Supplementary Materials

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supplemental table 1 Baseline characteristics of individuals included in and excluded from this analysis

Characteristics	Excluded (N=567)	Included (N=2413)	p value
Age, y	60.0 (6.8)	61.3 (6.6)	<0.001
Sex, female, n (%)	305 (53.8)	1300 (53.9)	0.97
Han ethnicity, n (%)	561 (98.9)	2329 (96.5)	0.002
Educational status, n (%)			
Illiteracy	159 (28.0)	389 (16.1)	<0.001
Primary school	176 (31.0)	594 (24.6)	
Junior school	173 (30.5)	732 (30.3)	
High school	58 (10.2)	510 (21.1)	
College school	1 (0.2)	188 (7.8)	
Current smoker, n (%)	132 (23.3)	482 (20.0)	0.08
Current drinker, n (%)	126 (22.2)	437 (18.1)	0.02
Medical history, n(%)			
Hypertension	205 (36.2)	1047 (43.4)	0.002
Diabetes mellitus	97 (17.1)	536 (22.2)	0.01
Dyslipidemia	70 (12.3)	524 (21.7)	<0.001
Coronary artery disease	3 (0.5)	10 (0.4)	0.71
Atrial fibrillation	6 (1.1)	19 (0.8)	0.52
Medication use, n(%)			
Antihypertensive	140 (24.7)	628 (26.0)	0.51
Antidiabetic	28 (4.9)	228 (9.5)	<0.001
Lipid-lowering	7 (1.2)	93 (3.9)	0.002
Anticoagulants	1 (0.2)	1 (0.04)	0.26

supplemental table 2 Difference in brain volumes and brain aging years in BMI groups of different age groups

Age group, year	N	MRI brain measures*	Mean brain volume,%†			Years of brain aging‡	
			BMI: <24.0 kg/m^2	BMI: 24.0-27.9 kg/m^2	BMI:≥28.0 kg/m^2	BMI: 24.0-27.9 kg/m^2	BMI: ≥28.0 kg/m^2
<60	1112	TCBV	69.96	70.03	69.74	-0.3	1.1
		GMV	39.35	39.23	39.02	1.3	3.6
		WMV	30.61	30.80	30.72	-1.7	-1.0
		WMHV	0.09	0.12	0.17	1.5	4.0
60-64	571	TCBV	68.96	68.53	68.65	2.1	1.5
		GMV	38.74	38.40	38.43	3.7	3.4
		WMV	30.22	30.13	30.22	0.8	0.0
		WMHV	0.15	0.19	0.21	2.0	3.0
≥65	730	TCBV	67.10	66.81	66.61	1.4	2.4
		GMV	38.00	37.74	37.54	2.9	5.0
		WMV	29.10	29.07	29.08	0.3	0.2
		WMHV	0.36	0.41	0.41	2.5	2.5
All participants	2413	TCBV	68.87	68.70	68.48	0.8	1.9
		GMV	38.80	38.59	38.42	2.3	4.2
		WMV	30.07	30.12	30.06	-0.4	0.1
		WMHV	0.18	0.22	0.26	2.0	4.0

* Expressed as percentage of total cranial volume.

† Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

‡ Calculation of years of brain aging is based on regressing each brain volume onto age at magnetic resonance imaging, where the slope is the estimate of the change in brain volume per year of age (TCBV=-0.2030%*age; GMV=-0.0911%*age; WMV=-0.1119%*age; WMHV=0.0210%*age).

BMI, body mass index; GMV, gray matter volume; TCBV, total cerebral brain volume; WMHV, white matter hyperintensities volume; WMV, white matter volume.

supplemental table 3 Difference in brain volumes and brain aging years in WHR groups of different age groups

Age group, year	N	MRI brain measures*	Mean brain volume,%†			Years of brain aging§	
			Low level WHR‡	Medium level WHR‡	High level WHR‡	Medium level WHR‡	High level WHR‡
<60	1112	TCBV	70.07	69.92	69.90	0.7	0.8
		GMV	39.43	39.19	39.29	2.7	1.6
		WMV	30.65	30.73	30.61	-0.7	0.4
		WMHV	0.09	0.11	0.14	1.0	2.5
60-64	571	TCBV	68.57	68.88	68.66	-1.5	-0.4
		GMV	38.51	38.67	38.24	-1.8	3.0
		WMV	30.06	30.20	30.42	-1.2	-3.2
		WMHV	0.14	0.17	0.23	1.5	4.5
≥65	730	TCBV	67.08	66.91	66.92	0.8	0.8
		GMV	37.98	37.88	37.51	1.1	5.3
		WMV	29.10	29.03	29.40	0.6	-2.7
		WMHV	0.36	0.39	0.37	1.5	0.5
All participants	2413	TCBV	68.83	68.76	68.70	0.3	0.6
		GMV	38.79	38.67	38.46	1.3	3.7
		WMV	30.04	30.09	30.24	-0.4	-1.8
		WMHV	0.18	0.21	0.23	1.5	2.5

* Expressed as percentage of total cranial volume.

† Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

‡ WHR groups: low level: <0.85 (Female), <0.90 (Male); medium level:0.85-1.00 (Female), 0.90-1.00 (Male); high level:>1.00 (Female), >1.00 (Male).

§ Calculation of years of brain aging is based on regressing each brain volume onto age at magnetic resonance imaging, where the slope is the estimate of the change in brain volume per year of age (TCBV=-0.2016%*age; GMV=-0.0889%*age; WMV=-0.1126%*age; WMHV=0.0198%*age).

GMV, gray matter volume; TCBV, total cerebral brain volume; WHR, waist hip ratio; WMHV, white matter hyperintensity volume; WMV, white matter volume.

supplemental table 4 Difference in brain volumes and brain aging years in obesity groups of different age and sex groups

Age group, year	MRI brain measures*	Sex	N	Mean brain volume, cm^3†			Years of brain aging §		Mean brain volume, cm^3†			Years of brain aging ¶	
				BMI: <24.0 kg/m^2	BMI: 24.0-27.9 kg/m^2	BMI: ≥28.0 kg/m^2	BMI: 24.0-27.9 kg/m^2	BMI:≥28.0 kg/m^2	Low level WHR‡	Medium level WHR‡	High level WHR‡	Medium level WHR‡	High level WHR‡
	TCBV	Men	485	1046.84	1051.53	1038.43	-1.5	2.7	1048.59	1046.95	1048.40	0.5	0.1
<60		Women	627	1051.50	1053.14	1057.44	-0.5	-2.0	1053.18	1053.00	1043.39	0.1	3.3
	GMV	Men	485	588.80	590.20	583.26	-0.9	3.7	591.50	587.40	586.70	2.8	3.3
		Women	627	589.21	588.12	590.21	0.8	-0.8	589.65	588.70	587.10	0.8	2.0
	WMV	Men	485	458.04	461.33	455.17	-2.1	1.8	457.09	459.55	461.70	-1.5	-2.9
		Women	627	462.30	465.02	467.23	-1.6	-2.8	463.53	464.30	456.29	-0.4	4.2
	WMHV	Men	485	1.36	1.82	3.32	1.4	5.9	1.37	1.88	2.56	1.6	3.7
		Women	627	1.23	1.92	1.99	2.5	2.8	1.44	1.62	1.45	0.7	0.0
60-64	TCBV	Men	273	1031.38	1033.02	1041.80	-0.5	-3.4	1027.63	1036.43	1032.39	-2.9	-1.6
		Women	298	1038.27	1028.67	1024.42	3.2	4.6	1038.08	1033.11	1028.92	1.7	3.1
	GMV	Men	273	580.21	579.91	582.24	0.2	-1.3	578.68	582.78	572.13	-2.8	4.5
		Women	298	580.79	575.73	572.80	4.0	6.3	579.69	578.23	575.50	1.2	3.4
	WMV	Men	273	451.17	453.11	459.56	-1.2	-5.4	448.95	453.65	460.26	-2.9	-7.1
		Women	298	457.48	452.93	451.62	2.6	3.4	458.39	454.88	453.42	2.0	2.9
	WMHV	Men	273	2.27	2.78	4.68	1.5	7.2	2.33	2.65	3.74	1.0	4.3
		Women	298	2.11	3.02	2.05	3.3	-0.2	1.79	2.49	3.24	2.6	5.3
≥65	TCBV	Men	355	1003.04	1002.20	1008.00	0.3	-1.6	1000.45	1003.47	1007.56	-1.0	-2.3
		Women	375	1010.43	1006.95	1000.31	1.2	3.4	1015.69	1006.93	1004.97	2.9	3.6
	GMV	Men	355	567.01	566.38	564.39	0.4	1.7	564.87	568.27	561.67	-2.3	2.2
		Women	375	570.61	568.12	565.45	2.0	4.0	575.61	568.46	564.99	5.7	8.5
	WMV	Men	355	436.03	435.82	443.61	0.1	-4.8	435.58	435.20	445.89	0.2	-6.5
		Women	375	439.82	438.83	434.86	0.6	2.8	440.08	438.47	439.98	0.9	0.1
	WMHV	Men	355	5.89	6.51	5.64	1.8	-0.8	6.01	6.23	5.72	0.7	-0.9
		Women	375	4.87	5.90	6.54	3.8	6.1	4.62	5.62	5.31	3.7	2.5
All participants	TCBV	Men	1113	1029.32	1031.16	1026.33	-0.6	1.0	1028.19	1030.25	1031.90	-0.7	-1.2
		Women	1300	1036.59	1034.36	1032.82	0.7	1.3	1038.12	1035.17	1030.03	1.0	2.7
	GMV	Men	1113	579.89	579.97	575.91	-0.1	2.7	580.01	579.99	575.27	0.0	3.2
		Women	1300	581.79	579.70	579.00	1.6	2.2	582.89	580.47	577.36	1.9	4.4

WMV	Men	1113	449.43	451.19	450.42	-1.1	-0.6	448.18	450.27	456.62	-1.3	-5.3
	Women	1300	454.80	454.66	453.82	0.1	0.6	455.23	454.69	452.68	0.3	1.5
WMHV	Men	1113	3.02	3.54	4.63	1.6	4.8	2.98	3.52	3.78	1.7	2.5
	Women	1300	2.50	3.29	3.43	2.9	3.4	2.59	2.94	3.06	1.3	1.7

* Expressed by residual method.

† Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

‡ WHR groups: low level: <0.85 (Female), <0.90 (Male); medium level:0.85-1.00 (Female), 0.90-1.00 (Male); high level:>1.00 (Female), >1.00 (Male).

§ Calculation of years of brain aging in the men population is based on regressing each brain volume onto age at magnetic resonance imaging, where the slope is the estimate of the change in residual adjusted brain volume per year of age (TCBV=-3.0660*age; GMV=-1.4987*age; WMV=-1.5673*age; WMHV=0.3332*age); calculation of years of brain aging in the women population is based on regressing each brain volume onto age at magnetic resonance imaging, where the slope is the estimate of the change in residual adjusted brain volume per year of age (TCBV=-3.0183*age; GMV=-1.2779*age; WMV=-1.7404*age; WMHV=0.2745*age)

¶ Calculation of years of brain aging in the men population is based on regressing each brain volume onto age at magnetic resonance imaging, where the slope is the estimate of the change in residual adjusted brain volume per year of age (TCBV=-3.0643*age; GMV=-1.4710*age; WMV=-1.5933*age; WMHV=0.3247*age); calculation of years of brain aging in the women population is based on regressing each brain volume onto age at magnetic resonance imaging, where the slope is the estimate of the change in residual adjusted brain volume per year of age (TCBV=-2.9776*age; GMV=-1.2494*age; WMV=-1.7282*age; WMHV=0.2715*age)

BMI, body mass index; GMV, gray matter volume; TCBV, total cerebral brain volume; WMHV, white matter hyperintensity volume; WMV, white matter volume.

supplemental table 5 Associations between BMI and cardiometabolic and inflammatory measures and MRI brain measures

	β*	95% CI	P value
MRI brain measures			
TCBV†,‡	-0.05	-0.32, 0.23	0.74
GMV†,‡	-0.22	-0.52, 0.07	0.14
WMV†,‡	0.13	-0.16, 0.42	0.38
WMHV†,‡	1.55	1.26, 1.84	<0.001
Cardiometabolic measures			
SBP‡	0.20	0.16, 0.24	<0.001
DBP‡	0.18	0.14, 0.22	<0.001
FPG‡	0.27	0.21, 0.33	<0.001
HOMA-IR‡	2.50	2.33, 2.66	<0.001
TC‡	0.04	-0.02, 0.10	0.15
TG‡	1.13	0.96, 1.30	<0.001
LDL-C‡	0.16	0.07, 0.26	<0.001
HDL-C‡	-0.56	-0.63, -0.48	<0.001
Inflammatory measures			
Leukocyte count‡	0.35	0.28, 0.43	<0.001
Neutrophil count‡	0.36	0.26, 0.47	<0.001
Neutrophil ratio‡	0.01	-0.04, 0.06	0.67

* Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed by residual method and standardization.

‡ Logarithmic transformation was performed for BMI, MRI brain measures, and all cardiometabolic and inflammatory measures.

β, regression coefficient; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GMV, gray matter volume; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; SBP, systolic blood pressure; TC, total cholesterol; TCBV, total cerebral brain volume; TG, triglyceride; WMHV, white matter hyperintensity volume; WMV, white matter volume.

supplemental table 6 Associations between WHR, cardiometabolic and inflammatory measures and MRI brain measures

	β*	95% CI	P value
MRI brain measures			
TCBV†,‡	-0.44	-0.94, 0.06	0.09
GMV†,‡	-0.68	-1.22, -0.14	0.01
WMV†,‡	-0.06	-0.59, 0.47	0.83
WMHV†,‡	2.12	1.58, 2.65	<0.001
Cardiometabolic measures			
SBP‡	0.27	0.20, 0.34	<0.001
DBP‡	0.26	0.19, 0.33	<0.001
FPG‡	0.64	0.53, 0.75	<0.001
HOMA-IR‡	3.79	3.47, 4.11	<0.001
TC‡	0.09	-0.02, 0.20	0.10
TG‡	2.16	1.86, 2.47	<0.001
LDL-C‡	0.17	-0.01, 0.35	0.06
HDL-C‡	-0.97	-1.10, -0.83	<0.001
Inflammatory measures			
Leukocyte count‡	0.59	0.45, 0.74	<0.001
Neutrophil count‡	0.63	0.44, 0.82	<0.001
Neutrophil ratio‡	0.04	-0.05, 0.13	0.44

* Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed by residual method and standardization.

‡ Logarithmic transformation was performed for WHR, MRI brain measures, and all cardiometabolic and inflammatory measures.

β, regression coefficient; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GMV, gray matter volume; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; SBP, systolic blood pressure; TC, total cholesterol; TCBV, total cerebral brain volume; TG, triglyceride; WHR, waist hip ratio; WMHV, white matter hyperintensity volume; WMV, white matter volume.

supplemental table 7 Associations between cardiometabolic and inflammatory measures and MRI brain measures

Cardiometabolic and inflammatory measures‡	MRI brain measures†,‡	β*	95% CI	P value
SBP	GMV	-0.86	-1.16, -0.56	<0.001
	WMHV	0.99	0.68, 1.29	<0.001
DBP	GMV	-0.75	-1.07, -0.44	<0.001
	WMHV	1.19	0.88, 1.50	<0.001
FPG	GMV	-0.52	-0.71, -0.34	<0.001
	WMHV	0.28	0.09, 0.47	0.003
HOMA-IR	GMV	-0.12	-0.18, -0.06	<0.001
	WMHV	0.22	0.16, 0.28	<0.001
TG	GMV	-0.07	-0.14, -0.002	0.04
	WMHV	0.21	0.15, 0.28	<0.001
LDL-C	GMV	-0.002	-0.12, 0.12	0.97
	WMHV	-0.10	-0.22, 0.03	0.12
HDL-C	GMV	-0.04	-0.19, 0.12	0.64
	WMHV	-0.31	-0.46, -0.15	<0.001
Leukocyte count	GMV	-0.31	-0.46, -0.16	<0.001
	WMHV	0.31	0.16, 0.46	<0.001
Neutrophil count	GMV	-0.24	-0.35, -0.13	<0.001
	WMHV	0.16	0.05, 0.27	0.01

* Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed by residual method and standardization.

‡ Logarithmic transformation was performed for MRI brain measures and all cardiometabolic and inflammatory measures.

β, regression coefficient; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GMV, gray matter volume; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; SBP, systolic blood pressure; TG, triglyceride; WMHV, white matter hyperintensity volume.

supplemental table 8 Associations between obesity indices and MRI brain measures

Obesity indices ‡	MRI brain measures†, ‡	β*	95% CI	P value
BMI	TCBV	-0.01	-0.02, 0.01	0.31
	GMV	-0.02	-0.03, -0.01	0.01
	WMV	0.01	-0.01, 0.03	0.19
	WMHV	2.66	2.16, 3.16	<0.001
WHR	TCBV	-0.02	-0.04, 0.002	0.07
	GMV	-0.04	-0.06, -0.01	0.01
	WMV	0.0003	-0.03, 0.03	0.99
	WMHV	3.67	2.75, 4.59	<0.001

* Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed by percentage of total cranial volume.

‡ Logarithmic transformation was performed for obesity indices and MRI brain measures.

β, regression coefficient; BMI, body mass index; GMV, gray matter volume; MRI, magnetic resonance imaging; TCBV, total cerebral brain volume; WHR, waist hip ratio; WMHV, white matter hyperintensity volume; WMV, white matter volume.

supplemental table 9 Associations between cardiometabolic and inflammatory measures and MRI brain measures

Cardiometabolic and inflammatory measures‡	MRI brain measures†, ‡	β*	95% CI	P value
SBP	GMV	-0.03	-0.04, -0.01	<0.001
	WMHV	1.75	1.23, 2.28	<0.001
DBP	GMV	-0.03	-0.05, -0.02	<0.001
	WMHV	2.09	1.55, 2.63	<0.001
FPG	GMV	-0.02	-0.02, -0.01	0.001
	WMHV	0.52	0.19, 0.84	0.002
HOMA-IR	GMV	-0.003	-0.01, 0.0004	0.10
	WMHV	0.40	0.29, 0.50	<0.001
TG	GMV	-0.002	-0.01, 0.001	0.27
	WMHV	0.38	0.26, 0.49	<0.001
LDL-C	GMV	-0.001	-0.01, 0.01	0.87
	WMHV	-0.17	-0.38, 0.04	0.11
HDL-C	GMV	-0.002	-0.01, 0.01	0.59
	WMHV	-0.53	-0.80, -0.26	<0.001
Leukocyte count	GMV	-0.01	-0.02, -0.004	0.004
	WMHV	0.54	0.28, 0.80	<0.001
Neutrophil count	GMV	-0.01	-0.01, -0.004	0.001
	WMHV	0.28	0.09, 0.48	0.01

* Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed by percentage of total cranial volume.

‡ Logarithmic transformation was performed for MRI brain measures and all cardiometabolic and inflammatory measures.

β, regression coefficient; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GMV, gray matter volume; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; SBP, systolic blood pressure; TG, triglyceride; WMHV, white matter hyperintensity volume.

supplemental table 10 Associations between obesity phenotype and MRI brain measures.

MRI brain measures	Total	Low BMI and low WHR‡	Low BMI and high WHR‡	High BMI and low WHR‡	High BMI and high WHR‡	P Value
TCBV, %*	68.77±2.95	68.75±3.04	68.93±2.92	69.10±2.91	68.61±2.94	0.08
GMV, %*	38.68±1.95	38.69±2.00	38.87±1.97	38.80±1.84	38.52±1.92	0.003
WMV, %*	30.09±1.88	30.07±1.84	30.07±1.84	30.30±1.84	30.09±1.92	0.64
WMHV, %*	0.10 (0.04–0.23)	0.07 (0.02–0.16)	0.09 (0.03–0.21)	0.10 (0.05–0.20)	0.13 (0.06–0.28)	0.004
TCBV, cm^3†	1032.39±100.04	1044.54±91.71	1015.03±95.95	1055.23±101.31	1036.81±105.01	<0.001
GMV, cm^3†	580.00±50.71	587.14±46.28	571.59±48.62	592.05±52.58	581.40±53.19	<0.001
WMV, cm^3†	452.39±54.72	457.40±50.88	443.44±52.74	463.18±54.29	455.41±57.23	<0.001
WMHV, cm^3†	3.10±5.18	2.54±5.58	2.95±5.77	2.85±4.01	3.54±4.54	0.003

* Expressed by percentage of total cranial volume.

† Expressed by residual method.

‡ Low BMI and low WHR: BMI < 24.0 kg/m^2 and WHR < 0.85 (Female) or WHR < 0.90 (Male); low BMI and high WHR: BMI < 24.0 kg/m^2 and WHR ≥ 0.85 (Female) or WHR ≥ 0.90 (Male); high BMI and low WHR: BMI ≥ 24.0 kg/m^2 and WHR < 0.85 (Female) or WHR < 0.90 (Male););high BMI and high WHR: BMI ≥ 24.0 kg/m^2 and WHR ≥ 0.85 (Female) or WHR ≥0.90 (Male)

supplemental table 11 Mediation analysis assessing obesity and brain volumes through cardiometabolic and inflammatory measures

			Total Effect			Natural Direct Effect			Natural Indirect Effect			Percentage Mediated		
Effector (E)	Outcome (Y)	Mediator (M)	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	estimate	95% CI	P value
BMI*, ‡	WMHV†, ‡	SBP‡	1.55	1.26, 1.84	<0.001	1.41	1.12, 1.70	<0.001	0.14	0.07, 0.2	<0.001	8.77	4.28, 13.26	<0.001
		DBP‡	1.55	1.26, 1.84	<0.001	1.39	1.10, 1.68	<0.001	0.16	0.1, 0.23	<0.001	10.43	5.93, 14.94	<0.001
		FPG‡	1.55	1.26, 1.84	<0.001	1.52	1.23, 1.81	<0.001	0.03	-0.02, 0.08	0.24	1.98	-1.31, 5.28	0.24
		HOMA-IR‡	1.55	1.26, 1.83	<0.001	1.36	1.03, 1.70	<0.001	0.19	0.01, 0.36	0.04	12.04	0.53, 23.56	0.04
		TG‡	1.55	1.26, 1.84	<0.001	1.40	1.11, 1.70	<0.001	0.15	0.07, 0.23	<0.001	9.42	4.00, 14.85	<0.001
		HDL-C‡	1.55	1.26, 1.84	<0.001	1.51	1.21, 1.81	<0.001	0.04	-0.05, 0.13	0.41	2.44	-3.35, 8.22	0.41
		Leukocyte count‡	1.55	1.26, 1.84	<0.001	1.49	1.20, 1.78	<0.001	0.06	0.01, 0.11	0.03	3.85	0.26, 7.44	0.04
		Neutrophil count‡	1.55	1.26, 1.84	<0.001	1.52	1.23, 1.81	<0.001	0.03	-0.01, 0.07	0.19	1.81	-0.89, 4.52	0.19
		Multiple mediators§	1.55	1.26, 1.84	<0.001	1.24	0.87, 1.60	<0.001	0.31	0.08, 0.55	0.01	20.20	10.10, 36.20	0.001
WHR*,‡	GMV†,‡	SBP‡	-0.68	-1.22, -0.14	0.01	-0.46	-1.00, 0.08	0.10	-0.22	-0.32, -0.12	<0.001	32.52	3.75, 61.29	0.03
		DBP‡	-0.68	-1.22, -0.14	0.01	-0.50	-1.04, 0.04	0.07	-0.19	-0.28, -0.09	<0.001	27.20	2.11, 52.29	0.03
		FPG‡	-0.68	-1.22, -0.14	0.01	-0.36	-0.91, 0.18	0.19	-0.32	-0.45, -0.18	<0.001	46.38	5.64, 87.12	0.03
		HOMA-IR‡	-0.68	-1.22, -0.14	0.01	-0.27	-0.86, 0.32	0.37	-0.42	-0.67, -0.16	<0.001	60.50	0.57, 120.43	0.048
		TG‡	-0.68	-1.22, -0.14	0.01	-0.57	-1.13, -0.02	0.04	-0.11	-0.26, 0.04	0.16	15.91	-9.65, 41.47	0.22
		Leukocyte count‡	-0.68	-1.22, -0.14	0.01	-0.51	-1.05, 0.03	0.07	-0.17	-0.27, -0.07	<0.001	24.79	0.68, 48.90	0.044
		Neutrophil count‡	-0.68	-1.22, -0.14	0.01	-0.54	-1.08, 0.004	0.052	-0.14	-0.22, -0.06	<0.001	20.89	0.70, 41.07	0.043
		Multiple mediators¶	-0.68	-1.22, -0.14	0.01	-0.15	-0.77, 0.48	0.65	-0.61	-0.95, -0.28	<0.001	78.70	4.60, 99.70	<0.001

WMHV†, ‡	SBP‡	2.12	1.59, 2.65	<0.001	1.89	1.36, 2.43	<0.001	0.22	0.12, 0.32	<0.001	10.42	5.19, 15.65	<0.001
	DBP‡	2.12	1.59, 2.65	<0.001	1.85	1.32, 2.38	<0.001	0.27	0.16, 0.37	<0.001	12.62	6.90, 18.35	<0.001
	FPG‡	2.12	1.59, 2.65	<0.001	2.04	1.49, 2.58	<0.001	0.08	-0.04, 0.20	0.21	3.70	-2.11, 9.50	0.21
	HOMA-IR‡	2.12	1.59, 2.65	<0.001	1.57	0.99, 2.16	<0.001	0.55	0.29, 0.80	<0.001	25.84	12.24, 39.45	<0.001
	TG‡	2.12	1.59, 2.65	<0.001	1.79	1.24, 2.34	<0.001	0.33	0.17, 0.48	<0.001	15.46	7.25, 23.68	<0.001
	HDL-C‡	2.12	1.59, 2.65	<0.001	1.98	1.42, 2.53	<0.001	0.14	-0.02, 0.30	0.08	6.61	-0.96, 14.17	0.09
	Leukocyte count‡	2.12	1.59, 2.65	<0.001	2.01	1.47, 2.55	<0.001	0.13	0.03, 0.22	0.01	5.86	1.30, 10.42	0.01
	Neutrophil count‡	2.12	1.59, 2.65	<0.001	2.07	1.54, 2.61	<0.001	0.06	-0.01, 0.13	0.08	2.94	-0.47, 6.35	0.09
	Multiple mediators**	2.12	1.59, 2.65	<0.001	1.37	0.73, 2.00	<0.001	0.72	0.36, 1.09	<0.001	35.50	21.90, 51.90	<0.001

* All models were adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed by residual method and z-transformation.

‡ Logarithmic transformation was performed for WMHV, GMV, BMI, WHR and all cardiometabolic and inflammatory measures.

§ Multiple mediators included SBP, DBP, HOMA-IR, TG, and leukocyte count.

¶ Multiple mediators included SBP, DBP, FPG, HOMA-IR, leukocyte count and neutrophil count.

** Multiple mediators included SBP, DBP, HOMA-IR, TG, and leukocyte count.

β, regression coefficient; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GMV, gray matter volume; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; TG, triglyceride; WHR, waist hip ratio; WMHV, white matter hyperintensity volume.

supplemental table 12 Mediation analysis assessing obesity and brain volumes through cardiometabolic and inflammatory measures

			Total Effect			Natural Direct Effect			Natural Indirect Effect			Percentage Mediated		
Effector (E)	Outcome (Y)	Mediator (M)	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	estimate	95% CI	P value
BMI*, ‡	GMV†, ‡	SBP‡	-0.02	-0.03, -0.01	0.01	-0.02	-0.03, -0.0007	0.04	-0.005	-0.01, -0.002	0.002	24.36	1.30, 47.41	0.04
		DBP‡	-0.02	-0.03, -0.01	0.01	-0.02	-0.03, -0.0009	0.04	-0.005	-0.01, -0.002	0.002	23.75	1.71, 45.80	0.03
		FPG‡	-0.02	-0.03, -0.01	0.01	-0.02	-0.03,-0.002	0.03	-0.004	-0.01, -0.001	0.01	18.08	-0.01, 36.17	0.0502
		Leukocyte count‡	-0.02	-0.03, -0.01	0.01	-0.02	-0.03, -0.002	0.02	-0.003	-0.01, -0.001	0.02	16.35	-1.36, 34.05	0.07
		Neutrophil count‡	-0.02	-0.03, -0.01	0.01	-0.02	-0.03, -0.003	0.02	-0.003	-0.01, -0.001	0.01	15.00	-0.06, 30.06	0.051
		Multiple mediators§	-0.02	-0.03, -0.01	0.01	-0.011	-0.03, 0.01	0.18	-0.01	-0.02,-0.004	0.001	47.50	14.20, 83.20	<0.001
	WMHV†, ‡	SBP‡	2.66	2.16, 3.16	<0.001	2.42	1.91, 2.92	<0.001	0.25	0.13, 0.36	<0.001	9.24	4.65, 13.83	<0.001
		DBP‡	2.66	2.16, 3.16	<0.001	2.37	1.87, 2.88	<0.001	0.29	0.17, 0.40	<0.001	10.76	6.17, 15.36	<0.001
		FPG‡	2.66	2.16, 3.16	<0.001	2.60	2.09, 3.10	<0.001	0.06	-0.03, 0.15	0.17	2.34	-1.00, 5.69	0.17
		HOMA-IR‡	2.66	2.16, 3.16	<0.001	2.28	1.70, 2.86	<0.001	0.38	0.08, 0.68	0.01	14.28	2.55, 26.01	0.02
		TG‡	2.66	2.16, 3.16	<0.001	2.40	1.88, 2.91	<0.001	0.26	0.12, 0.40	<0.001	9.89	4.38, 15.41	<0.001
		HDL-C‡	2.66	2.16, 3.16	<0.001	2.59	2.07, 3.11	<0.001	0.07	-0.09, 0.22	0.38	2.62	-3.23, 8.47	0.38
		Leukocyte count‡	2.66	2.16, 3.16	<0.001	2.55	2.04, 3.06	<0.001	0.11	0.01, 0.20	0.02	4.10	0.45, 7.75	0.03
		Neutrophil count‡	2.66	2.16, 3.16	<0.001	2.61	2.10, 3.11	<0.001	0.05	-0.02, 0.12	0.16	1.95	-0.80, 4.69	0.16
		Multiple mediators¶	2.66	2.16, 3.16	<0.001	2.06	1.42, 2.69	<0.001	0.60	0.20, 1.01	0.004	22.70	12.10, 38.40	<0.001
WHR*, ‡	GMV†, ‡	SBP‡	-0.04	-0.06, -0.01	0.01	-0.03	-0.05, -0.002	0.04	-0.01	-0.01, -0.002	0.002	19.57	0.60, 38.54	0.04
		DBP‡	-0.04	-0.06, -0.01	0.01	-0.03	-0.05, -0.002	0.04	-0.01	-0.01, -0.003	0.002	20.43	0.93, 39.92	0.04
		FPG‡	-0.04	-0.06, -0.01	0.01	-0.03	-0.05, 0.0001	0.051	-0.01	-0.01, -0.002	0.01	24.10	-0.78, 48.97	0.058
		Leukocyte count‡	-0.03	-0.06, -0.01	0.01	-0.03	-0.06, -0.003	0.03	-0.01	-0.01, -0.001	0.02	16.18	-1.60, 33.96	0.07
		Neutrophil count‡	-0.03	-0.06, -0.01	0.01	-0.03	-0.06, -0.003	0.03	-0.01	-0.01, -0.001	0.01	15.07	-0.44, 30.58	0.057

	Multiple mediators§	-0.03	-0.06, -0.01	0.01	-0.02	-0.05, 0.01	0.01	-0.02	-0.03, 0.01	0.001	49.20	14.70, 84.50	<0.001
WMHV†, ‡	SBP‡	3.67	2.75, 4.59	<0.001	3.28	2.35, 4.20	<0.001	0.39	0.22, 0.57	<0.001	10.74	5.44, 16.04	<0.001
	DBP‡	3.67	2.75, 4.59	<0.001	3.20	2.28, 4.12	<0.001	0.47	0.28, 0.66	<0.001	12.82	7.05, 18.59	<0.001
	FPG‡	3.67	2.75, 4.59	<0.001	3.52	2.57, 4.46	<0.001	0.16	-0.06, 0.37	0.15	4.24	-1.60, 10.08	0.15
	HOMA-IR‡	3.67	2.75, 4.59	<0.001	2.67	1.65, 3.68	<0.001	1.01	0.57, 1.46	<0.001	27.56	13.74, 41.38	<0.001
	TG‡	3.67	2.75, 4.59	<0.001	3.09	2.14, 4.04	<0.001	0.58	0.31, 0.85	<0.001	15.89	7.61, 24.16	<0.001
	HDL-C‡	3.67	2.75, 4.59	<0.001	3.43	2.47, 4.38	<0.001	0.25	-0.03, 0.52	0.08	6.68	-0.89, 14.25	0.08
	Leukocyte count‡	3.67	2.75, 4.59	<0.001	3.48	2.55, 4.41	<0.001	0.22	0.06, 0.39	0.01	6.06	1.48, 10.65	0.01
	Neutrophil count‡	3.67	2.75, 4.59	<0.001	3.59	2.66, 4.52	<0.001	0.11	-0.01, 0.24	0.07	3.05	-0.37, 6.48	0.08
	Multiple mediators**	3.67	2.75, 4.59	<0.001	2.30	1.21, 3.40	<0.001	1.31	0.68, 1.95	<0.001	37.20	23.20, 53.70	<0.001

* All models were adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed as percentage of total cranial volume.

‡ Logarithmic transformation was performed for WMHV, GMV, BMI, WHR and all cardiometabolic and inflammatory measures.

§ Multiple mediators included SBP, DBP, FPG, leukocyte count and neutrophil count.

¶ Multiple mediators included SBP, DBP, HOMA-IR, TG, and leukocyte count.

** Multiple mediators included SBP, DBP, HOMA-IR, TG, HDL-L, leukocyte count and neutrophil count.

β, regression coefficient; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GMV, gray matter volume; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; TG, triglyceride; WHR, waist hip ratio; WMHV, white matter hyperintensity volume.

supplemental table 13 Associations between CVAI, cardiometabolic and inflammatory measures and MRI brain measures

	β*	95% CI	P value
MRI brain measures			
TCBV†,‡	0.03	-0.06, 0.13	0.50
GMV†,‡	-0.05	-0.15, 0.06	0.37
WMV†,‡	0.09	-0.01, 0.19	0.09
WMHV†,‡	0.57	0.47, 0.67	<0.001
Cardiometabolic measures			
SBP‡	0.07	0.06, 0.09	<0.001
DBP‡	0.07	0.06, 0.08	<0.001
FPG‡	0.12	0.10, 0.14	<0.001
HOMA-IR‡	1.00	0.94, 1.05	<0.001
TC‡	0.04	0.02, 0.06	<0.001
TG‡	0.80	0.74, 0.85	<0.001
LDL-C‡	0.05	0.02, 0.09	0.002
HDL-C‡	-0.34	-0.36, -0.32	<0.001
Inflammatory measures			
Leukocyte count‡	0.16	0.13, 0.19	<0.001
Neutrophil count‡	0.17	0.13, 0.21	<0.001
Neutrophil ratio‡	0.01	-0.01, 0.03	0.22

* Adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed by residual method and standardization.

‡ Logarithmic transformation was performed for CVAI, MRI brain measures, and all cardiometabolic and inflammatory measures.

β, regression coefficient; CVAI, Chinese visceral adiposity index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GMV, gray matter volume; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; SBP, systolic blood pressure; TC, total cholesterol; TCBV, total cerebral brain volume; TG, triglyceride; WHR, waist hip ratio; WMHV, white matter hyperintensity volume; WMV, white matter volume.

supplemental table 14 Mediation analysis assessing CVAI and brain volumes through cardiometabolic and inflammatory measures

			Total Effect			Natural Direct Effect			Natural Indirect Effect			Percentage Mediated		
Effector (E)	Outcome (Y)	Mediator (M)	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	estimate	95% CI	P value
CVAI*,‡	WMHV†,‡	SBP‡	0.57	0.47, 0.67	<0.001	0.52	0.42, 0.63	<0.001	0.05	0.02, 0.07	0.001	8.35	4.01, 12.69	<0.001
		DBP‡	0.57	0.47, 0.67	<0.001	0.51	0.41, 0.61	<0.001	0.06	0.04, 0.08	<0.001	10.37	5.86, 14.87	<0.001
		FPG‡	0.57	0.47, 0.67	<0.001	0.56	0.46, 0.67	<0.001	0.01	-0.02, 0.03	0.54	1.25	-2.75, 5.25	0.54
		HOMA-IR‡	0.57	0.47, 0.67	<0.001	0.53	0.41, 0.66	<0.001	0.04	-0.03, 0.11	0.3	6.82	-6.15, 19.78	0.30
		TG‡	0.57	0.47, 0.67	<0.001	0.55	0.43, 0.66	<0.001	0.02	-0.04, 0.08	0.44	4.21	-6.51, 14.93	0.44
		HDL-C‡,¶	0.57	0.47, 0.67	<0.001	0.63	0.51, 0.75	<0.001	-0.06	-0.12, 0.01	0.051	—	—	—
		Leukocyte count‡	0.57	0.47, 0.68	<0.001	0.55	0.45, 0.66	<0.001	0.02	-0.01, 0.04	0.12	3.39	-0.87, 7.66	0.12
		Neutrophil count‡	0.57	0.47, 0.68	<0.001	0.57	0.46, 0.67	<0.001	0.01	-0.01, 0.03	0.42	1.36	-1.96, 4.69	0.42
		Multiple mediator§	0.57	0.47, 0.68	<0.001	0.51	0.40,0.61	0.054	0.06	0.03,0.09	0.02	10.80	6.70,17.00	<0.001

* All models were adjusted for age, sex, current smoking, current drinking, ethnicity, and educational level.

† Expressed by residual method and standardization.

‡ Logarithmic transformation was performed for WMHV, CVAI, and all cardiometabolic and inflammatory measures.

§ Multiple mediators included SBP and DBP.

¶ Proportions of the total association not given because the nonsignificance of the total association would lead to numerically instable numbers.

β, regression coefficient; CVAI, Chinese visceral adiposity index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; TG, triglyceride; WHR, waist hip ratio; WMHV, white matter hyperintensity volume.