follow-up. Changes of MMSE scores were calculated by subtracting the score at the last follow-up visit from the MMSE score at baseline. However, baseline MMSE scores were not available for the study participants. Therefore, we used values at 1-year visit to represent missing baseline MMSE values.

Table S1. Characteristics of included and excluded participants in the present analysis

Variable	Total men	Men included	Men excluded	*P* value	Total women	Women included	Women excluded	*P* value
No. of participants	8497	6758	1739		12205	10033	2172	
Age (years), mean (SD)	60.9 (7.6)	61.3 (7.4)	59.7 (8.1)	<0.001	59.3 (7.4)	59.3 (7.4)	59.3 (7.7)	0.938
Marital status (Married), n (%)	7345 (87.4)	5880 (87.5)	1465 (87.0)	0.371	10258 (84.8)	8555 (85.6)	1703 (81.2)	<0.001
Educational level, n (%)				0.100				0.341
Illiteracy	3159 (37.2)	2549 (37.7)	610 (35.1)		10067 (82.6)	8304 (82.8)	1763 (81.5)	
Primary school	2232 (26.3)	1749 (25.9)	483 (27.8)		1249 (10.2)	1010 (10.1)	239 (11.1)	
Middle school and higher	3103 (36.5)	2460 (36.4)	643 (37.0)		879 (7.2)	719 (7.2)	160 (7.4)	
Living conditions, n (%)				0.060				0.922
Low	1221 (14.4)	942 (13.9)	279 (16.1)		1247 (10.2)	1021 (10.2)	226 (10.4)	
Moderate	6427 (75.7)	5147 (76.2)	1280 (73.7)		9436 (77.4)	7762 (77.4)	1674 (77.3)	
High	847 (10.0)	669 (9.9)	178 (10.2)		1516 (12.4)	1250 (12.5)	266 (12.3)	
SBP at baseline (mmHg), mean (SD)	165.2 (20.5)	165.7 (20.6)	162.9 (19.6)	<0.001	168.1 (20.3)	168.4 (20.4)	166.5 (19.7)	<0.001
Follow-up mean SBP (mmHg), mean (SD)	139.3 (10.8)	138.7 (10.2)	141.4 (12.5)	<0.001	139.5 (11.0)	139.0 (10.7)	142.0 (12.3)	<0.001
eGFR (mL/min/1.73 m^2), mean (SD)	92.0 (13.6)	91.9 (13.4)	92.6 (14.3)	0.045	94.5 (12.9)	94.6 (12.7)	94.2 (13.7)	0.281
BMI (kg/m^2), mean (SD)	24.2 (3.4)	24.3 (3.4)	24.0 (3.4)	<0.001	25.4 (3.8)	25.5 (3.8)	24.9 (3.8)	<0.001
WC (cm), mean (SD)	84.2 (10.1)	84.4 (10.1)	83.7 (10.1)	0.006	84.4 (9.8)	84.5 (9.8)	83.6 (9.8)	<0.001
Current smoking, n (%)	4467 (52.6)	3498 (51.8)	969 (55.8)	0.008	402 (3.3)	321 (3.2)	81 (3.7)	0.205
Current alcohol drinking, n (%)	4468 (52.6)	3528 (52.2)	940 (54.1)	0.332	492 (4.0)	390 (3.9)	102 (4.7)	0.105
Low physical activity, n (%)	2979 (35.1)	2421 (35.9)	558 (32.1)	<0.001	4561 (37.4)	3749 (37.4)	812 (37.5)	0.881
Treatment allocation, n (%)				0.546				0.081
Enalapril	4252 (50.0)	3393 (50.2)	859 (49.4)		6102 (50.0)	5053 (50.4)	1049 (48.3)	
Enalapril–folic acid	4245 (50.0)	3365 (49.8)	880 (50.6)		6103 (50.0)	4980 (49.6	1123 (51.7)	
Medical comorbidities, n (%)								
Diabetes at baseline	849 (10.2)	677 (10.3)	172 (10.0)	0.798	1439 (12.0)	1212 (12.3)	227 (10.6)	0.028
New diabetes*	752 (11.3)	677 (11.3)	75 (10.9)	0.775	1119 (11.3)	1017 (11.3)	102 (11.1)	0.832
Stroke	302 (3.6)	210 (3.1)	92 (5.3)	<0.001	335 (2.7)	237 (2.4)	98 (4.5)	<0.001

Abbreviations: SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); WC, waist circumference.

*New diabetes is defined as having no diabetes at baseline and being diabetic at final follow-up visit.

Table S2. Demographic and clinical characteristics of the study participants according to categories of BMI and sex

Characteristics	Men					Women				
BMI category	Underweight (n=209)	Normal (n=3018)	Overweight (n=2528)	Obesity (n=1003)	*P* value	Underweight (n=191)	Normal (n=3352)	Overweight (n=4082)	Obesity (n=2408)	*P* value
Age (years), mean (SD)	65.5 (6.0)	62.6 (7.1)	60.5 (7.4)	58.5 (7.5)	<0.001	63.1 (6.8)	60.4 (7.2)	58.9 (7.3)	58.2 (7.4)	<0.001
Marital status (Married), n (%)	170 (81.7)	2555 (85.4)	2237 (88.9)	918 (91.8)	<0.001	155 (82.4)	2749 (82.6)	3543 (87.0)	2108 (87.8)	<0.001
Educational, n (%)					<0.001					<0.001
Illiteracy	104 (49.8)	1351 (44.8)	830 (32.8)	264 (26.3)		170 (89.0)	2838 (84.7)	3346 (82.0)	1950 (81.0)	
Primary school	66 (31.6)	807 (26.7)	629 (24.9)	247 (24.6)		16 (8.4)	336 (10.0)	415 (10.2)	243 (10.1)	
Middle school and higher	39 (18.7)	860 (28.5)	1069 (42.3)	492 (49.1)		5 (2.6)	178 (5.3)	321 (7.9)	215 (8.9)	
Living conditions, n (%)					<0.001					<0.001
Low	23 (11.0)	311 (10.3)	420 (16.6)	188 (18.7)		13 (6.8)	284 (8.5)	455 (11.1)	269 (11.2)	
Moderate	155 (74.2)	2334 (77.3)	1908 (75.5)	750 (74.8)		141 (73.8)	2612 (77.9)	3144 (77.0)	1865 (77.5)	
High	31 (14.8)	373 (12.4)	200 (7.9)	65 (6.5)		37 (19.4)	456 (13.6)	483 (11.8)	274 (11.4)	
SBP at baseline (mmHg), mean (SD)	162.2 (18.1)	165.8 (21.0)	165.9 (20.2)	165.9 (21.1)	0.098	167.7 (16.6)	167.2 (19.6)	168.5 (20.5)	170.1 (21.4)	<0.001
Follow-up mean SBP (mmHg), mean (SD)	138.1 (10.1)	138.6 (10.4)	138.8 (10.2)	138.9 (9.9)	0.684	138.5 (9.8)	138.0 (10.6)	138.9 (10.5)	140.5 (10.9)	<0.001
eGFR (mL/min/1.73 m^2), mean (SD)	89.8 (12.3)	91.4 (13.0)	92.1 (13.7)	93.1 (13.8)	<0.001	92.0 (12.8)	93.4 (12.3)	95.1 (12.6)	95.4 (13.3)	<0.001
Current smoking, n (%)	147 (70.3)	1790 (59.3)	1146 (45.3)	415 (41.4)	<0.001	6 (3.1)	120 (3.6)	116 (2.8)	79 (3.3)	0.610
Current alcohol drinking, n (%)	90 (43.1)	1651 (54.7)	1299 (51.4)	488 (48.7)	0.002	11 (5.8)	155 (4.6)	151 (3.7)	73 (3.0)	0.062
Low physical activity, n (%)	64 (30.6)	902 (29.9)	1007 (39.9)	448 (44.7)	<0.001	58 (30.4)	1092 (32.6)	1582 (38.8)	1017 (42.3)	<0.001
Treatment allocation, n (%)					0.833					0.290
Enalapril	108 (51.7)	1498 (49.6)	1276 (50.5)	511 (50.9)		97 (50.8)	1728 (51.6)	2048 (50.2)	1180 (49.0)	
Enalapril–folic acid	101 (48.3)	1520 (50.4)	1252 (49.5)	492 (49.1)		94 (49.2)	1624 (48.4)	2034 (49.8)	1228 (51.0)	
Medical comorbidities, n (%)										
Diabetes at baseline	3 (1.4)	196 (6.6)	320 (13.0)	158 (16.1)	<0.001	14 (7.4)	286 (8.6)	520 (12.9)	392 (16.6)	<0.001
New diabetes*	13 (7.3)	270 (10.2)	251 (11.1)	143 (15.7)	<0.001	13 (7.7)	269 (9.2)	418 (11.3)	317 (14.6)	<0.001
Stroke	7 (3.3)	79 (2.6)	83 (3.3)	41 (4.1)	0.116	4 (2.1)	73 (2.2)	95 (2.3)	65 (2.7)	0.623

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate.

*New diabetes is defined as having no diabetes at baseline and being diabetic at final follow-up visit.

Table S3. Effects of continuous WC levels on longitudinal change in MMSE score*

		Men		Women	
		Coefficient β (SE)†	***P* value**	**Coefficient β (SE)†**	***P* value**
Effect of time on change in MMSE score (per year/test)					
Model I‡	time	-0.4814 (0.1013)	<0.001	-0.4015 (0.1068)	<0.001
Model II§	time (2)	-1.2336 (0.4069)	0.002	-1.1374 (0.4235)	0.007
	time (3)	-1.9241 (0.4049)	<0.001	-1.5922 (0.4258)	<0.001
Additional effect of WC on change in MMSE score (per year/test)					
Model I	WC× time	0.0044 (0.0012)	<0.001	0.0014 (0.0013)	0.252
Model II	WC× time (2)	0.0136 (0.0048)	0.005	0.0122 (0.0050)	0.014
	WC× time (3)	0.0178 (0.0048)	<0.001	0.0056 (0.0050)	0.261

Abbreviations: WC, waist circumference; MMSE, Mini-Mental State Examination

* The mixed model is adjusted for study center, age and education.

† Coefficient β (SE) represents mean change over time for an individual in the reference group (with a WC level of 90/80 cm, which is the higher bound of the normal WC category) and the additional effect of a 1-unit increase in WC on change in MMSE score per year (or per test).

‡ In Model I, time is modeled as a continuous variable to reflect change in MMSE score per year for an individual in the reference group.

§ In Model II, time is modeled as a categorical variable to reflect change in MMSE score per test for an individual in the reference group, and time (2) represents comparison of MMSE score at the 3-year follow-up visit vs. the 1-year follow-up visit while time (3) represents comparison of MMSE score between the final follow-up visit and the 1-year follow-up visit.

Table S4. Effects of categorical WC status on longitudinal change in MMSE score[*]

		Men		Women	
		Coefficient β (SE)[†]	***P* value**	**Coefficient β (SE)[†]**	***P* value**
Effect of time on change in MMSE score (per year/test)					
Model I[‡]	time	-0.1269 (0.0145)	<0.001	-0.3152 (0.0224)	<0.001
Model II[§]	time (2)	-0.1360 (0.0585)	0.020	-0.2976 (0.0894)	<0.001
	time (3)	-0.5056 (0.0581)	<0.001	-1.2568 (0.0893)	<0.001
Additional effect of WC categories on change in MMSE score (per year/test)					
Model I	Abdominal obesity× time	0.0663 (0.0257)	0.010	0.0502 (0.0268)	0.060
Model II	Abdominal obesity× time (2)	0.1521 (0.1033)	0.141	0.2686 (0.1065)	0.012
	Abdominal obesity× time (3)	0.2643 (0.1029)	0.010	0.1991 (0.1066)	0.062

Abbreviations: WC, waist circumference; MMSE, Mini-Mental State Examination

[*] The mixed model is adjusted for study center, age and education.

[†] Coefficient β (SE) represents mean change over time for an individual with a WC level in the reference group of the normal WC category and the additional effect of abdominal obesity (WC ≥ 90/80 cm for men/women) on change in MMSE score per year (or per MMSE test).

[‡] In Model I, time is modeled as a continuous variable to reflect change in MMSE score per year for an individual in the reference group.

[§] In Model II, time is modeled as a categorical variable to reflect change in MMSE score per test for an individual in the reference group, and time (2) represents comparison of MMSE score at the 3-year follow-up visit vs. the 1-year follow-up visit while time (3) represents comparison of MMSE score between the final follow-up visit and the 1-year follow-up visit.

Table S5. Multivariate-adjusted associations between WC at baseline and change in MMSE score during the follow-up*

		Men		Women	
		Coefficient β (SE)†	***P* value**	**Coefficient β (SE)†**	***P* value**
Effect of time on change in MMSE score (per year/test)					
Model I‡	time	-0.4505 (0.1060)	<0.001	-0.4044 (0.1123)	<0.001
Model II§	time (2)	-1.1417 (0.4392)	0.009	-1.4601 (0.4559)	0.001
	time (3)	-1.8024 (0.4240)	<0.001	-1.6155 (0.4472)	<0.001
Additional effect of WC on change in MMSE score (per year/test)					
Model I	WC× time	0.0041 (0.0012)	0.001	0.0015 (0.0013)	0.260
Model II	WC× time (2)	0.0129 (0.0052)	0.012	0.0169 (0.0053)	0.002
	WC× time (3)	0.0166 (0.0050)	0.001	0.0062 (0.0053)	0.241
Effect of time on change in MMSE score (per year/test)					
Model I‡	time	-0.1205 (0.0152)	<0.001	-0.3168 (0.0236)	<0.001
Model II§	time (2)	-0.0862 (0.0632)	0.172	-0.2969 (0.0965)	0.002
	time (3)	-0.4730 (0.0609)	<0.001	-1.2507 (0.0939)	<0.001
Additional effect of WC categories on change in MMSE score (per year/test)					
Model I	Abdominal obesity× time	0.0548 (0.0269)	0.042	0.0539 (0.0281)	0.055
Model II	Abdominal obesity× time (2)	0.1094 (0.1113)	0.326	0.3752 (0.1146)	0.001
	Abdominal obesity× time (3)	0.2168 (0.1077)	0.044	0.2209 (0.1119)	0.048

Abbreviations: WC, waist circumference; MMSE, Mini-Mental State Examination.

* The mixed model is adjusted for study center, age, education, smoking, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, systolic blood pressure at baseline, mean systolic blood pressure during the follow-up, estimated glomerular filtration rate, new stroke, diabetes mellitus, and treatment allocation;

† Coefficient β (SE) represents mean change over time for an individual in the reference group (with a WC level of 90/80 cm, which is the higher bound of the normal WC category) and the additional effect of a 1-unit increase in WC on change in MMSE score per year, or mean change over time for an individual with a WC level in the reference group of the normal WC category and the additional effect of abdominal obesity (WC ≥ 90/80 cm for men/women) on change in MMSE score per year.

‡ In Model I, time is modeled as a continuous variable to reflect change in MMSE score per year for an individual in the reference group.

§ In Model II, time is modeled as a categorical variable to reflect change in MMSE score per test for an individual in the reference group, and time (2) represents comparison of MMSE score at the 3-year follow-up visit vs. the 1-year follow-up visit while time (3) represents comparison of MMSE score between the final follow-up visit and the 1-year follow-up visit.

Table S6. Associations between baseline WC and longitudinal changes in cognitive domains represented by MMSE subscores[*]

MMSE subscores	Men				Women			
	Time[†]		WC× time[‡]		Time		WC× time	
	Coefficient β (SE)	*P* value	Coefficient β (SE)	*P* value	Coefficient β (SE)	*P* value	Coefficient β (SE)	*P* value
Orientation to time (0-5 points)	-0.2270 (0.0346)	<0.001	0.0020 (0.0004)	<0.001	-0.1644 (0.0398)	<0.001	0.0002 (0.0005)	0.694
Orientation to place (0-5 points)	-0.0417 (0.0119)	<0.001	0.0003 (0.0001)	0.022	-0.0921 (0.0244)	<0.001	0.0005 (0.0003)	0.083
Registration (0–3 points)	-0.0265 (0.0190)	0.162	0.0001 (0.0002)	0.518	-0.0095 (0.0216)	0.659	-0.0004 (0.0003)	0.162
Attention/calculation (0–5 points)	-0.1240 (0.0493)	0.012	0.0012 (0.0006)	0.047	-0.0630 (0.0495)	0.203	0.0005 (0.0006)	0.428
Recall (0–3 points)	-0.0260 (0.0349)	0.456	0.0006 (0.0004)	0.123	-0.0233 (0.0328)	0.476	0.0004 (0.0004)	0.314
Language (0–9 points)	-0.0335 (0.0331)	0.311	0.0002 (0.0004)	0.635	-0.0463 (0.0261)	0.076	0.0002 (0.0003)	0.490

Abbreviations: WC, waist circumference; MMSE, Mini-Mental State Examination

[*] The mixed model is adjusted for study center, age and education.

[†] Time is modeled as a continuous variable to reflect changes in MMSE subscores per year for an individual in the reference group (with a WC level of 80/90 cm for men/women).

[‡] The term of WC × time represents the additional effect of a 1-unit increase in WC on annual changes in MMSE subscores for an individual in the reference group.

Table S7. Multivariate-adjusted associations between baseline WC and changes in cognitive domains represented by MMSE subscores*

MMSE subscores		Orientation to time (0-5 points)		Orientation to place (0-5 points)		Registration (0–3 points)		Attention/calculation (0–5 points)		Recall (0–3 points)		Language (0–9 points)	
		Coefficient β (SE) †	*P* value	Coefficient β (SE) †	*P* value	Coefficient β (SE) †	*P* value	Coefficient β (SE) †	*P* value	Coefficient β (SE) †	*P* value	Coefficient β (SE) †	*P* value
Men													
Effect of time (per year/test)													
Model I‡	time	-0.2197 (0.0362)	<0.001	-0.0418 (0.0129)	0.001	-0.0289 (0.0198)	0.144	-0.1172 (0.0517)	0.023	-0.0296 (0.0366)	0.418	-0.0223 (0.0345)	0.517
Model II§	time (2)	-0.2950 (0.1493)	0.048	-0.0249 (0.0531)	0.639	-0.1132 (0.0812)	0.163	-0.4928 (0.2140)	0.021	-0.3413 (0.1507)	0.024	0.0604 (0.1427)	0.672
	time (3)	-0.8652 (0.1445)	<0.001	-0.1629 (0.0517)	0.002	-0.1156 (0.0790)	0.144	-0.4813 (0.2069)	0.020	-0.1279 (0.1463)	0.382	-0.0876 (0.1379)	0.525
Additional effect of WC (per year/test)													
Model I	WC×time	0.0019 (0.0004)	<0.001	0.0003 (0.0002)	0.039	0.0002 (0.0002)	0.481	0.0011 (0.0006)	0.070	0.0007 (0.0004)	0.111	0.0001 (0.0004)	0.871
Model II	WC×time (2)	0.0033 (0.0018)	0.062	0.0003 (0.0006)	0.593	0.0014 (0.0010)	0.138	0.0051 (0.0025)	0.041	0.0051 (0.0018)	0.004	-0.0017 (0.0017)	0.323
	WC×time (3)	0.0074 (0.0017)	<0.001	0.0012 (0.0006)	0.044	0.0007 (0.0009)	0.469	0.0045 (0.0024)	0.062	0.0029 (0.0017)	0.096	0.0002 (0.0016)	0.893
Women													
Effect of time (per year/test)													
Model I	time	-0.1606 (0.0421)	<0.001	-0.1043 (0.0259)	<0.001	-0.0225 (0.0227)	0.322	-0.0500 (0.0522)	0.338	-0.0233 (0.0345)	0.500	-0.0480 (0.0271)	0.077
Model II	time (2)	-0.5556 (0.1697)	0.001	-0.0153 (0.1047)	0.884	-0.0523 (0.0919)	0.570	-0.6516 (0.2128)	0.002	-0.1693 (0.1400)	0.227	-0.0627 (0.1103)	0.570
	time (3)	-0.6362 (0.1667)	<0.001	-0.4052 (0.1031)	<0.001	-0.0860 (0.0905)	0.342	-0.2259 (0.2087)	0.279	-0.0916 (0.1377)	0.506	-0.1934 (0.1084)	0.074
Additional effect of WC (per year/test)													
Model I	WC×time	0.0001 (0.0005)	0.795	0.0006 (0.0003)	0.041	-0.0002 (0.0003)	0.446	0.0003 (0.0006)	0.601	0.0004 (0.0004)	0.332	0.0002 (0.0003)	0.458
Model II	WC×time (2)	0.0066 (0.0020)	0.001	0.0007 (0.0012)	0.574	0.0008 (0.0011)	0.431	0.0061 (0.0025)	0.015	0.0037 (0.0016)	0.026	-0.0006 (0.0013)	0.644
	WC×time (3)	0.0006 (0.0020)	0.772	0.0024 (0.0012)	0.047	-0.0008 (0.0011)	0.439	0.0015 (0.0025)	0.529	0.0016 (0.0016)	0.322	0.0009 (0.0013)	0.461

Abbreviations: WC, waist circumference; MMSE, Mini-Mental State Examination

* The mixed model is adjusted for study center, age, education, smoking, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, systolic blood pressure at baseline, mean systolic blood pressure during the follow-up, estimated glomerular filtration rate, new stroke, diabetes mellitus, and treatment allocation.

† Coefficient β (SE) represents mean changes over time for an individual in the reference group (with a WC level of 90/80 cm, which is the higher bound of the normal WC category) and the additional effect of a 1-unit increase in WC on the changes in MMSE subscores per year (or per test).

‡ In Model I, time is modeled as a continuous variable to reflect changes in MMSE subscores per year for an individual in the reference group.

§ In Model II, time is modeled as a category variable to reflect changes in MMSE subscores per test for an individual in the reference group, and time (2) represents comparison of MMSE subscores at the 3-year follow-up visit vs. the 1-year follow-up visit while time (3) represents comparison of MMSE subscores between the final follow-up visit and the 1-year follow-up visit.

Table S8. Multivariable Cox proportional hazards model for cognitive impairment according to WC at baseline*

Variables	Cognitive Impairment			Cognitive Impairment with stroke			Other Cognitive Impairment		
	Events (%)	Model I	Model II	Events (%)	Model I	Model II	Events (%)	Model I	Model II
Men									
WC (cm)	1037 (15.3)	0.98 (0.98, 0.99)	0.98 (0.98, 0.99)	66 (1.0)	0.98 (0.95, 1.00)	0.97 (0.94, 1.00)	971 (14.4)	0.98 (0.98, 0.99)	0.98 (0.98, 0.99)
WC category†									
0	796 (17.2)	1.00 (Ref)	1.00 (Ref)	50 (1.1)	1.00 (Ref)	1.00 (Ref)	746 (16.1)	1.00 (Ref)	1.00 (Ref)
1	241 (11.3)	0.74 (0.64, 0.86)	0.76 (0.65, 0.89)	16 (0.7)	0.70 (0.40, 1.24)	0.61 (0.32, 1.17)	225 (10.5)	0.74 (0.64, 0.87)	0.78 (0.66, 0.92)
Women									
WC (cm)	3317 (33.1)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	93 (0.9)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	3224 (32.1)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)
WC category									
0	1099 (36.5)	1.00 (Ref)	1.00 (Ref)	31 (1.0)	1.00 (Ref)	1.00 (Ref)	1068 (35.4)	1.00 (Ref)	1.00 (Ref)
1	2218 (31.6)	0.87 (0.81, 0.93)	0.86 (0.80, 0.93)	62 (0.9)	0.80 (0.52, 1.24)	0.79 (0.48, 1.29)	2156 (30.7)	0.87 (0.81, 0.94)	0.87 (0.80, 0.94)

Abbreviations: WC, waist circumference

* For the multivariate-adjusted hazard ratios, data are adjusted for study center, age and education in Model I and additional adjustment for smoking, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, systolic blood pressure at baseline, mean systolic blood pressure during the follow-up, estimated glomerular filtration rate, new stroke (for all cognitive impairment only), diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation in model II.

† WC category: 0=normal waistline; 1=abdominal obesity (defined as waist circumference ≥ 90/80 cm for men/women).

Table S9. Cox proportional hazard model for the risk (hazard ratios and 95% CIs) of cognitive impairment related to adiposity measures before and after imputation of missing data*

Adiposity measures	Total patients		Age <55 y		Age (55-<65 y)		Age ≥65 y	
	Before imputation	After imputation	Before imputation	After imputation	Before imputation	After imputation	Before imputation	After imputation
Men								
BMI category								
<18.5	1.25 (0.90, 1.76)	1.30 (0.97, 1.76)	1.74 (0.22, 13.77)	1.93 (0.43, 9.30)	2.25 (1.27, 3.98)	1.92 (1.11, 3.31)	0.93 (0.61, 1.44)	1.06 (0.73, 1.54)
18.5-23.9	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
24-27.9	0.78 (0.67, 0.91)	0.74 (0.64, 0.85)	1.06 (0.69, 1.64)	0.95 (0.63, 1.42)	0.76 (0.58, 1.00)	0.71 (0.55, 0.95)	0.75 (0.61, 0.92)	0.73 (0.60, 0.89)
≥28	0.75 (0.60, 0.94)	0.72 (0.58, 0.89)	0.79 (0.45, 1.38)	0.62 (0.38, 1.00)	0.81 (0.56, 1.17)	0.78 (0.56, 1.10)	0.70 (0.50, 0.99)	0.72 (0.52, 0.99)
BMI (per kg/m^2)	0.96 (0.94, 0.98)	0.95 (0.93, 0.97)	0.97 (0.92, 1.03)	0.94 (0.89, 0.99)	0.96 (0.92, 1.00)	0.95 (0.92, 0.99)	0.96 (0.93, 0.99)	0.95 (0.93, 0.98)
WC category†								
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	0.76 (0.65, 0.89)	0.73 (0.63, 0.85)	0.90 (0.60, 1.35)	0.76 (0.52, 1.11)	0.77 (0.59, 1.02)	0.74 (0.57, 0.95)	0.74 (0.59, 0.93)	0.73 (0.59, 0.90)
WC (per cm)	0.98 (0.98, 0.99)	0.98 (0.97, 0.99)	0.99 (0.97, 1.01)	0.98 (0.96, 1.00)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)
Women								
BMI category								
<18.5	1.21 (0.96, 1.53)	1.20 (0.99, 1.52)	2.04 (0.99, 4.18)	1.95 (0.95, 3.98)	1.44 (1.00, 2.06)	1.38 (0.98, 1.93)	1.03 (0.73, 1.44)	1.07 (0.79, 1.46)
18.5-23.9	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
24-27.9	0.87 (0.80, 0.95)	0.86 (0.79, 0.93)	1.16 (0.95, 1.43)	1.11 (0.92, 1.35)	0.82 (0.72, 0.94)	0.81 (0.71, 0.92)	0.78 (0.68, 0.90)	0.78 (0.69, 0.88)
≥28	0.82 (0.74, 0.91)	0.84 (0.77, 0.93)	0.90 (0.70, 1.14)	0.93 (0.75, 1.16)	0.81 (0.69, 0.95)	0.83 (0.72, 0.97)	0.78 (0.66, 0.92)	0.79 (0.67, 0.92)
BMI (per kg/m^2)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.97 (0.95, 0.99)	0.97 (0.96, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.99)
WC category†								
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	0.86 (0.80, 0.93)	0.86 (0.79, 0.92)	0.96 (0.80, 1.16)	0.93 (0.79, 1.11)	0.80 (0.71, 0.91)	0.81 (0.72, 0.91)	0.87 (0.77, 0.99)	0.86 (0.77, 0.97)
WC (per cm)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.99, 1.00)

Abbreviations: BMI, body mass index; WC, waist circumference.

* Data are adjusted for study center, age, education, smoking, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, systolic blood pressure at baseline, mean systolic blood pressure during the follow-up, estimated glomerular filtration rate, new stroke, diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation.

† WC category: 0=normal waistline; 1=abdominal obesity (defined as waist circumference ≥ 90/80 cm for men/women, respectively.

Table S10. Cox regression analysis for multivariable-adjusted risk of cognitive impairment related to baseline adiposity measures stratified by age (age < 60 y vs. ≥ 60 y)*

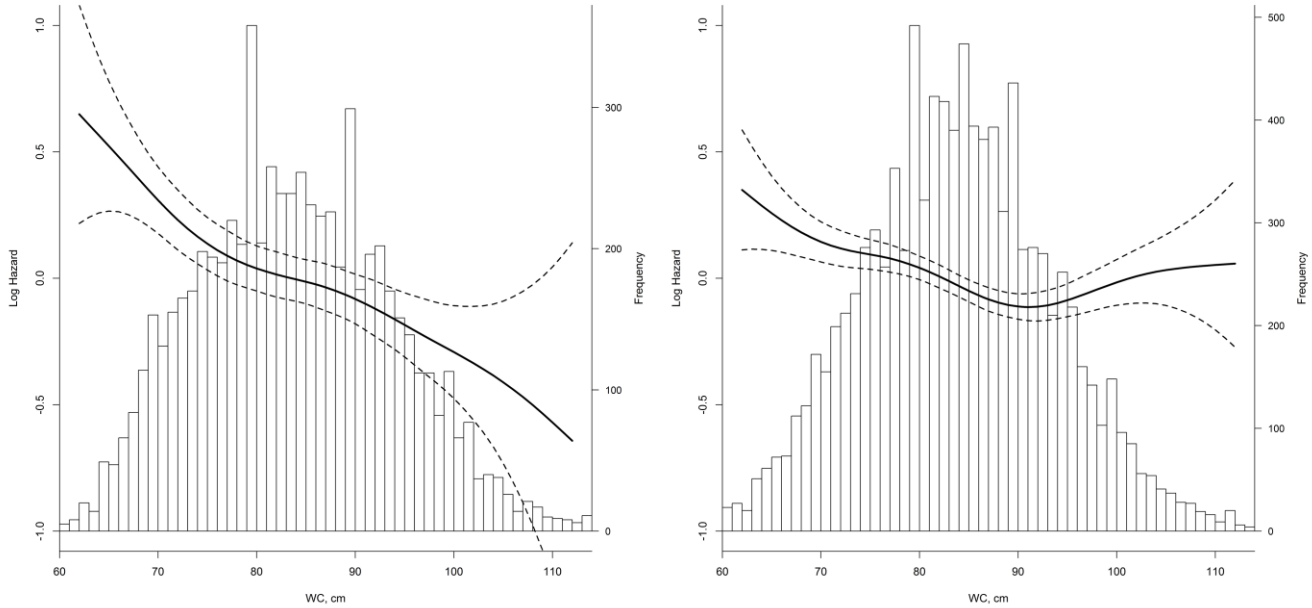
Adiposity measures	Men				*P*-value for interaction	Women				*P*-value for interaction
	age < 60 y		age ≥ 60 y			age < 60 y		age ≥ 60 y		
	HR (95%CI)	*P* value	HR (95%CI)	*P* value		HR (95%CI)	*P* value	HR (95%CI)	*P* value	
BMI (per kg/m^2)	0.96 (0.92, 1.00)	0.038	0.95 (0.92, 0.97)	<0.001	0.525	0.98 (0.97, 1.00)	0.048	0.96 (0.95, 0.98)	<0.001	0.039
BMI category										
<18.5	3.03 (1.43, 6.38)	0.004	1.16 (0.80, 1.69)	0.437		1.61 (1.02, 2.53)	0.040	1.22 (0.93, 1.60)	0.150	
18.5-23.9	1.00 (Ref)		1.00 (Ref)			1.00 (Ref)		1.00 (Ref)		
24-27.9	0.90 (0.67, 1.21)	0.486	0.70 (0.59, 0.84)	<0.001		0.95 (0.83, 1.10)	0.496	0.80 (0.72, 0.90)	<0.001	
≥28	0.71 (0.48, 1.05)	0.090	0.70 (0.53, 0.93)	0.013		0.86 (0.73, 1.01)	0.071	0.74 (0.65, 0.85)	<0.001	
P value for trend		0.017		<0.001			0.020		<0.001	
WC (per cm)	0.985 (0.971, 0.999)	0.033	0.980 (0.971, 0.988)	<0.001	0.452	0.997 (0.990, 1.003)	0.330	0.990 (0.985, 0.995)	<0.001	0.068
WC category†										
0	1.00 (Ref)		1.00 (Ref)			1.00 (Ref)		1.00 (Ref)		
1	0.78 (0.58, 1.04)	0.087	0.73 (0.60, 0.88)	0.001		0.91 (0.80, 1.04)	0.167	0.84 (0.76, 0.92)	<0.001	

Abbreviations: BMI, body mass index; WC, waist circumference; HR, hazard ratio

* Data are adjusted for study center, age, education, smoking, alcohol drinking, marital status, living conditons, physical activity, PHQ scores, systolic blood pressure at baseline, mean systolic blood pressure during the follow-up, estimated glomerular filtration rate, new stroke, diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation.

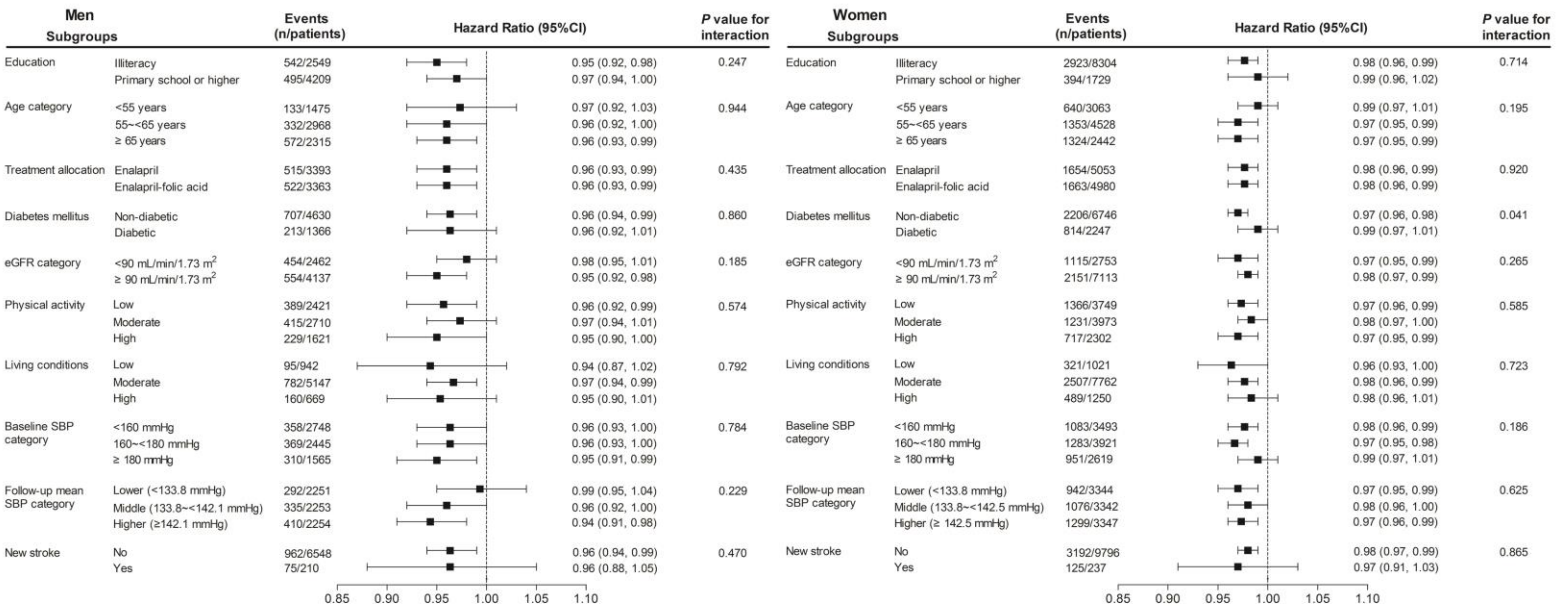
† WC category: 0=normal waistline; 1=abdominal obesity (defined as waist circumference ≥ 90/80 cm for men/women, respectively).

Figure S1. Relationship between WC at baseline and risk of cognitive impairment by penalized splines



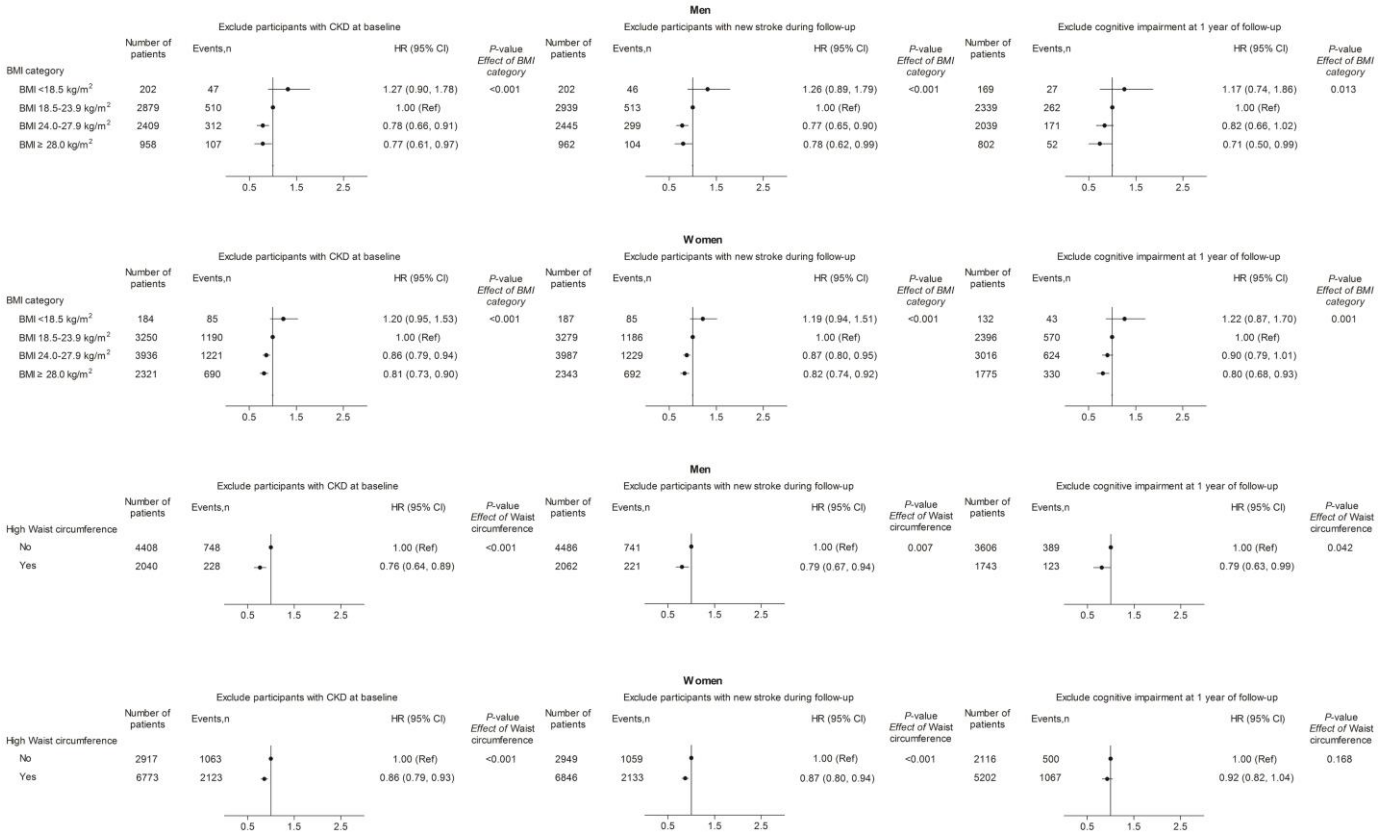
The relative risk of cognitive impairment in association with WC is shown in Panel A for men and Panel B for women. Solid lines represent the log hazard ratios for WC as a continuous variable and dashed lines represent the 95% confidence intervals. The graphs are truncated at the 1st and 99th percentiles of WC. Analyses are adjusted for study center, age, education, smoking status, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, SBP at baseline, mean SBP during the follow-up, eGFR, new stroke, diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation. Abbreviations: WC, waist circumference; PHQ, Patient Health Questionnaire; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate.

Figure S2. Relationship between BMI at baseline and risk of cognitive impairment in exploratory subgroups



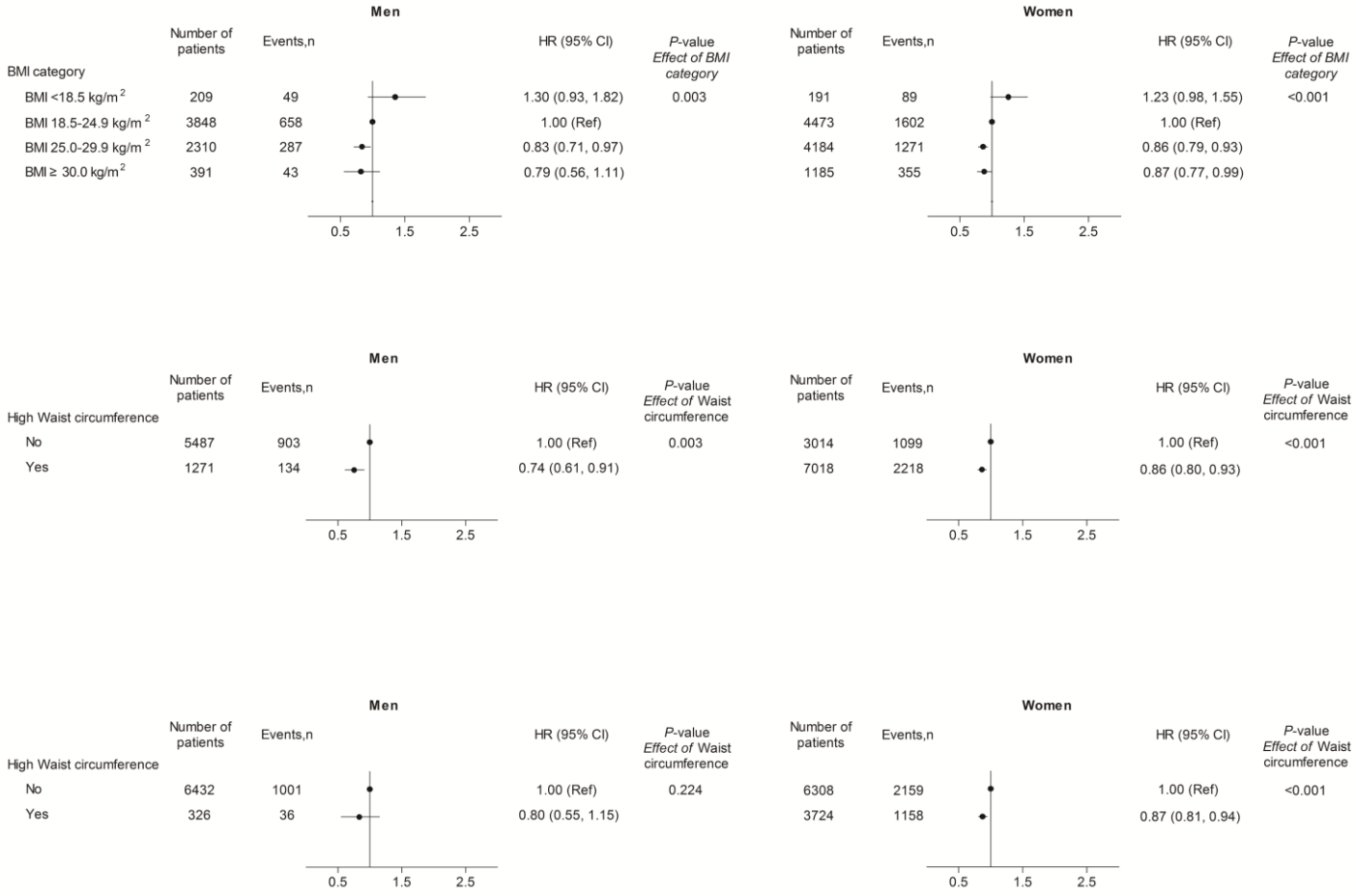
The squares and horizontal lines indicate hazard ratios and 95% confidence interval, respectively. These analyses are restricted to participants with non-missing data of subgroup variables at baseline. Hazard ratios are adjusted, if not stratified, for study center, age, education, smoking status, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, SBP at baseline, mean SBP during the follow-up, eGFR, new stroke, diabetes mellitus, and treatment allocation. Diabetes mellitus in the subgroup analysis includes both diabetes mellitus at baseline and new diabetes mellitus during the follow-up. Abbreviations: BMI, body mass index; PHQ, Patient Health Questionnaire; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate

Figure S3. Sensitivity analyses according to baseline BMI and WC after excluding participants with chronic kidney diseases (CKD) at baseline, new stroke during the follow-up and cognitive impairment at the 1-year follow-up



Analyses are adjusted for study center, age, education, smoking status, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, SBP at baseline, mean SBP during the follow-up, eGFR, new stroke (not adjusted if participants with new stroke are excluded), diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation. Abbreviations: BMI, body mass index; WC, waist circumference; PHQ, Patient Health Questionnaire; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate

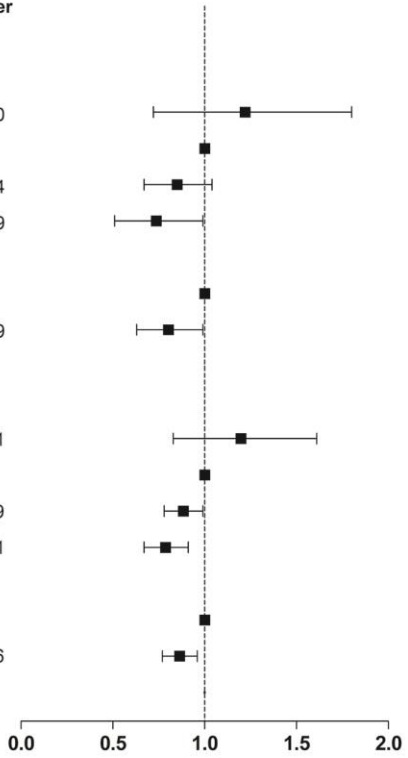
Figure S4. Sensitivity analyses according to baseline BMI and WC categories using other ethnic-specific cut-points



Analyses are adjusted for study center, age, education, smoking status, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, SBP at baseline, mean SBP during the follow-up, eGFR, new stroke, diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation. Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate. High waist circumference is defined as ≥ 94 cm for men and ≥ 80 cm for women in the middle row, and ≥ 102 cm for men and ≥ 88 cm for women in the last row

Figure S5. Relationship between BMI and WC at baseline and risk of cognitive impairment when using alternative definition

	Number of patients	Number of events	Hazard ratio	95% Confidence interval	
				Lower	Upper
Men					
BMI category					
< 18.5 kg/m^2	184	27	1.14	0.72	1.80
18.5~23.9 kg/m^2	2531	268	1.00	/	/
24.0~27.9 kg/m^2	2150	178	0.84	0.67	1.04
≥ 28 kg/m^2	842	54	0.71	0.51	0.99
WC category					
Normal	3879	401	1.00	/	/
High	1828	126	0.79	0.63	0.99
Women					
BMI category					
< 18.5 kg/m^2	164	45	1.15	0.83	1.61
18.5~23.9 kg/m^2	2866	634	1.00	/	/
24.0~27.9 kg/m^2	3470	654	0.88	0.78	0.99
≥ 28 kg/m^2	2050	346	0.78	0.67	0.91
WC category					
Normal	2537	555	1.00	/	/
High	6012	1124	0.86	0.77	0.96



Cognitive impairment is defined as a decrease of MMSE scores of 3 or more and to a level of less than education-specific cut-off points at any time during the follow-up. Adjusted for study center, age, education, smoking, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, SBP at baseline, mean SBP during the follow-up, eGFR, new stroke, diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation. The references are the normal-weight BMI category (18.5–23.9 kg/m^2) and normal WC category (< 90 cm for men and < 80 cm for women). These analyses are restricted to participants with non-missing data of MMSE value at the 1-year follow-up visit. The squares and horizontal lines indicate hazard ratios and 95% confidence intervals, respectively. Abbreviations: BMI, body mass index; WC, waist circumference; PHQ, Patient Health Questionnaire; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate

Figure S6. Number of concomitant antihypertensive drugs according to treatment allocation and BMI categories at final follow-up visit

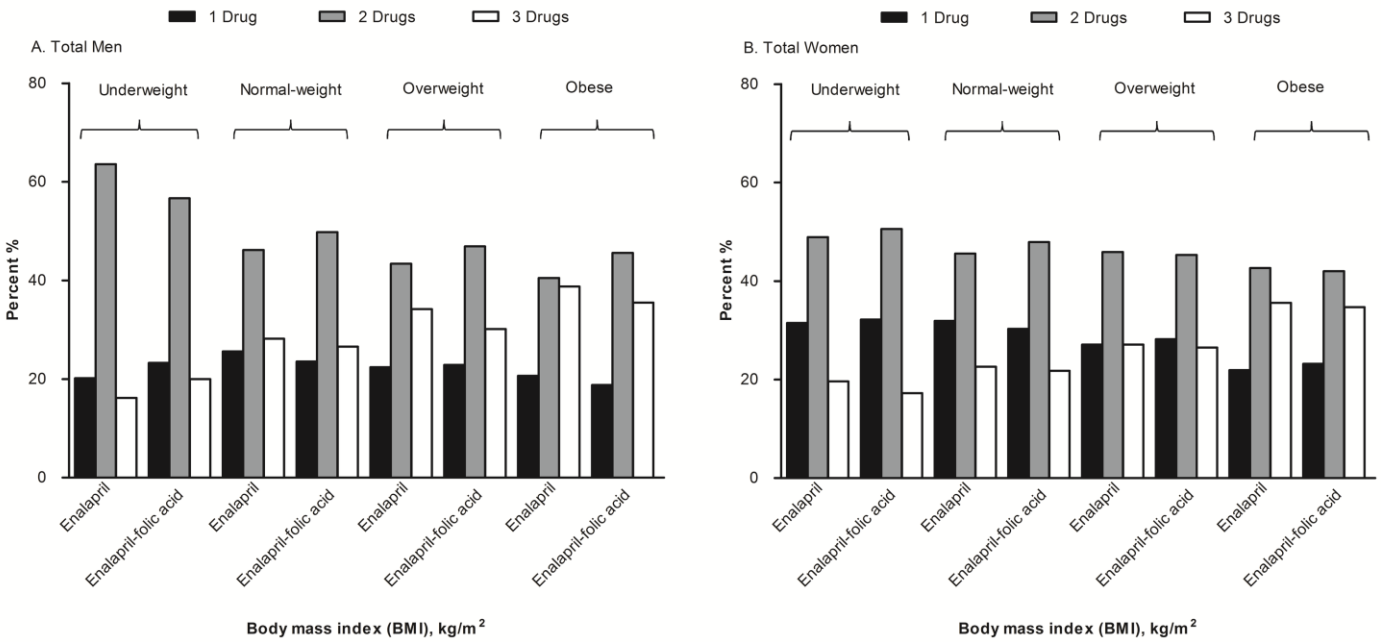
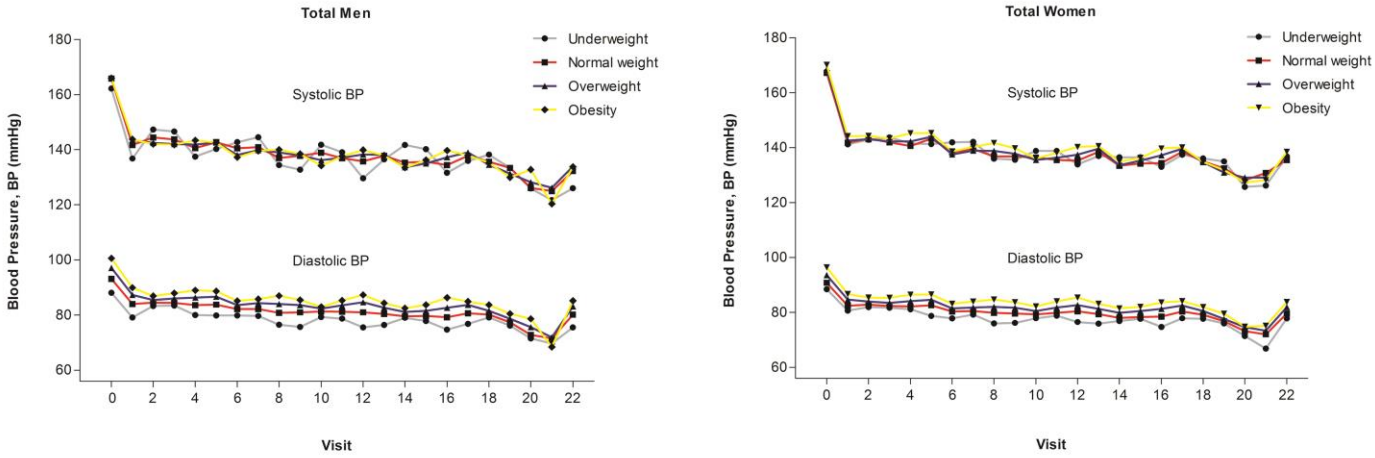


Figure S7. Blood pressures at baseline and during the follow-up by baseline BMI categories



Longitudinal change in blood pressure (BP, mmHg) over the trail period by baseline BMI category

	Men		Women	
	SBP [β (SE)][a]	DBP [β (SE)][a]	SBP [β (SE)][a]	DBP [β (SE)][a]
Associations Between Obesity Status and Baseline BP Levels				
Obesity Status[b]				
Underweight	-0.851 (0.836)	-3.263 (0.576)[c]	0.639 (0.901)	-1.905 (0.549)[c]
Overweight	-0.588 (0.318)	2.474 (0.219)[c]	0.392 (0.284)	1.843 (0.173)[c]
Obese	-0.655 (0.431)	4.738 (0.296)[c]	2.144 (0.325)[c]	3.973 (0.198)[c]
Normal-weight	Reference	Reference	Reference	Reference
Associations Between Obesity Status and Longitudinal Change in BP Levels				
Time	-0.854 (0.012)[c]	-0.395 (0.007)[c]	-0.791 (0.011)[c]	-0.332 (0.006)[c]
Obesity Status				
Underweight× time	0.027 (0.043)	-0.012 (0.024)	-0.002 (0.046)	-0.022 (0.024)
Overweight× time	0.067 (0.017)[c]	0.002 (0.010)	0.045 (0.015)[c]	0.017 (0.008)[c]
Obese× time	0.091 (0.024)[c]	-0.011 (0.013)	0.019 (0.017)	0.003 (0.009)
Normal-weight× time	Reference	Reference	Reference	Reference

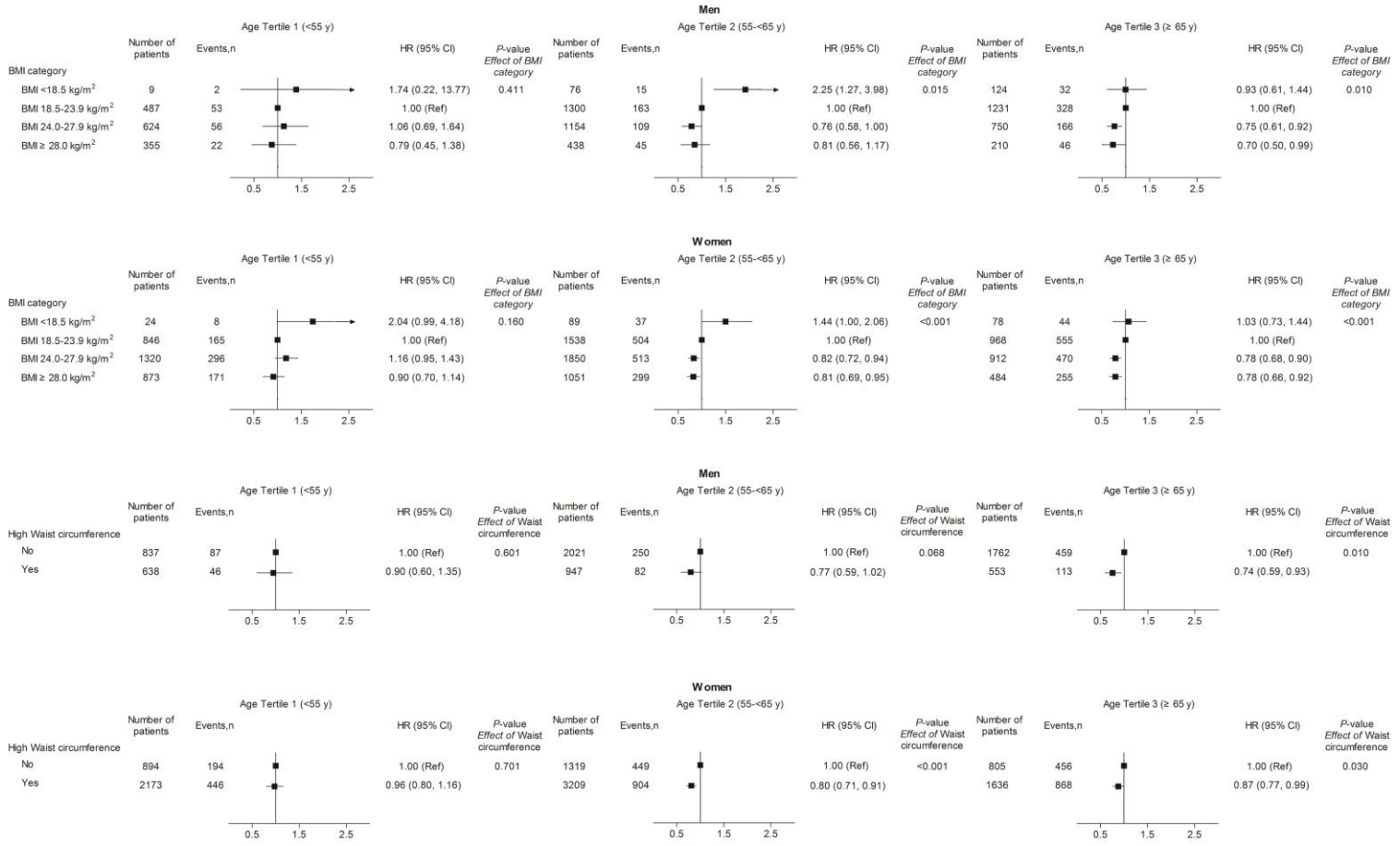
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure .

[a] Coefficient β (SE) represented average change over time for an individual with a BMI level in the normal -weight category and additional effect of being underweight or overweight or obese on the change in SBP and DBP levels.

[b] Obesity status as defined according to the Chinese crit erion based on Cooperative Meta -Analysis Group of the Working Group on Obesity in China. Underweight indicates less than 18.5 kg/m^2; normal-weight, 18.5 to less than 24 kg/m^2; overweight, 24 to less than 28 kg/m^2, and obese, 28 kg/m^2 or more.

[c] $P < 0.05$.

Figure S8. Cox regression analysis of sex-specific risk of cognitive impairment related to baseline BMI and WC categories according to age tertiles



Adjusted for study center, age, education, smoking, alcohol drinking, marital status, living conditions, physical activity, PHQ scores, SBP at baseline, mean SBP during the follow-up, eGFR, new stroke, diabetes mellitus at baseline, new diabetes mellitus during the follow-up, and treatment allocation. The references are the normal-weight BMI category (18.5–23.9 kg/m^2) and normal WC category (< 90 cm for men and < 80 cm for women). Squares and horizontal lines represent hazard ratios and 95% confidence intervals, respectively. The y-axis corresponds to an HR of 1.
Abbreviations: BMI, body mass index; WC, waist circumference; PHQ, Patient Health Questionnaire; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate