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)*

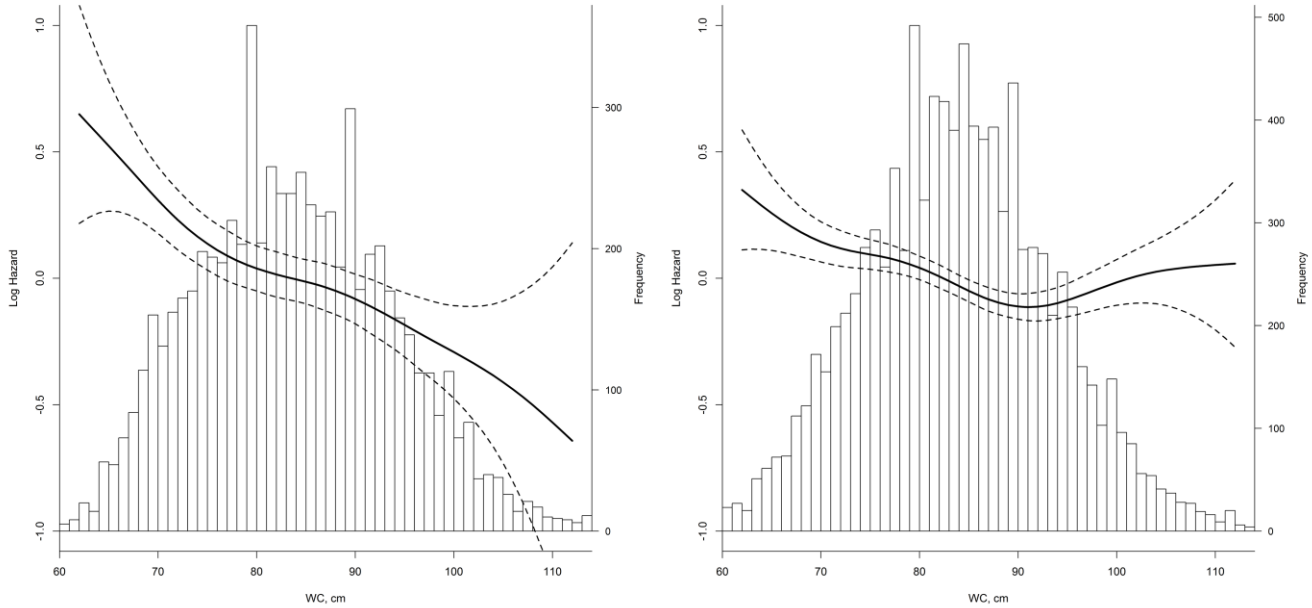
Adiposity measures	Men				*P*-value for interaction	Women				*P*-value for interaction
	age < 60 y		age ≥ 60 y			age < 60 y		age ≥ 60 y		
	HR (95%CI)	*P* value	HR (95%CI)	*P* value		HR (95%CI)	*P* value	HR (95%CI)	*P* value	
BMI (per kg/m^2)	0.96 (0.92, 1.00)	0.038	0.95 (0.92, 0.97)	<0.001	0.525	0.98 (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.

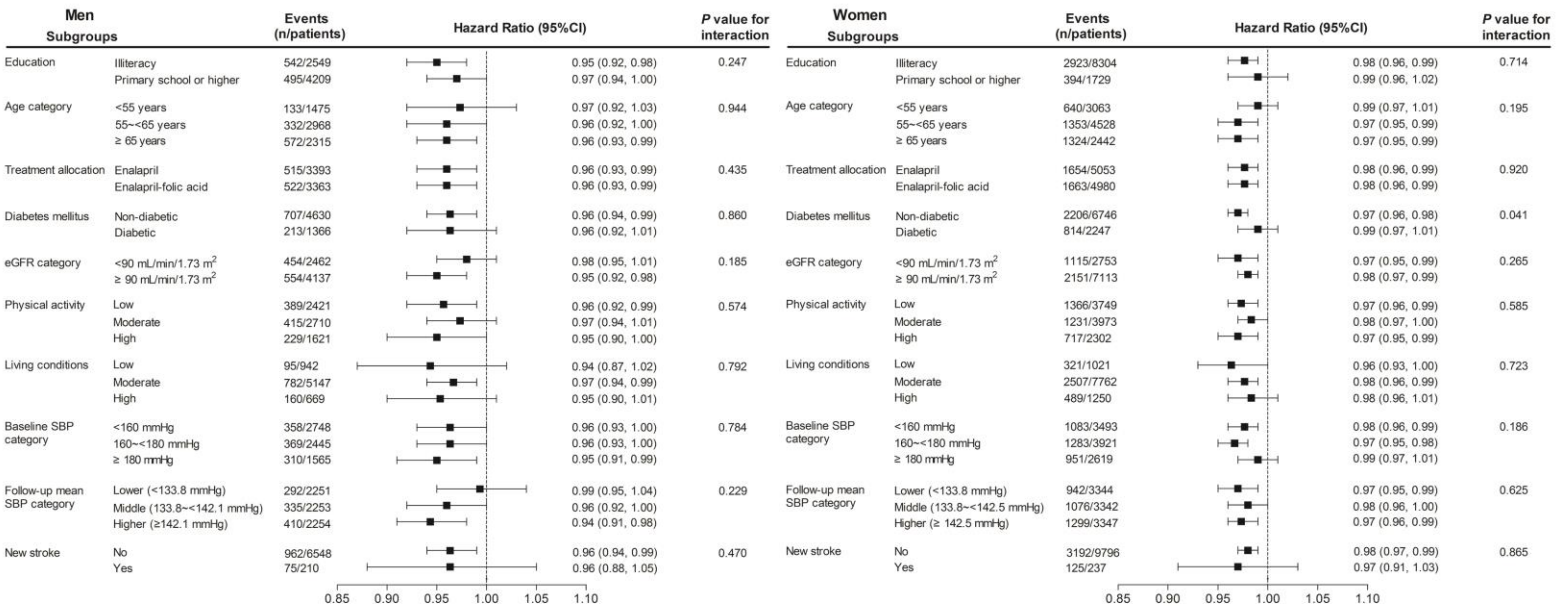
† WC category: 0=normal waistline; 1=abdominal obesity (defined as waist circumference ≥ 90/80 cm for men/women, respectively).

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



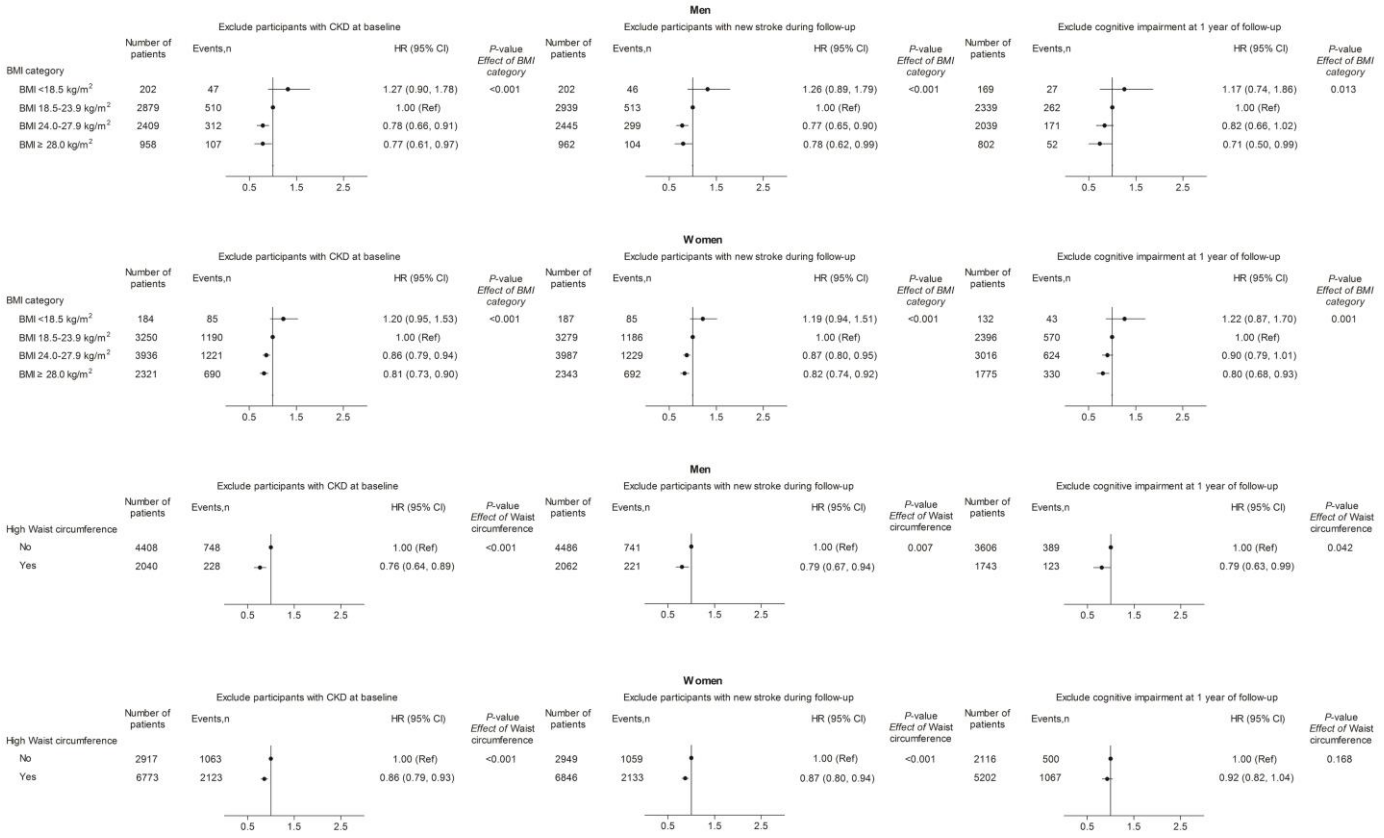
The relative risk of cognitive impairment in association with WC is shown in Panel A for men and Panel B for women. Solid lines represent the log hazard ratios for WC as a continuous variable and dashed lines represent the 95% confidence intervals. The graphs are truncated at the 1st and 99th percentiles 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



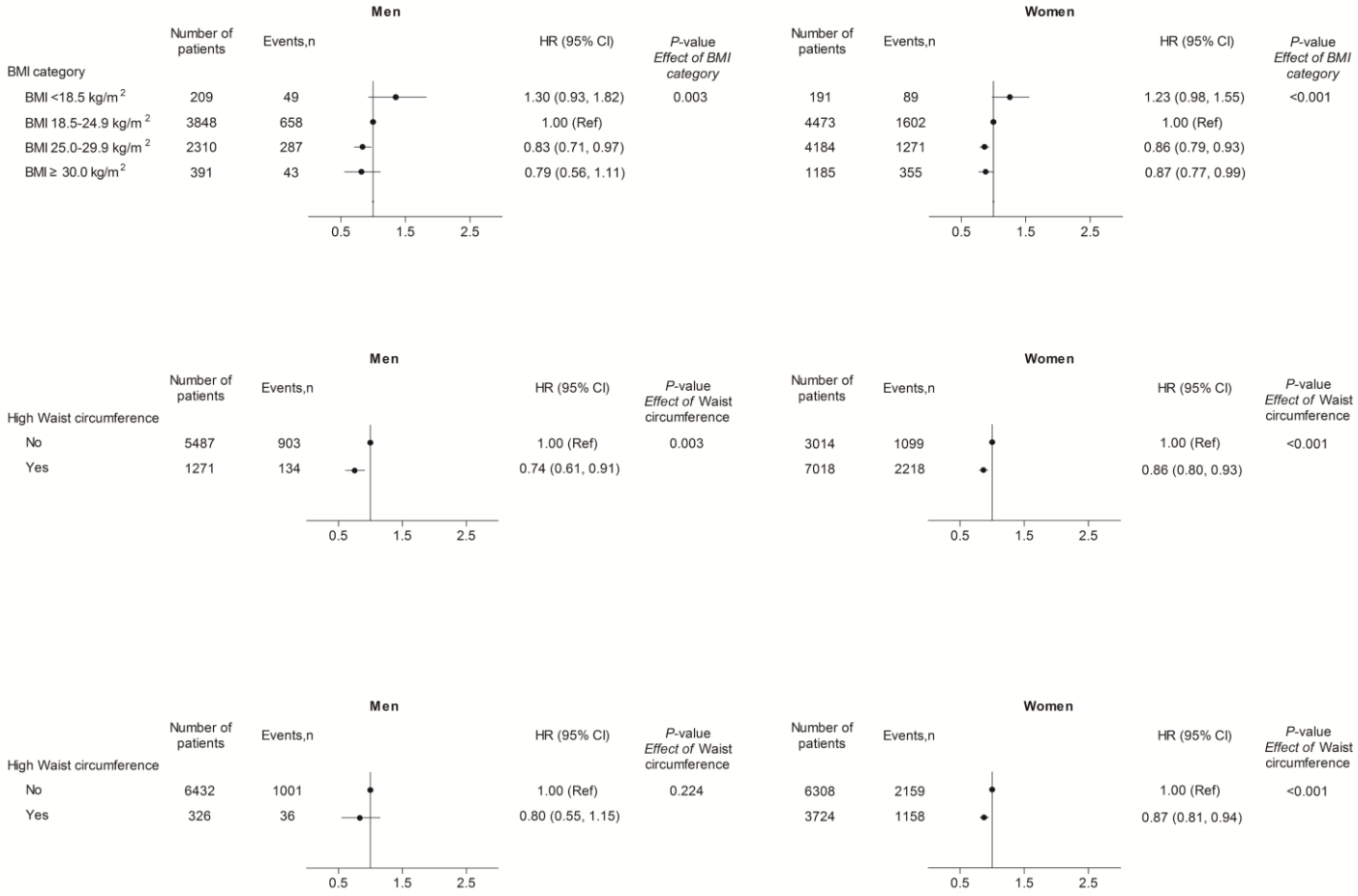
The squares and horizontal lines indicate hazard ratios and 95% confidence interval, respectively. These analyses are restricted to participants with non-missing data of subgroup variables at baseline. Hazard ratios are adjusted, if not stratified, for study center, age, education, smoking status, alcohol 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

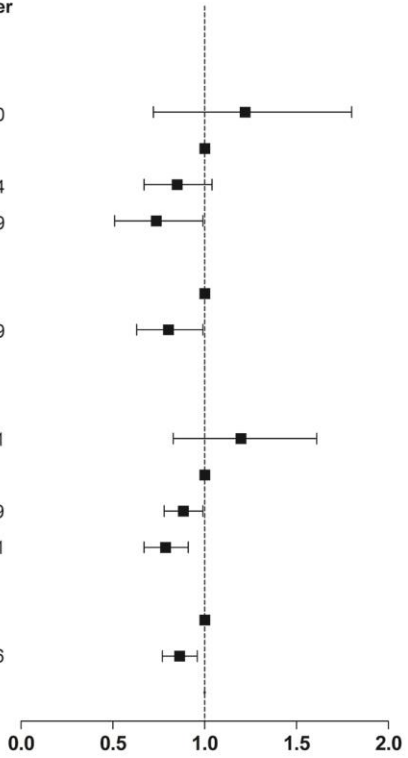
Figure S4. Sensitivity analyses according to baseline BMI and WC categories using other ethnic-specific cut-points



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

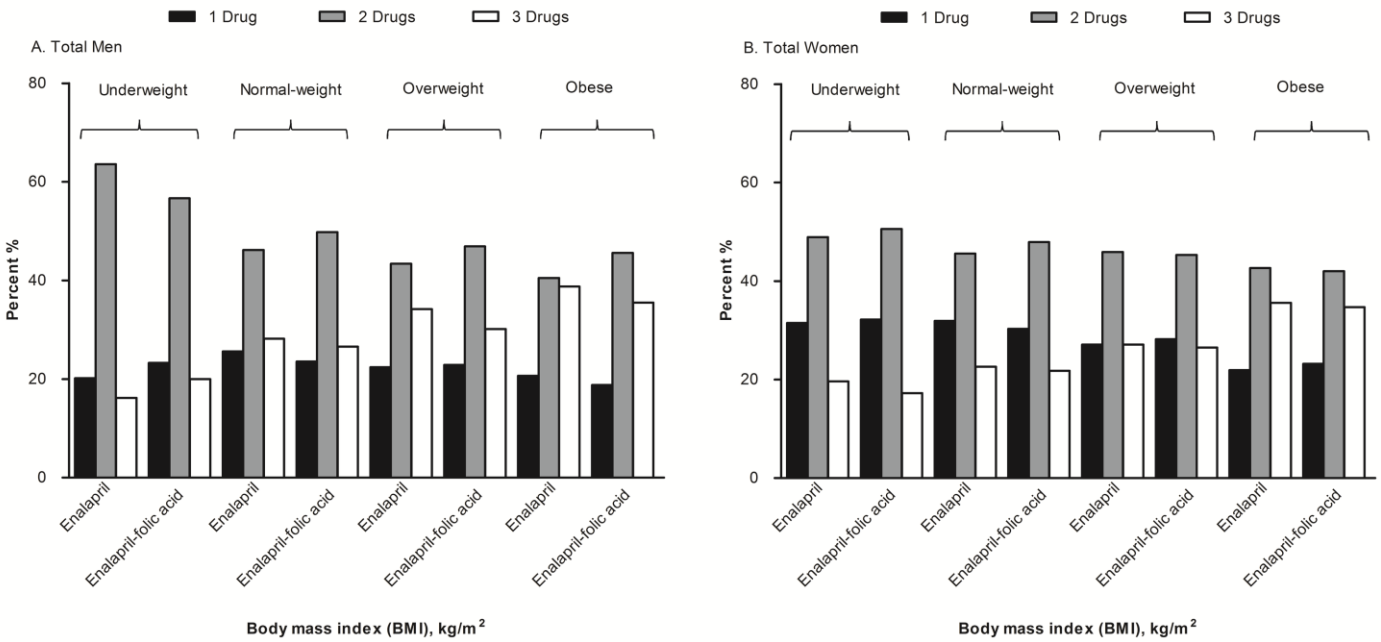
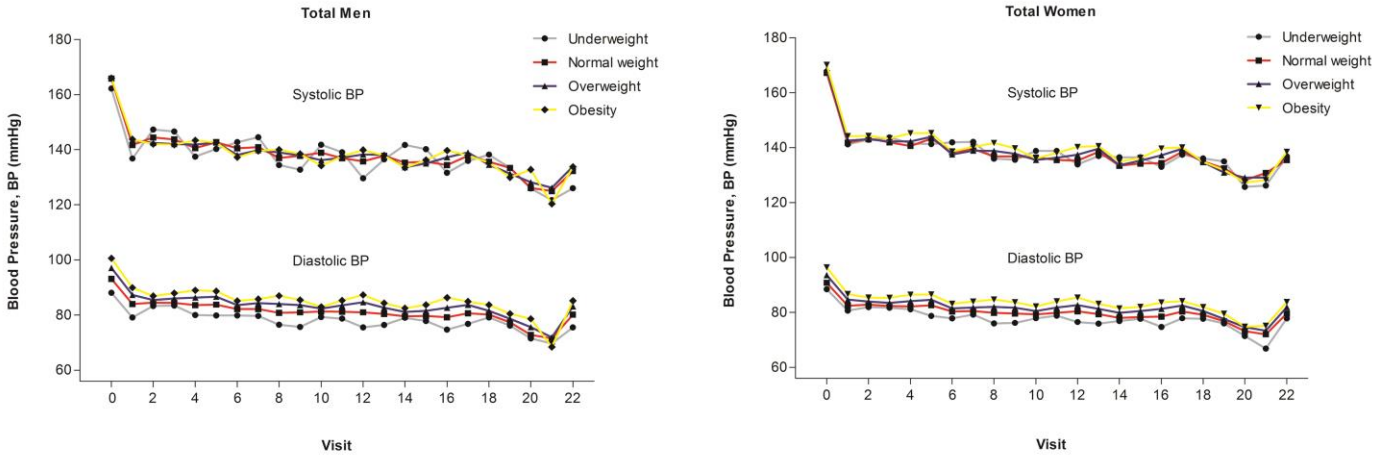


Figure S7. Blood pressures at baseline and during the follow-up by baseline BMI categories



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

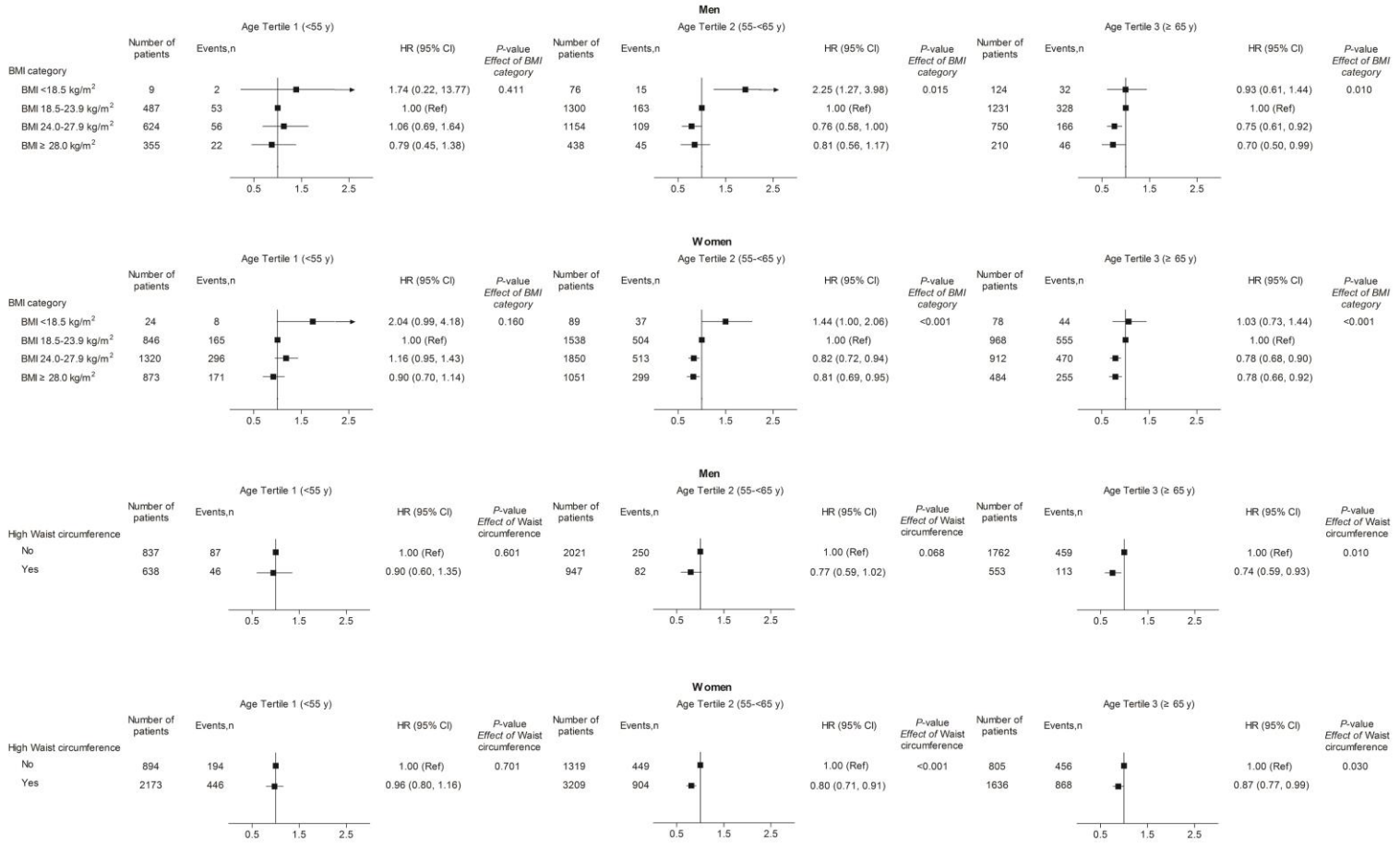
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure .

[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