

Supplementary Material

Frenzel et al. “Left Ventricular Hypertrophy as a Risk Factor for Accelerated Brain Ageing: Results from the Study of Health in Pomerania”

Supplementary Text 1: Data collection.

Supplementary Figure 1: Calibration of brain age scores.

Supplementary Figure 2: Prediction plots of inverse probability weighting (step 1).

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Supplementary Figure 5: Values of Cook’s distance and DFBETA for model 1 of global cortical thickness.

Supplementary Figure 6: Point estimates of direct effects of LVMI on regional cortical thickness at follow-up (model 2).

Supplementary Tables 1-8: Analyses of variance (model 1-3).

Supplementary Table 9: Point estimates of direct effects of LVMI on regional cortical thicknesses at follow-up (model 2).

Supplementary Tables 10-17: Analyses of variance (model 1-3; complete case analyses).

Supplementary Text 1 – Data Collection

Medical history and socio-demographic variables were assessed by standardized questionnaires during a computer-assisted face-to-face interview. Employment status was defined by four categories (0=unemployed; 1=student; 2=employed; 3=pensioner). Marital status was defined by 4 categories (1=single, living alone=1; 2=living together with partner; 3=divorced, living alone; 4=widows, living alone). Smoking status (0=never, 1=former, 2=current) and alcohol consumption (in g/d during last 30 days) were assessed based on questionnaires. Blood pressure (BP), body height, body weight, and waist circumference were measured during subsequent medical examinations. BP was measured three times from the right brachial artery after a 10-minute rest in a supine position and the average of the second and third measurement was considered. Pulse pressure was calculated as the difference between systolic and diastolic BP.

Hypertension was defined according ISH-WHO 1999 (1=either systolic BP \geq 140mmHg, or diastolic BP \geq 90mmHg, or intake of antihypertensive medications; 0=otherwise).

Diabetes (1=yes; 0=no) was defined either based on self-report, intake of anti-diabetic medication (anatomical-therapeutic-chemical [ATC] code A10), glycated hemoglobin \geq 6.5% (International Expert Committee 2009), or blood glucose \geq 11.1 mmol/l (IDF-WHO 2006).

Antihypertensive medication was defined by ATC codes C02A, C02CA, C03C, C03E, C04A, C07A, C08C, C08DA, C09AA, C09CA. Lipid-lowering medication was defined by ATC codes C10AA and C10AB.

Echocardiography, electrocardiography, and collection of blood samples were performed during the day of the interview. Blood samples were taken from the cubital vein of the fasting participants and analysed directly or stored at -80°C in the Integrated Research Biobank of the University Medicine Greifswald ¹. Glomerular filtration rate was calculated from serum creatinine and cystatin c according to the CKD-EPI equation ².

Brain MRI was performed during a second visit with a median time interval of 15 days (max. 345 days). Follow-up examinations of similar extent were conducted about 7 years later (median 7.3 years; max. 10.2 years). Again, MRIs were performed during a second visit with a median time interval of 22 days (max. 750 days).

Electrocardiography

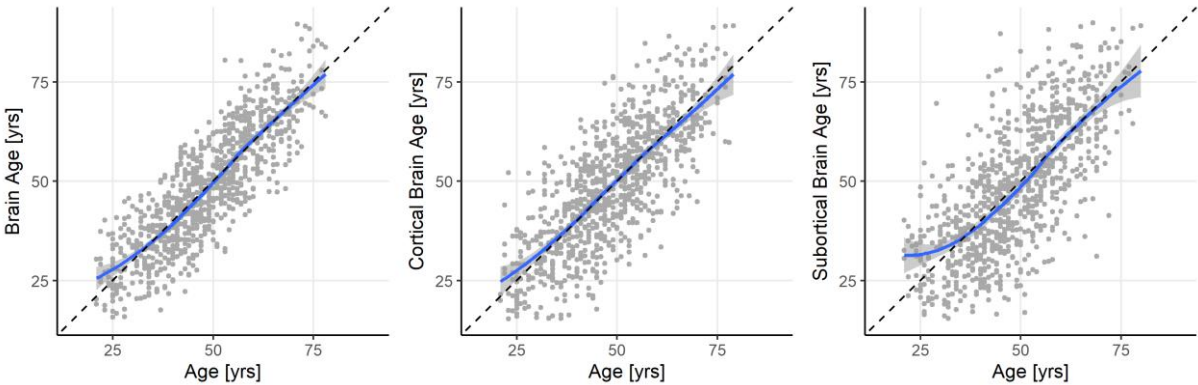
A standard ten second twelve lead electrocardiography was conducted after resting for five minutes in supine position. Electrocardiograms were analyzed using the analysis system MEANS³.

Brain MRI

T₁-weighted and T₂-weighted fluid-attenuated inversion recovery (FLAIR) scans of the brain were obtained using a 1.5T Siemens Magnetom Avanto scanner (Siemens Healthineers, Erlangen, Germany)^{4,5}. The following parameters were used: T₁: orientation=axial plane, TR=1,900ms, TE=3.37ms, flip angle 15°, slice thickness=1mm, and resolution 1mm x 1mm, FLAIR: orientation=axial plane, TR=5,000ms, TE=325ms, slice thickness=3mm, and resolution 0.9mm × 0.9mm.

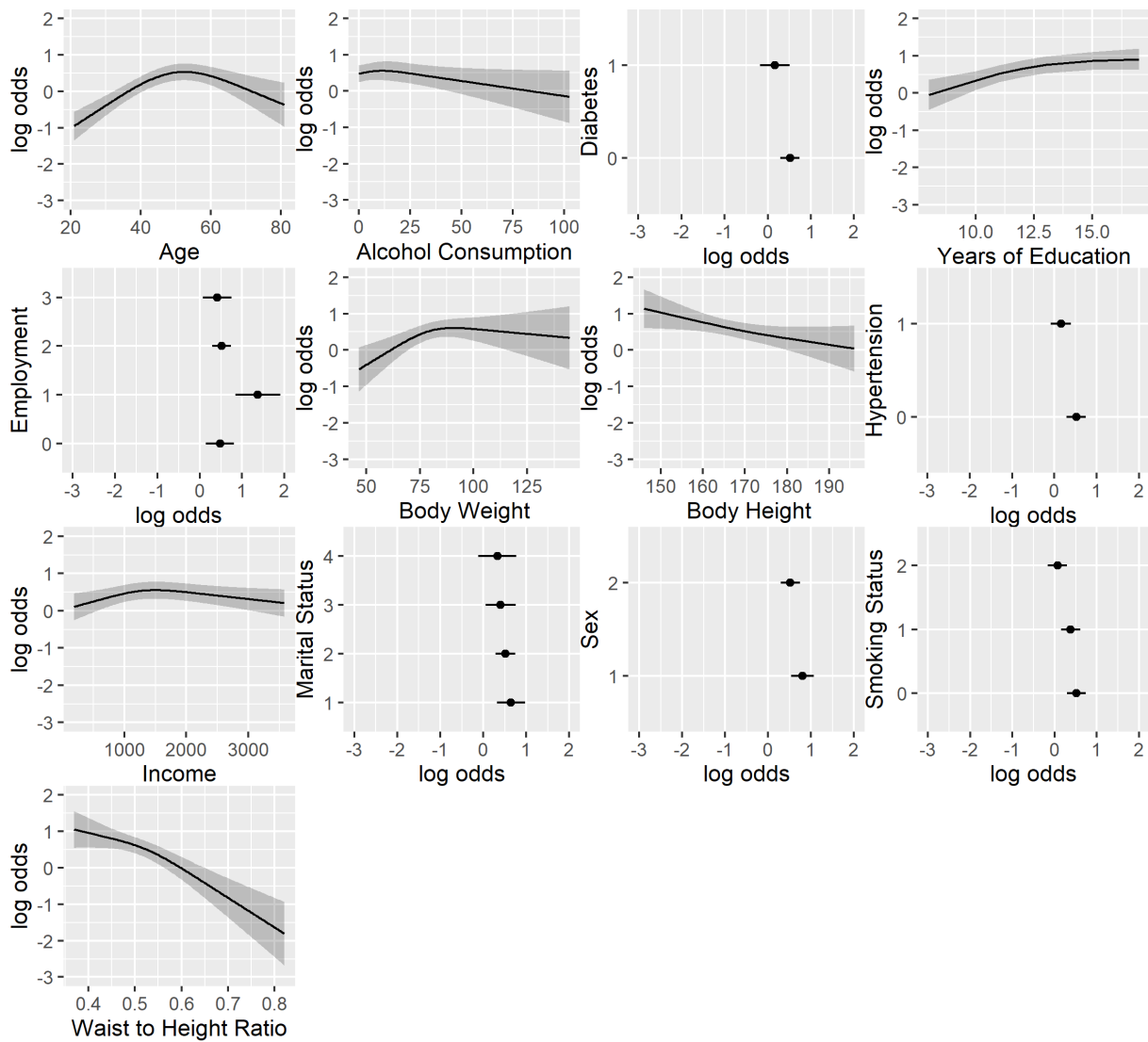
1. Winter T, Friedrich N, Lamp S, Schäfer C, Schattschneider M, Bollmann S, Brümmer D, Riemann K, Petersmann A, Nauck M. The Integrated Research Biobank of the University Medicine Greifswald. **Open Journal of Bioresources**. 2020; 7:2.
2. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. **N Engl J Med**. 2012; 367:20–29.
3. van Bommel JH, Kors JA, van Herpen G. Methodology of the modular ECG analysis system MEANS. **Methods Inf Med**. 1990; 29:346–353.
4. Hegenscheid K, Kühn JP, Völzke H, Biffar R, Hosten N, Puls R. Whole-body magnetic resonance imaging of healthy volunteers: pilot study results from the population-based SHIP study. **Rofo**. 2009; 181:748–759.
5. Hosten N, Bülow R, Völzke H, Domin M, Schmidt CO, Teumer A, Ittermann T, Nauck M, Felix S, Dörr M, et al. SHIP-MR and Radiology: 12 Years of Whole-Body Magnetic Resonance Imaging in a Single Center. **Healthcare**. 2022; 10:33.

Supplementary Figure 1 – Calibration of Brain Age Scores



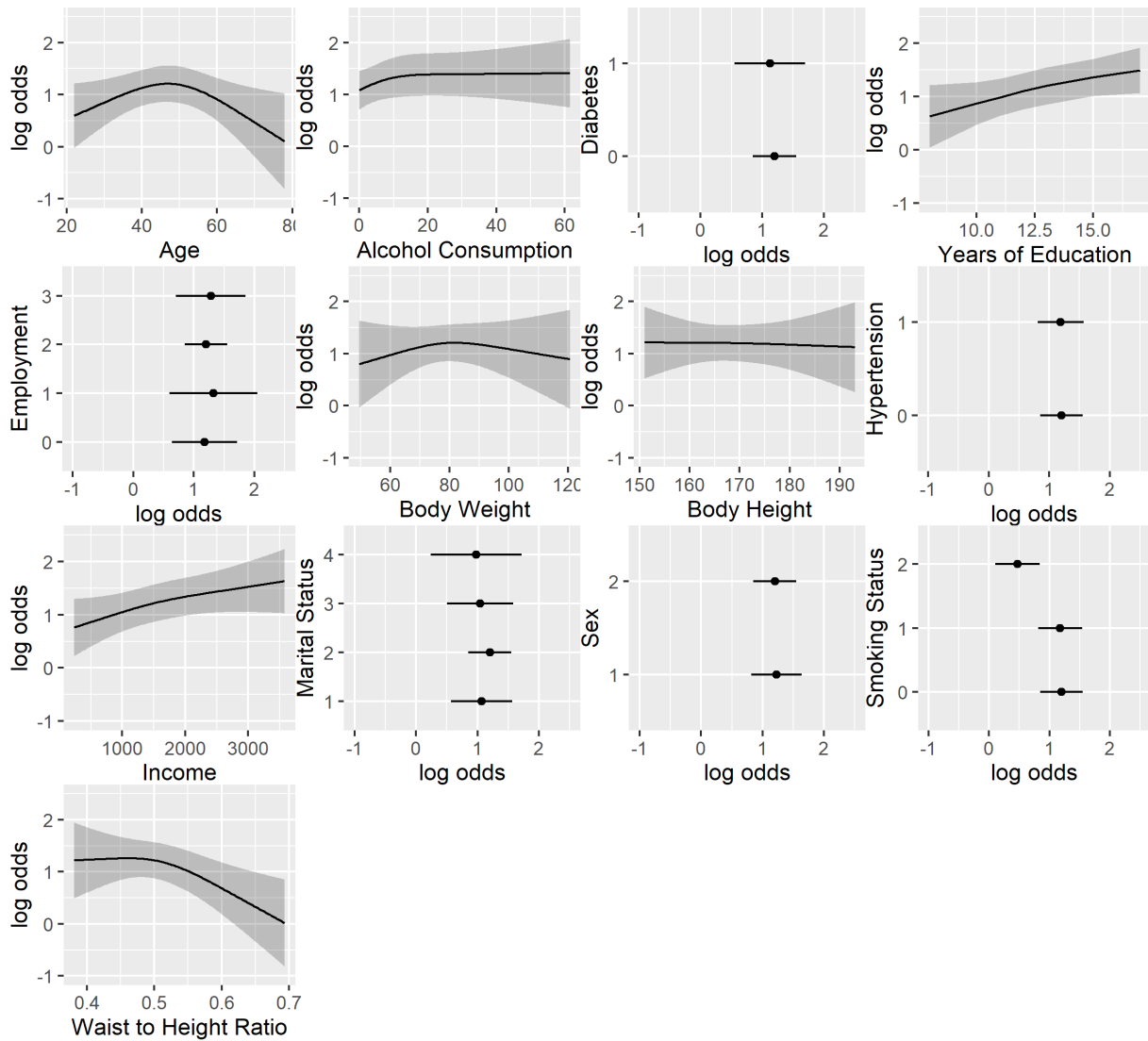
Supplementary Figure 1: Estimated brain age scores at baseline versus chronological age at baseline (n=926).

Supplementary Figure 2 – Inverse Probability Weighting (Step 1)



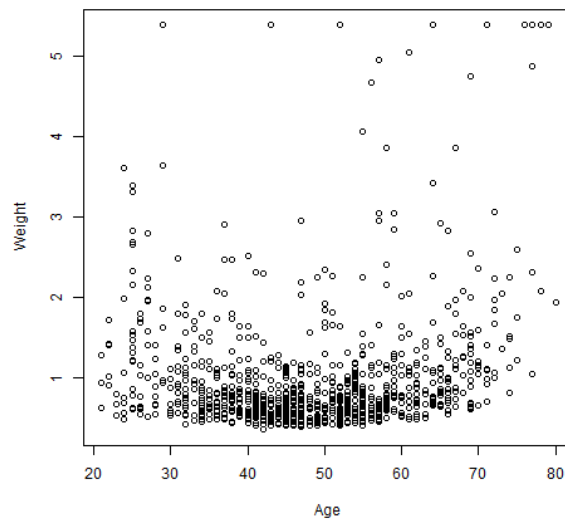
Supplementary Figure 2: For participants without history of myocardial infarction or stroke, availability of echocardiography and brain MRI at baseline was modelled by logistic regressions on baseline values of socio-demographic variables, smoking status, alcohol consumption, diabetes, hypertension, and waist-to-height ratio (AUC=0.680).

Supplementary Figure 3 – Inverse Probability Weighting (Step 2)



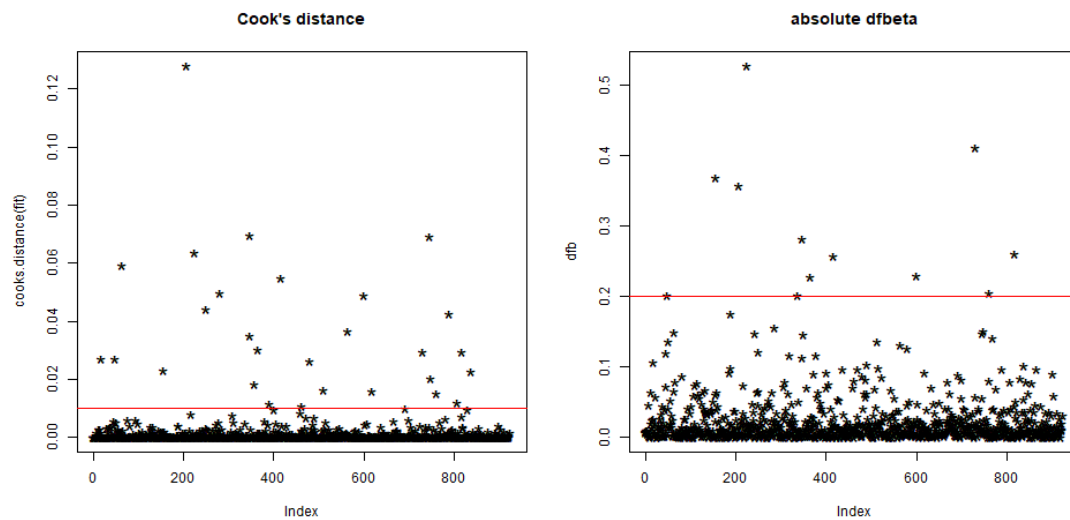
Supplementary Figure 3: For participants who underwent echocardiography and brain MRI at baseline, availability of brain MRI at the follow-up was modelled by logistic regressions on baseline values of socio-demographic variables, smoking status, alcohol consumption, diabetes, hypertension, and waist-to-height ratio (AUC=0.681).

Supplementary Figure 4



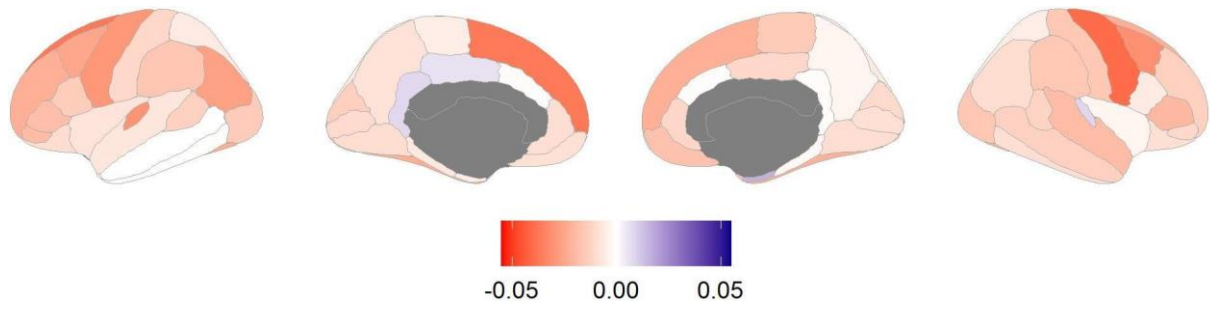
Supplementary Figure 4: Sample weights used in the regression analyses. 10 cases were trimmed down to the 99% quantile of 5.3.

Supplementary Figure 5



Supplementary Figure 5: Values of Cook's distance (left) and absolute values of DFBETA (right) for the base model (model 1) of global cortical thickness. Highly influential points were defined by the thresholds 0.01 and 0.2, respectively (indicated by red lines), and were excluded from the analyses ($n=29$).

Supplementary Figure 6



Supplementary Figure 6: Point estimates of direct effects of left ventricular mass index on regional cortical thickness at follow-up. Effects adjusted for socio-demographic factors, anthropometric variables, lifestyle factors, cardiovascular risk factors and medication, follow-up time, and baseline value of the outcome (model 2).

Supplementary Table 1 – Total Brain Volume

Variable	model 1 (n=891)					model 2 (n=885)				model 3 (n=885)			
	df	SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	1579.3	789.6	7.5	0.0006	1585.2	792.6	7.7	0.0005	1784.5	892.3	8.7	0.0002
Baseline value of outcome	2	1311559	655779.5	6231.7	< 0.0001	1367375	683687.3	6629.9	< 0.0001	1375806	687903.1	6689	< 0.0001
Age	4	24065.5	6016.4	57.2	< 0.0001	18926.6	4731.7	45.9	< 0.0001	20877.8	5219.5	50.8	< 0.0001
Sex	3	2823.9	941.3	8.9	< 0.0001	3011.2	1003.7	9.7	< 0.0001	2850.2	950.1	9.2	< 0.0001
Age * Sex	2	2821.2	1410.6	13.4	< 0.0001	3011	1505.5	14.6	< 0.0001	2849.9	1425	13.9	< 0.0001
Intracranial Volume	2	302.1	151.1	1.4	0.2386	160.5	80.2	0.8	0.4596	309.9	154.9	1.5	0.2223
Body height	2	1047.6	523.8	5	0.0071	1382.2	691.1	6.7	0.0013	1138	569	5.5	0.0041
Body weight	2	154	77	0.7	0.4815	197.4	98.7	1	0.3844	206.5	103.2	1	0.3669
Years of education	2	170.5	85.3	0.8	0.4451	143.9	72	0.7	0.4979	91.9	45.9	0.4	0.6398
Employment	3	154.2	51.4	0.5	0.6903	400.9	133.6	1.3	0.2746	439.9	146.6	1.4	0.2338
Income	2	535.4	267.7	2.5	0.0792	536.8	268.4	2.6	0.0747	399.5	199.8	1.9	0.144
Marital status	3	1470.4	490.1	4.7	0.0031	2244	748	7.3	< 0.0001	2156.6	718.9	7	0.0001
Smoking status	2	587.2	293.6	2.8	0.062	772.7	386.4	3.7	0.024	537	268.5	2.6	0.0741
Alcohol consumption	2	165.9	83	0.8	0.4549	230.9	115.5	1.1	0.3269	403.7	201.8	2	0.1412
Left Ventricular Mass Index	2	191.3	95.7	0.9	0.4033	62.8	31.4	0.3	0.7376	186.3	93.2	0.9	0.4046
Diabetes	1					278.1	278.1	2.7	0.1009	436.1	436.1	4.2	0.0398
Hypertension	1					39.8	39.8	0.4	0.5346	1.3	1.3	0	0.912
Waist to height ratio	2					691	345.5	3.4	0.0355	776.4	388.2	3.8	0.0233
Cholesterol ratio	4					126.8	31.7	0.3	0.8731	101.4	25.4	0.2	0.9118
Intake of lipid-lowering drugs	3					93.8	31.3	0.3	0.8231	53.1	17.7	0.2	0.9153
Intake of antihypertensive drugs	5					2239.4	447.9	4.3	0.0007	2030	406	3.9	0.0015
Pulse pressure	4					526.2	131.6	1.3	0.2779	479.8	120	1.2	0.3242
Diastolic BP	4					1886.6	471.7	4.6	0.0012	1773.3	443.3	4.3	0.0019
Cholesterol ratio * Intake of lipid-lowering drugs	2					64.6	32.3	0.3	0.7313	48.4	24.2	0.2	0.7902
Pulse pressure * Intake of antihypertensive drugs	2					276.1	138	1.3	0.2628	171.4	85.7	0.8	0.435
Diastolic BP * Intake of antihypertensive drugs	2					1790.3	895.1	8.7	0.0002	1644.1	822	8	0.0004
E/e'	2									173.5	86.7	0.8	0.4306
E/A	2									546.3	273.2	2.7	0.0708
Left atrial size index	2									99.4	49.7	0.5	0.6168
Total	Σdf	17332425	559110.5	5313.1	< 0.0001	17780075	362858.7	3518.8	< 0.0001	18602175	338221.4	3288.8	< 0.0001
Error	n-Σdf	90395.2	105.2			86106.1	103.1			85255	102.8		

Supplementary Table 1: Analyses of variance of model 1, 2, and 3 of total brain volume (imputed analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 2 – Subcortical Gray Matter Volume

Variable	df	model 1 (n=891)				model 2 (n=885)				model 3 (n=885)			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	8.2	4.1	7.3	0.0007	8.9	4.4	8.3	0.0003	9.5	4.7	8.9	0.0001
Baseline value of outcome	2	7562	3781	6686.2	< 0.0001	7011.8	3505.9	6584.8	< 0.0001	7125.1	3562.6	6691.5	< 0.0001
Age	4	84.7	21.2	37.4	< 0.0001	71	17.7	33.3	< 0.0001	58.1	14.5	27.3	< 0.0001
Sex	3	3.8	1.3	2.2	0.0816	3.8	1.3	2.4	0.0687	4	1.3	2.5	0.0587
Age * Sex	2	3.7	1.8	3.2	0.0399	3.7	1.9	3.5	0.0304	3.7	1.9	3.5	0.0305
Intracranial Volume	2	6	3	5.3	0.005	5.1	2.6	4.8	0.0083	5.3	2.7	5	0.007
Body height	2	0	0	0	0.9867	0.1	0.1	0.1	0.9069	0.1	0	0.1	0.926
Body weight	2	2.9	1.5	2.6	0.0749	2.5	1.2	2.3	0.0969	1.6	0.8	1.5	0.2223
Years of education	2	0.2	0.1	0.2	0.8116	0.1	0	0.1	0.9168	0.1	0.1	0.1	0.8803
Employment	3	2.2	0.7	1.3	0.2683	0.9	0.3	0.6	0.6416	0.8	0.3	0.5	0.6746
Income	2	1.1	0.5	1	0.3824	0.8	0.4	0.7	0.483	0.5	0.2	0.4	0.6493
Marital status	3	14.3	4.8	8.4	< 0.0001	11.7	3.9	7.3	< 0.0001	8.4	2.8	5.2	0.0014
Smoking status	2	5	2.5	4.4	0.0123	4.4	2.2	4.1	0.0162	4	2	3.7	0.0242
Alcohol consumption	2	4.9	2.5	4.4	0.013	2.7	1.4	2.5	0.0792	3.5	1.8	3.3	0.0373
Left Ventricular Mass Index	2	0.4	0.2	0.4	0.6758	0.3	0.1	0.2	0.7847	0	0	0	0.9706
Diabetes	1					0.1	0.1	0.1	0.7401	0	0	0	0.9523
Hypertension	1					0.5	0.5	1	0.3234	0.5	0.5	0.9	0.354
Waist to height ratio	2					2.3	1.2	2.2	0.1147	1.3	0.7	1.2	0.2929
Cholesterol ratio	4					1.5	0.4	0.7	0.5945	2.9	0.7	1.4	0.2432
Intake of lipid-lowering drugs	3					1.3	0.4	0.8	0.5018	2	0.7	1.2	0.301
Intake of antihypertensive drugs	5					3.9	0.8	1.5	0.2031	3.9	0.8	1.5	0.1968
Pulse pressure	4					4.4	1.1	2	0.086	5.2	1.3	2.5	0.0443
Diastolic BP	4					2.3	0.6	1.1	0.3674	2.3	0.6	1.1	0.3726
Cholesterol ratio * Intake of lipid-lowering drugs	2					0.6	0.3	0.6	0.5469	1.7	0.8	1.6	0.2057
Pulse pressure * Intake of antihypertensive drugs	2					1.4	0.7	1.3	0.2762	1.8	0.9	1.7	0.1883
Diastolic BP * Intake of antihypertensive drugs	2					2	1	1.8	0.1596	1.9	0.9	1.8	0.1728
E/e'	2									4.3	2.1	4	0.0182
E/A	2									0.8	0.4	0.8	0.4599
Left atrial size index	2									2.7	1.3	2.5	0.0835
Total	Σdf	44035.5	1420.5	2512	< 0.0001	44838.6	915.1	1718.7	< 0.0001	46445.2	844.5	1586.1	< 0.0001
Error	n-Σdf	485.8	0.6			444.6	0.5			441.4	0.5		

Supplementary Table 2: Analyses of variance of model 1, 2, and 3 of subcortical gray matter volume (imputed analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 3 – White Matter Volume

Variable	model 1 (n=894)					model 2 (n=894)				model 3 (n=892)			
	df	SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	176.7	88.4	1.2	0.3165	307.8	153.9	2	0.1369	441	220.5	2.9	0.0562
Baseline value of outcome	2	796195.5	398097.7	5189	< 0.0001	799399.6	399699.8	5175.6	< 0.0001	812829.3	406414.7	5324.7	< 0.0001
Age	4	20946.3	5236.6	68.3	< 0.0001	17960.2	4490.1	58.1	< 0.0001	14048.1	3512	46	< 0.0001
Sex	3	2512.1	837.4	10.9	< 0.0001	1822.4	607.5	7.9	< 0.0001	1699.4	566.5	7.4	< 0.0001
Age * Sex	2	2475.1	1237.5	16.1	< 0.0001	1797.8	898.9	11.6	< 0.0001	1674.3	837.1	11	< 0.0001
Intracranial Volume	2	882.8	441.4	5.8	0.0033	620.7	310.3	4	0.0183	489.1	244.5	3.2	0.0411
Body height	2	693.3	346.6	4.5	0.0112	749.1	374.5	4.8	0.008	789.1	394.5	5.2	0.0059
Body weight	2	124.1	62	0.8	0.4457	47.4	23.7	0.3	0.736	47.6	23.8	0.3	0.7321
Years of education	2	149.1	74.6	1	0.3788	115.8	57.9	0.7	0.4727	120.6	60.3	0.8	0.4543
Employment	3	271.5	90.5	1.2	0.3164	420.9	140.3	1.8	0.1425	338.4	112.8	1.5	0.2191
Income	2	944	472	6.2	0.0022	627.3	313.7	4.1	0.0176	600	300	3.9	0.02
Marital status	3	302.3	100.8	1.3	0.2688	197.3	65.8	0.9	0.4658	212.3	70.8	0.9	0.427
Smoking status	2	16.4	8.2	0.1	0.8988	18.7	9.4	0.1	0.8858	6.7	3.4	0	0.957
Alcohol consumption	2	45.2	22.6	0.3	0.7449	72	36	0.5	0.6275	41.1	20.6	0.3	0.7639
Left Ventricular Mass Index	2	66.4	33.2	0.4	0.6488	62.5	31.3	0.4	0.6673	73.6	36.8	0.5	0.6178
Diabetes	1					509.7	509.7	6.6	0.0104	596	596	7.8	0.0053
Hypertension	1					42.7	42.7	0.6	0.4575	64.7	64.7	0.8	0.3573
Waist to height ratio	2					247.4	123.7	1.6	0.2021	297.6	148.8	1.9	0.143
Cholesterol ratio	4					175.3	43.8	0.6	0.6863	294.9	73.7	1	0.4254
Intake of lipid-lowering drugs	3					391.8	130.6	1.7	0.1674	665.7	221.9	2.9	0.0338
Intake of antihypertensive drugs	5					237.3	47.5	0.6	0.6888	144.6	28.9	0.4	0.8634
Pulse pressure	4					412.9	103.2	1.3	0.2545	340	85	1.1	0.3488
Diastolic BP	4					285.5	71.4	0.9	0.4491	315.6	78.9	1	0.3888
Cholesterol ratio * Intake of lipid-lowering drugs	2					168.9	84.5	1.1	0.3355	289.8	144.9	1.9	0.1505
Pulse pressure * Intake of antihypertensive drugs	2					152.6	76.3	1	0.3727	116.3	58.2	0.8	0.467
Diastolic BP * Intake of antihypertensive drugs	2					11.4	5.7	0.1	0.9291	0.6	0.3	0	0.996
E/é	2									184.6	92.3	1.2	0.2988
E/A	2									95.9	48	0.6	0.5336
Left atrial size index	2									47.1	23.5	0.3	0.7347
Total	Σdf	4854462	156595.5	2041.1	< 0.0001	5285459	107866.5	1396.7	< 0.0001	5417685	98503.4	1290.6	< 0.0001
Error	n-Σdf	66132.2	76.7			65179.8	77.2			63808.5	76.3		

Supplementary Table 3: Analyses of variance of model 1, 2, and 3 of white matter volume (imputed analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 4 – White Matter Hyperintensities Volume

Variable	df	model 1 (N=890)				model 2 (n=889)				model 3 (n=890)			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	0.4	0.2	0.3	0.7768	1.2	0.6	0.8	0.4424	1	0.5	0.7	0.5056
Baseline value of outcome	2	3248.2	1624.1	2128.8	< 0.0001	3095.8	1547.9	2070	< 0.0001	3087.6	1543.8	2094.3	< 0.0001
Age	4	71.9	18	23.6	< 0.0001	72.2	18	24.1	< 0.0001	57.1	14.3	19.4	< 0.0001
Sex	3	48.7	16.2	21.3	< 0.0001	32	10.7	14.3	< 0.0001	22.8	7.6	10.3	< 0.0001
Age * Sex	2	32.3	16.1	21.2	< 0.0001	21.5	10.8	14.4	< 0.0001	16.1	8	10.9	< 0.0001
Intracranial Volume	2	12.1	6	7.9	0.0004	14.7	7.3	9.8	< 0.0001	11.9	6	8.1	0.0003
Body height	2	3.3	1.6	2.2	0.1157	2	1	1.4	0.2583	3.4	1.7	2.3	0.1034
Body weight	2	4.2	2.1	2.8	0.0643	0.7	0.3	0.5	0.6338	2.3	1.1	1.5	0.2132
Years of education	2	0.2	0.1	0.1	0.8859	0.3	0.2	0.2	0.7932	0.4	0.2	0.3	0.7774
Employment	3	6	2	2.6	0.0495	5.5	1.8	2.4	0.0627	5.9	2	2.7	0.046
Income	2	0.5	0.3	0.4	0.7015	0.2	0.1	0.1	0.8715	0	0	0	0.992
Marital status	3	2.1	0.7	0.9	0.4241	5.9	2	2.6	0.0501	3.3	1.1	1.5	0.2194
Smoking status	2	6.3	3.1	4.1	0.0169	8.7	4.3	5.8	0.0032	8.7	4.4	5.9	0.0028
Alcohol consumption	2	3	1.5	1.9	0.1433	2.6	1.3	1.8	0.173	3.2	1.6	2.2	0.112
Left Ventricular Mass Index	2	4.7	2.3	3.1	0.0472	3.4	1.7	2.3	0.1045	3.1	1.5	2.1	0.1244
Diabetes	1					3.6	3.6	4.8	0.0279	4.1	4.1	5.5	0.0188
Hypertension	1					0.3	0.3	0.4	0.5155	0.4	0.4	0.6	0.4509
Waist to height ratio	2					0.3	0.1	0.2	0.8282	1.3	0.6	0.9	0.4234
Cholesterol ratio	4					6.4	1.6	2.1	0.0738	8.6	2.1	2.9	0.0209
Intake of lipid-lowering drugs	3					9.4	3.1	4.2	0.0058	12.2	4.1	5.5	0.001
Intake of antihypertensive drugs	5					2.3	0.5	0.6	0.6953	1.1	0.2	0.3	0.9148
Pulse pressure	4					3.7	0.9	1.2	0.3003	5.2	1.3	1.7	0.1376
Diastolic BP	4					4.8	1.2	1.6	0.1683	3.1	0.8	1.1	0.3755
Cholesterol ratio * Intake of lipid-lowering drugs	2					5.4	2.7	3.6	0.0283	7.1	3.6	4.8	0.0082
Pulse pressure * Intake of antihypertensive drugs	2					0	0	0	0.9805	0.3	0.2	0.2	0.8108
Diastolic BP * Intake of antihypertensive drugs	2					2.2	1.1	1.5	0.2306	0.9	0.5	0.6	0.5288
E/e'	2									8.3	4.2	5.6	0.0037
E/A	2									0.8	0.4	0.5	0.5855
Left atrial size index	2									7.8	3.9	5.3	0.0052
Total	Σdf	16073.7	518.5	679.6	< 0.0001	16885.5	344.6	460.8	< 0.0001	16590.7	301.6	409.2	< 0.0001
Error	n-Σdf	654.6	0.8			627.4	0.7			614.8	0.7		

Supplementary Table 4: Analyses of variance of model 1, 2, and 3 of white matter hyperintensities volume (imputed analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 5 – Global Cortical Thickness

Variable	df	model 1 (n=896)				model 2 (n=889)				model 3 (n=888)			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	0.0016	0.0008	0.6	0.5326	0.0019	0.001	0.8	0.4586	0.0038	0.0019	1.6	0.2109
Baseline value of outcome	2	6.0825	3.0412	2427.7	< 0.0001	5.5177	2.7588	2228	< 0.0001	6.0988	3.0494	2529.7	< 0.0001
Age	4	0.0612	0.0153	12.2	< 0.0001	0.0481	0.012	9.7	< 0.0001	0.043	0.0107	8.9	< 0.0001
Sex	3	0.0014	0.0005	0.4	0.7658	0.0024	0.0008	0.6	0.5882	0.0043	0.0014	1.2	0.3166
Age * Sex	2	0.001	0.0005	0.4	0.6724	0.0021	0.0011	0.9	0.4202	0.0029	0.0014	1.2	0.3023
Intracranial Volume	2	0.0041	0.002	1.6	0.1991	0.0097	0.0049	3.9	0.0201	0.0083	0.0042	3.5	0.032
Body height	2	0.0065	0.0033	2.6	0.074	0.0029	0.0015	1.2	0.308	0.0042	0.0021	1.7	0.1766
Body weight	2	0.0006	0.0003	0.2	0.8006	0.0018	0.0009	0.7	0.4907	0.0008	0.0004	0.3	0.7226
Years of education	2	0.0039	0.002	1.6	0.2113	0.0019	0.0009	0.8	0.4712	0.0021	0.001	0.9	0.4206
Employment	3	0.0023	0.0008	0.6	0.6128	0.0049	0.0016	1.3	0.2656	0.0037	0.0012	1	0.3838
Income	2	0.0001	0.0001	0.1	0.9476	0.0013	0.0006	0.5	0.5918	0.0002	0.0001	0.1	0.9045
Marital status	3	0.014	0.0047	3.7	0.0113	0.008	0.0027	2.1	0.0937	0.012	0.004	3.3	0.0192
Smoking status	2	0.0068	0.0034	2.7	0.0656	0.0058	0.0029	2.4	0.0955	0.0027	0.0013	1.1	0.3323
Alcohol consumption	2	0.012	0.006	4.8	0.0086	0.009	0.0045	3.6	0.0272	0.0115	0.0057	4.8	0.0088
Left Ventricular Mass Index	2	0.0234	0.0117	9.3	< 0.0001	0.0229	0.0114	9.2	0.0001	0.0215	0.0108	8.9	0.0001
Diabetes	1					0.0131	0.0131	10.5	0.0012	0.0145	0.0145	12	0.0005
Hypertension	1					0.0024	0.0024	2	0.1616	0.0018	0.0018	1.5	0.2202
Waist to height ratio	2					0.0085	0.0042	3.4	0.0334	0.007	0.0035	2.9	0.0562
Cholesterol ratio	4					0.003	0.0008	0.6	0.6554	0.0034	0.0008	0.7	0.5948
Intake of lipid-lowering drugs	3					0.0022	0.0007	0.6	0.624	0.0017	0.0006	0.5	0.6975
Intake of antihypertensive drugs	5					0.0051	0.001	0.8	0.5383	0.0041	0.0008	0.7	0.6405
Pulse pressure	4					0.0008	0.0002	0.2	0.954	0.0036	0.0009	0.8	0.5577
Diastolic BP	4					0.0047	0.0012	1	0.4301	0.0037	0.0009	0.8	0.5474
Cholesterol ratio * Intake of lipid-lowering drugs	2					0.0004	0.0002	0.2	0.8465	0.0004	0.0002	0.2	0.8455
Pulse pressure * Intake of antihypertensive drugs	2					0.0003	0.0001	0.1	0.8997	0.0017	0.0008	0.7	0.5018
Diastolic BP * Intake of antihypertensive drugs	2					0.0046	0.0023	1.8	0.1582	0.0031	0.0016	1.3	0.2752
E/é	2									0.001	0.0005	0.4	0.6711
E/A	2									0.0016	0.0008	0.7	0.5086
Left atrial size index	2									0.0019	0.0009	0.8	0.4565
Total	∑df	24.3193	0.7845	626.2	< 0.0001	25.4333	0.519	419.2	< 0.0001	30.9778	0.5632	467.2	< 0.0001
Error	n-∑df	1.0824	0.0013			1.0389	0.0012			1.0029	0.0012		

Supplementary Table 5: Analyses of variance of model 1, 2, and 3 of global cortical thickness (imputed analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 6 – Cortical Brain Age

Variable	df	model 1 (n=885)				model 2 (n=886)				model 3 (n=886)			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	225	112.5	3.8	0.0235	505.9	253	8.8	0.0002	469.1	234.6	8.1	0.0003
Baseline value of outcome	2	62306	31153	1043.1	< 0.0001	64597.8	32298.9	1124.1	< 0.0001	65545.2	32772.6	1133.4	< 0.0001
Age	4	1021.1	255.3	8.5	< 0.0001	1098.1	274.5	9.6	< 0.0001	919.8	230	8	< 0.0001
Sex	3	669.5	223.2	7.5	< 0.0001	773.4	257.8	9	< 0.0001	742.2	247.4	8.6	< 0.0001
Age * Sex	2	634.6	317.3	10.6	< 0.0001	762.6	381.3	13.3	< 0.0001	722.7	361.3	12.5	< 0.0001
Intracranial Volume	2	222.6	111.3	3.7	0.0245	185.7	92.8	3.2	0.04	160.4	80.2	2.8	0.0631
Body height	2	9.7	4.8	0.2	0.8507	17.4	8.7	0.3	0.7387	15.5	7.7	0.3	0.7652
Body weight	2	29.5	14.7	0.5	0.6107	92.4	46.2	1.6	0.2011	72.7	36.4	1.3	0.2848
Years of education	2	125.3	62.7	2.1	0.1233	63.6	31.8	1.1	0.3312	67.5	33.7	1.2	0.312
Employment	3	75.7	25.2	0.8	0.4695	42.5	14.2	0.5	0.6872	33.5	11.2	0.4	0.7629
Income	2	23.5	11.7	0.4	0.6751	53.2	26.6	0.9	0.3968	45.4	22.7	0.8	0.4564
Marital status	3	188.5	62.8	2.1	0.0983	157.8	52.6	1.8	0.14	129.4	43.1	1.5	0.2152
Smoking status	2	706.2	353.1	11.8	< 0.0001	492.5	246.2	8.6	0.0002	377.1	188.6	6.5	0.0015
Alcohol consumption	2	203.4	101.7	3.4	0.0337	160.3	80.2	2.8	0.062	198.3	99.1	3.4	0.0329
Left Ventricular Mass Index	2	431.3	215.6	7.2	0.0008	621.4	310.7	10.8	< 0.0001	642.6	321.3	11.1	< 0.0001
Diabetes	1					194.2	194.2	6.8	0.0095	201.6	201.6	7	0.0084
Hypertension	1					35.3	35.3	1.2	0.2679	38.3	38.3	1.3	0.2499
Waist to height ratio	2					164.5	82.2	2.9	0.0577	120.7	60.3	2.1	0.1248
Cholesterol ratio	4					405.6	101.4	3.5	0.0072	413.1	103.3	3.6	0.0067
Intake of lipid-lowering drugs	3					36.5	12.2	0.4	0.7366	38.5	12.8	0.4	0.722
Intake of antihypertensive drugs	5					736.1	147.2	5.1	0.0001	686.4	137.3	4.7	0.0003
Pulse pressure	4					800.2	200.1	7	< 0.0001	718.6	179.7	6.2	< 0.0001
Diastolic BP	4					255.9	64	2.2	0.0645	239.4	59.8	2.1	0.0829
Cholesterol ratio * Intake of lipid-lowering drugs	2					35.1	17.5	0.6	0.5436	38.4	19.2	0.7	0.5148
Pulse pressure * Intake of antihypertensive drugs	2					556.7	278.4	9.7	< 0.0001	526.9	263.4	9.1	0.0001
Diastolic BP * Intake of antihypertensive drugs	2					56.6	28.3	1	0.3739	58.2	29.1	1	0.3659
E/e'	2									69.1	34.6	1.2	0.3031
E/A	2									20	10	0.3	0.7074
Left atrial size index	2									7.9	3.9	0.1	0.8724
Total	Σdf	396706.9	12797	428.5	< 0.0001	527924.2	10774	375	< 0.0001	486188.5	8839.8	305.7	< 0.0001
Error	n-Σdf	25476.4	29.9			24021.8	28.7			24000.2	28.9		

Supplementary Table 6: Analyses of variance of model 1, 2, and 3 of cortical brain age (imputed analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 7 – Subcortical Brain Age

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	458.2	229.1	11.6	< 0.0001	532.6	266.3	13.5	< 0.0001	572.8	286.4	14.4	< 0.0001
Baseline value of outcome	2	105385.5	52692.8	2670.2	< 0.0001	100505.1	50252.6	2548.9	< 0.0001	103241.5	51620.7	2600.9	< 0.0001
Age	4	1738.3	434.6	22	< 0.0001	1785.1	446.3	22.6	< 0.0001	1311.5	327.9	16.5	< 0.0001
Sex	3	350.4	116.8	5.9	0.0005	234.7	78.2	4	0.008	136.2	45.4	2.3	0.0773
Age * Sex	2	33.8	16.9	0.9	0.4247	27.2	13.6	0.7	0.5019	34.8	17.4	0.9	0.4166
Intracranial Volume	2	281.7	140.8	7.1	0.0008	263.7	131.8	6.7	0.0013	262.6	131.3	6.6	0.0014
Body height	2	46.8	23.4	1.2	0.3057	53.9	27	1.4	0.2553	45.2	22.6	1.1	0.3205
Body weight	2	62	31	1.6	0.2084	6.7	3.3	0.2	0.8438	26.2	13.1	0.7	0.517
Years of education	2	20.6	10.3	0.5	0.5936	49.5	24.7	1.3	0.2855	63.6	31.8	1.6	0.2022
Employment	3	99.9	33.3	1.7	0.1683	168.1	56	2.8	0.0369	79.4	26.5	1.3	0.2621
Income	2	27.2	13.6	0.7	0.5026	35.2	17.6	0.9	0.4105	18.7	9.3	0.5	0.6252
Marital status	3	289.2	96.4	4.9	0.0023	155.4	51.8	2.6	0.0492	173.6	57.9	2.9	0.0335
Smoking status	2	105.2	52.6	2.7	0.0701	147.6	73.8	3.7	0.0241	158.5	79.2	4	0.0188
Alcohol consumption	2	233.4	116.7	5.9	0.0028	214.4	107.2	5.4	0.0045	257.8	128.9	6.5	0.0016
LVMl	2	58.4	29.2	1.5	0.2285	28	14	0.7	0.4918	40	20	1	0.3656
Diabetes	1					0.7	0.7	0	0.846	4.8	4.8	0.2	0.6218
Hypertension	1					5.3	5.3	0.3	0.6037	0.2	0.2	0	0.9267
Waist to height ratio	2					1.5	0.8	0	0.9626	17.2	8.6	0.4	0.6489
Cholesterol ratio	4					28.3	7.1	0.4	0.8377	41.1	10.3	0.5	0.7232
Intake of lipid-lowering drugs	3					13.8	4.6	0.2	0.8732	31.9	10.6	0.5	0.6582
Intake of antihypertensive drugs	5					163.3	32.7	1.7	0.1427	234.2	46.8	2.4	0.0386
Pulse pressure	4					44.7	11.2	0.6	0.6865	61.2	15.3	0.8	0.5445
Diastolic BP	4					355.9	89	4.5	0.0013	339.5	84.9	4.3	0.002
Cholesterol ratio * Intake of lipid-lowering drugs	2					10.3	5.1	0.3	0.7702	23.2	11.6	0.6	0.5581
Pulse pressure * Intake of antihypertensive drugs	2					32.2	16.1	0.8	0.4423	40.5	20.2	1	0.3613
Diastolic BP * Intake of antihypertensive drugs	2					132.7	66.3	3.4	0.0351	197.1	98.6	5	0.0072
E/e'	2					0	0			291.3	145.7	7.3	0.0007
E/A	2					0	0			0.6	0.3	0	0.9855
LAI	2					0	0			30.1	15.1	0.8	0.4683
Total	55	669740.6	21604.5	1094.8	< 0.0001	739206.5	15085.8	765.2	< 0.0001	781531.3	14209.7	715.9	< 0.0001
Error	829	16832.7	19.7			16442.6	19.7			16453.7	19.8		

Supplementary Table 7: Analyses of variance of model 1, 2, and 3 of subcortical brain age (imputed analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 8 – Brain Age

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	76.5	38.2	4.4	0.013	109.7	54.9	6.3	0.0019	99	49.5	5.9	0.003
Baseline value of outcome	2	19533.3	9766.7	1115.7	< 0.0001	19244.3	9622.2	1108.9	< 0.0001	19479.2	9739.6	1154	< 0.0001
Age	4	497	124.3	14.2	< 0.0001	414.9	103.7	12	< 0.0001	305.1	76.3	9	< 0.0001
Sex	3	33.2	11.1	1.3	0.2858	52.2	17.4	2	0.1119	51.1	17	2	0.11
Age * Sex	2	25.4	12.7	1.5	0.2349	49.6	24.8	2.9	0.058	50.5	25.2	3	0.0509
Intracranial Volume	2	88.5	44.3	5.1	0.0066	44	22	2.5	0.08	32.7	16.4	1.9	0.1444
Body height	2	7.1	3.5	0.4	0.6685	0.4	0.2	0	0.9748	0.9	0.5	0.1	0.947
Body weight	2	19.8	9.9	1.1	0.3224	20.5	10.3	1.2	0.307	21.9	11	1.3	0.2734
Years of education	2	117.1	58.5	6.7	0.0013	94.8	47.4	5.5	0.0044	95.7	47.9	5.7	0.0036
Employment	3	18.2	6.1	0.7	0.5557	10.9	3.6	0.4	0.7409	8.3	2.8	0.3	0.8066
Income	2	0.6	0.3	0	0.9665	4.6	2.3	0.3	0.7691	2.8	1.4	0.2	0.8453
Marital status	3	119.9	40	4.6	0.0035	48.7	16.2	1.9	0.1329	32.6	10.9	1.3	0.2781
Smoking status	2	182.4	91.2	10.4	< 0.0001	204.7	102.4	11.8	< 0.0001	161.1	80.5	9.5	< 0.0001
Alcohol consumption	2	38.7	19.3	2.2	0.1104	47	23.5	2.7	0.0674	71.4	35.7	4.2	0.0148
LVMI	2	45.8	22.9	2.6	0.0738	23.5	11.7	1.4	0.2591	30.8	15.4	1.8	0.1619
Diabetes	1					0.3	0.3	0	0.8617	0.5	0.5	0.1	0.8156
Hypertension	1					0.5	0.5	0.1	0.8075	1	1	0.1	0.7369
Waist to height ratio	2					15.3	7.7	0.9	0.4135	21.8	10.9	1.3	0.2746
Cholesterol ratio	4					44.9	11.2	1.3	0.2708	38.3	9.6	1.1	0.3389
Intake of lipid-lowering drugs	3					2.7	0.9	0.1	0.9575	2.3	0.8	0.1	0.965
Intake of antihypertensive drugs	5					194.5	38.9	4.5	0.0005	159	31.8	3.8	0.0022
Pulse pressure	4					289.3	72.3	8.3	< 0.0001	218.8	54.7	6.5	< 0.0001
Diastolic BP	4					93.7	23.4	2.7	0.0297	87.1	21.8	2.6	0.0362
Cholesterol ratio * Intake of lipid-lowering drugs	2					1.7	0.9	0.1	0.905	1.4	0.7	0.1	0.9218
Pulse pressure * Intake of antihypertensive drugs	2					165	82.5	9.5	< 0.0001	135.4	67.7	8	0.0004
Diastolic BP * Intake of antihypertensive drugs	2					27.7	13.8	1.6	0.2034	28.8	14.4	1.7	0.1827
E/e'	2					0	0			57.5	28.7	3.4	0.0337
E/A	2					0	0			31.6	15.8	1.9	0.1542
LAI	2					0	0			71.2	35.6	4.2	0.015
Total	55	189402	6109.7	698	< 0.0001	262425.9	5355.6	617.2	< 0.0001	274053.9	4982.8	590.4	< 0.0001
Error	831	7484.4	8.8			7289.1	8.7			7013.6	8.4		

Supplementary Table 8: Analyses of variance of model 1, 2, and 3 of brain age (imputed analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 9

Outcome	Left Hemisphere		Right Hemisphere	
	Effect size (95% CI)	<i>t</i>	Effect size (95% CI)	<i>t</i>
Banks of the superior temporal sulcus	-0.013 (-0.024, -0.002)	-2.41*	-0.012 (-0.024, 0)	-2.04
Caudal anterior cingulate cortex	-0.001 (-0.012, 0.01)	-0.15	-0.001 (-0.013, 0.011)	-0.1
Caudal middle frontal gyrus	-0.025 (-0.038, -0.011)	-3.62**	-0.031 (-0.047, -0.015)	-3.85***
Cuneus cortex	-0.014 (-0.022, -0.005)	-3.23**	-0.01 (-0.02, -0.001)	-2.19
Entorhinal cortex	-0.005 (-0.026, 0.017)	-0.41	0.016 (-0.003, 0.035)	1.65
Fusiform gyrus	-0.023 (-0.034, -0.011)	-3.94***	-0.022 (-0.033, -0.011)	-3.83***
Inferior parietal cortex	-0.027 (-0.039, -0.014)	-4.05***	-0.01 (-0.021, 0.001)	-1.71
Inferior temporal gyrus	0 (-0.011, 0.011)	-0.02	-0.009 (-0.019, 0)	-1.95
Isthmus cingulate cortex	0.008 (-0.004, 0.02)	1.27	-0.001 (-0.009, 0.007)	-0.2
Lateral occipital cortex	-0.015 (-0.025, -0.004)	-2.81*	-0.016 (-0.025, -0.007)	-3.52**
Lateral orbitofrontal cortex	-0.01 (-0.023, 0.004)	-1.42	-0.009 (-0.021, 0.003)	-1.51
Lingual gyrus	-0.01 (-0.019, 0)	-1.93	-0.009 (-0.017, -0.002)	-2.47*
Medial orbitofrontal cortex	-0.009 (-0.02, 0.003)	-1.46	-0.017 (-0.028, -0.007)	-3.3**
Middle temporal gyrus	0 (-0.013, 0.013)	0.01	-0.013 (-0.024, -0.002)	-2.29
Parahippocampal gyrus	-0.006 (-0.016, 0.004)	-1.16	-0.002 (-0.013, 0.01)	-0.28
Paracentral lobule	-0.005 (-0.021, 0.012)	-0.59	-0.015 (-0.029, -0.001)	-2.04
Pars opercularis	-0.014 (-0.025, -0.004)	-2.66*	-0.006 (-0.017, 0.006)	-1
Pars orbitalis	-0.019 (-0.038, 0)	-1.98	-0.011 (-0.028, 0.006)	-1.28
Pars triangularis	-0.019 (-0.029, -0.008)	-3.47**	-0.02 (-0.031, -0.01)	-3.71**
Pericalcarine cortex	-0.01 (-0.02, -0.001)	-2.13	-0.009 (-0.017, -0.001)	-2.23
Postcentral gyrus	-0.011 (-0.02, -0.003)	-2.58*	-0.016 (-0.025, -0.006)	-3.17**
Posterior cingulate cortex	0.006 (-0.003, 0.015)	1.31	-0.011 (-0.021, -0.001)	-2.23
Precentral gyrus	-0.029 (-0.044, -0.015)	-3.95***	-0.04 (-0.058, -0.022)	-4.4***
Precuneus cortex	-0.008 (-0.019, 0.002)	-1.52	-0.003 (-0.012, 0.006)	-0.57
Rostral anterior cingulate cortex	-0.009 (-0.02, 0.002)	-1.65	-0.011 (-0.023, 0)	-1.94
Rostral middle frontal gyrus	-0.023 (-0.032, -0.013)	-4.82***	-0.013 (-0.025, -0.002)	-2.26
Superior frontal gyrus	-0.037 (-0.051, -0.023)	-5.22***	-0.023 (-0.037, -0.008)	-3**
Superior parietal cortex	-0.006 (-0.018, 0.006)	-0.96	-0.005 (-0.017, 0.008)	-0.76
Superior temporal gyrus	-0.007 (-0.018, 0.004)	-1.31	-0.019 (-0.029, -0.009)	-3.76**
Supramarginal gyrus	-0.016 (-0.028, -0.005)	-2.76*	-0.016 (-0.025, -0.006)	-3.16**
Frontal pole	-0.052 (-0.077, -0.028)	-4.2***	-0.001 (-0.022, 0.021)	-0.06
Temporal pole	-0.006 (-0.026, 0.014)	-0.58	-0.016 (-0.033, 0.001)	-1.89
Transverse temporal cortex	-0.03 (-0.05, -0.009)	-2.88*	0.008 (-0.017, 0.033)	0.64
Insular cortex	-0.008 (-0.02, 0.005)	-1.22	-0.003 (-0.013, 0.007)	-0.6

*Supplementary Table 9: Point estimates of direct effects of baseline LVMI on regional cortical thicknesses at follow-up (model 2; imputed analyses). Effects adjusted for socio-demographic factors, anthropometric variables, lifestyle factors, cardiovascular risk factors and medication, follow-up time, and baseline value of the outcome (model 2). * $p_{FDR}<0.05$, ** $p_{FDR}<0.01$, *** $p_{FDR}<0.001$*

Supplementary Table 10 – Total Brain Volume (Complete Case Analysis)

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	1796.7	898.3	8.5	0.0002	2413.3	1206.6	11.8	< 0.0001	2748.3	1374.2	14.6	< 0.0001
Baseline value of outcome	2	1189785	594892.4	5638.8	< 0.0001	1300883	650441.4	6386.8	< 0.0001	1242438	621219.1	6587.8	< 0.0001
Age	4	21524.8	5381.2	51	< 0.0001	18583.6	4645.9	45.6	< 0.0001	16085.8	4021.5	42.6	< 0.0001
Sex	3	2242.9	747.6	7.1	0.0001	2137.3	712.4	7	0.0001	2076.1	692	7.3	< 0.0001
Age * Sex	2	2216.1	1108	10.5	< 0.0001	1991.5	995.7	9.8	< 0.0001	2009.7	1004.9	10.7	< 0.0001
Intracranial Volume	2	237.1	118.6	1.1	0.3255	489.9	244.9	2.4	0.0909	425.9	213	2.3	0.1052
Body height	2	754.7	377.4	3.6	0.0284	561.2	280.6	2.8	0.0642	707.6	353.8	3.8	0.0239
Body weight	2	115.1	57.5	0.5	0.5799	600.1	300	2.9	0.0531	167.5	83.8	0.9	0.4118
Years of education	2	127.2	63.6	0.6	0.5474	214.6	107.3	1.1	0.3491	132.9	66.4	0.7	0.4947
Employment	3	231.3	77.1	0.7	0.5337	392.9	131	1.3	0.278	258.7	86.2	0.9	0.4335
Income	2	654.5	327.2	3.1	0.0455	558.4	279.2	2.7	0.0651	413.7	206.9	2.2	0.1122
Marital status	3	1931.4	643.8	6.1	0.0004	1569.6	523.2	5.1	0.0016	2869.5	956.5	10.1	< 0.0001
Smoking status	2	454	227	2.2	0.1169	466.6	233.3	2.3	0.1018	222.9	111.4	1.2	0.3073
Alcohol consumption	2	151.1	75.6	0.7	0.4889	185.4	92.7	0.9	0.4028	238.1	119.1	1.3	0.2835
LVMl	2	506.8	253.4	2.4	0.0912	138.7	69.3	0.7	0.5065	178	89	0.9	0.3895
Diabetes	1					474.8	474.8	4.7	0.0311	536.4	536.4	5.7	0.0173
Hypertension	1					6.9	6.9	0.1	0.7941	8.2	8.2	0.1	0.7688
Waist to height ratio	2					733.8	366.9	3.6	0.0277	631	315.5	3.3	0.0358
Cholesterol ratio	4					168.1	42	0.4	0.7996	79.4	19.9	0.2	0.9326
Intake of lipidlowering drugs	3					119.5	39.8	0.4	0.7595	14	4.7	0	0.9854
Intake of antihypertensive drugs	5					1872.4	374.5	3.7	0.0027	2286.8	457.4	4.9	0.0002
Pulse pressure	4					165.4	41.4	0.4	0.8043	221	55.2	0.6	0.673
Diastolic BP	4					1667.1	416.8	4.1	0.0027	2176.2	544.1	5.8	0.0001
Cholesterol ratio * Intake of antihypertensives drugs	2					108.7	54.4	0.5	0.5866	9.4	4.7	0	0.9514
Pulse pressure * Intake of antihypertensive drugs	2					36.8	18.4	0.2	0.8348	24.1	12.1	0.1	0.88
Diastolic BP * Antihypertensives	2					1574.5	787.3	7.7	0.0005	2137.3	1068.7	11.3	< 0.0001
E/é	2									241.3	120.6	1.3	0.2789
E/A	2									334.4	167.2	1.8	0.1705
LAI	2									94.6	47.3	0.5	0.6057
Total	55	16467992	531225.5	5035.3	< 0.0001	17426898	355651	3492.2	< 0.0001	16346421	297207.6	3151.8	< 0.0001
Error	747	86087.6	105.5			80760.8	101.8			70440.9	94.3		

Supplementary Table 10: Analyses of variance of model 1, 2, and 3 of total brain volume (complete case analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 11 – Subcortical Gray Matter Volume (Complete Case Analysis)

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	7	3.5	6.4	0.0017	8.9	4.4	8.3	0.0003	10.1	5	10	< 0.0001
Baseline value of outcome	2	8072	4036	7377.2	< 0.0001	6551.8	3275.9	6104.6	< 0.0001	6234.7	3117.3	6187.1	< 0.0001
Age	4	80.2	20	36.6	< 0.0001	72.1	18	33.6	< 0.0001	51.2	12.8	25.4	< 0.0001
Sex	3	3.1	1	1.9	0.1291	3.9	1.3	2.4	0.0657	10.6	3.5	7	0.0001
Age * Sex	2	2.9	1.4	2.6	0.0731	3.1	1.6	2.9	0.0548	6.7	3.3	6.6	0.0014
Intracranial Volume	2	4.7	2.3	4.3	0.0144	2.2	1.1	2	0.1318	1.8	0.9	1.8	0.1725
Body height	2	0	0	0	0.9783	0.3	0.2	0.3	0.7488	0.7	0.3	0.7	0.5184
Body weight	2	2.1	1	1.9	0.1522	4.2	2.1	3.9	0.0209	3.4	1.7	3.4	0.0353
Years of education	2	0.5	0.3	0.5	0.6334	0.1	0	0.1	0.9313	0.1	0.1	0.1	0.897
Employment	3	1.7	0.6	1	0.3888	0.7	0.2	0.4	0.7464	0.3	0.1	0.2	0.9092
Income	2	1.6	0.8	1.4	0.2374	1.7	0.9	1.6	0.199	2.3	1.2	2.3	0.0995
Marital status	3	11.6	3.9	7.1	0.0001	10.9	3.6	6.7	0.0002	7.9	2.6	5.2	0.0014
Smoking status	2	5.3	2.6	4.8	0.0083	4.5	2.3	4.2	0.0154	5.7	2.9	5.7	0.0036
Alcohol consumption	2	2.2	1.1	2	0.1387	1.6	0.8	1.5	0.2164	2.3	1.1	2.3	0.1037
LVMl	2	0.6	0.3	0.6	0.5757	0.5	0.3	0.5	0.6185	0.5	0.3	0.5	0.5868
Diabetes	1					0	0	0	0.8498	0.3	0.3	0.5	0.4622
Hypertension	1					0.1	0.1	0.2	0.6309	0.1	0.1	0.3	0.5997
Waist to height ratio	2					6.2	3.1	5.7	0.0034	3.4	1.7	3.4	0.0334
Cholesterol ratio	4					1.5	0.4	0.7	0.5895	0.2	0.1	0.1	0.9786
Intake of lipidlowering drugs	3					1.1	0.4	0.7	0.5491	0.2	0.1	0.2	0.9197
Intake of antihypertensive drugs	5					5.3	1.1	2	0.0791	5.2	1	2	0.0699
Pulse pressure	4					4.4	1.1	2.1	0.0847	2.3	0.6	1.2	0.3286
Diastolic BP	4					5.4	1.4	2.5	0.0392	5.3	1.3	2.6	0.0326
Cholesterol ratio * Intake of antihypertensives drugs	2					0.5	0.2	0.4	0.6562	0.1	0	0.1	0.9188
Pulse pressure * Intake of antihypertensive drugs	2					1.4	0.7	1.3	0.2699	1.2	0.6	1.2	0.2924
Diastolic BP * Antihypertensives	2					3.2	1.6	3	0.0513	2.2	1.1	2.2	0.1128
E/é	2									8.9	4.5	8.9	0.0002
E/A	2									1	0.5	1	0.3676
LAI	2									1.3	0.6	1.2	0.2877
Total	55	39986.7	1289.9	2357.7	< 0.0001	40431.7	825.1	1537.6	< 0.0001	41486.1	754.3	1497.1	< 0.0001
Error	744	446.4	0.5			423.4	0.5			374.9	0.5		

Supplementary Table 11: Analyses of variance of model 1, 2, and 3 of subcortical gray matter volume (complete case analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 12 – White Matter Volume (Complete Case Analysis)

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	510.7	255.4	3.3	0.0357	419.1	209.5	2.7	0.0676	926.2	463.1	6.1	0.0023
Baseline value of outcome	2	738618	369309	4840.2	< 0.0001	731893	365946.5	4720.3	< 0.0001	712392.6	356196.3	4697.7	< 0.0001
Age	4	18677.4	4669.4	61.2	< 0.0001	15298.8	3824.7	49.3	< 0.0001	11696.9	2924.2	38.6	< 0.0001
Sex	3	2260	753.3	9.9	< 0.0001	1479.4	493.1	6.4	0.0003	1127.7	375.9	5	0.0021
Age * Sex	2	2204.1	1102	14.4	< 0.0001	1475.4	737.7	9.5	< 0.0001	1085.5	542.8	7.2	0.0008
Intracranial Volume	2	459.5	229.7	3	0.0498	347.4	173.7	2.2	0.107	357.7	178.8	2.4	0.0953
Body height	2	527.4	263.7	3.5	0.032	355.8	177.9	2.3	0.1015	518.5	259.3	3.4	0.0332
Body weight	2	130.6	65.3	0.9	0.4254	53	26.5	0.3	0.7104	18.3	9.1	0.1	0.8864
Years of education	2	92.7	46.3	0.6	0.5451	81.5	40.7	0.5	0.5914	69.9	35	0.5	0.6307
Employment	3	375.1	125	1.6	0.1789	285.8	95.3	1.2	0.2982	230.5	76.8	1	0.3861
Income	2	1151.3	575.6	7.5	0.0006	742.8	371.4	4.8	0.0085	418.9	209.5	2.8	0.0638
Marital status	3	315.6	105.2	1.4	0.248	329.3	109.8	1.4	0.2368	385.5	128.5	1.7	0.1667
Smoking status	2	38.6	19.3	0.3	0.7764	40.6	20.3	0.3	0.7699	62.7	31.3	0.4	0.6616
Alcohol consumption	2	9.9	5	0.1	0.937	32.9	16.5	0.2	0.8089	62.5	31.2	0.4	0.6626
LVMl	2	10.3	5.1	0.1	0.935	26.4	13.2	0.2	0.8437	2.4	1.2	0	0.9844
Diabetes	1					647.9	647.9	8.4	0.0039	1233	1233	16.3	< 0.0001
Hypertension	1					23.6	23.6	0.3	0.5814	0.1	0.1	0	0.9731
Waist to height ratio	2					113.6	56.8	0.7	0.4809	341.5	170.7	2.3	0.1059
Cholesterol ratio	4					102.2	25.6	0.3	0.8581	49.3	12.3	0.2	0.9572
Intake of lipidlowering drugs	3					244.1	81.4	1	0.3699	209.9	70	0.9	0.4293
Intake of antihypertensive drugs	5					187.6	37.5	0.5	0.7883	370.8	74.2	1	0.4302
Pulse pressure	4					261.2	65.3	0.8	0.4986	318	79.5	1	0.3811
Diastolic BP	4					229.6	57.4	0.7	0.5645	723.3	180.8	2.4	0.0499
Cholesterol ratio * Intake of antihypertensives drugs	2					90.2	45.1	0.6	0.5593	42.9	21.4	0.3	0.7539
Pulse pressure * Intake of antihypertensive drugs	2					73.8	36.9	0.5	0.6214	15.8	7.9	0.1	0.9011
Diastolic BP * Antihypertensives	2					30.3	15.1	0.2	0.8228	345.4	172.7	2.3	0.1032
E/é	2									42	21	0.3	0.7582
E/A	2									199.6	99.8	1.3	0.2688
LAI	2									107	53.5	0.7	0.4943
Total	55	4692191	151361	1983.8	< 0.0001	4951006	101040.9	1303.3	< 0.0001	4941698	89849	1185	< 0.0001
Error	753	62489.7	76.3			62021	77.5			57095.2	75.8		

Supplementary Table 12: Analyses of variance of model 1, 2, and 3 of white matter volume (complete case analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 13 – White Matter Hyperintensities Volume (Complete Case Analysis)

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	0.4	0.2	0.3	0.7469	1.5	0.7	1	0.3705	1.1	0.5	0.8	0.4613
Baseline value of outcome	2	3028.7	1514.4	2002.4	< 0.0001	2856.9	1428.5	1895.5	< 0.0001	2571.7	1285.9	1828.4	< 0.0001
Age	4	70.3	17.6	23.3	< 0.0001	67.6	16.9	22.4	< 0.0001	52.8	13.2	18.8	< 0.0001
Sex	3	40.6	13.5	17.9	< 0.0001	27.6	9.2	12.2	< 0.0001	20.7	6.9	9.8	< 0.0001
Age * Sex	2	27.5	13.8	18.2	< 0.0001	20.9	10.4	13.8	< 0.0001	17	8.5	12.1	< 0.0001
Intracranial Volume	2	8.5	4.2	5.6	0.0038	11.5	5.8	7.6	0.0005	9.8	4.9	6.9	0.001
Body height	2	2.9	1.5	1.9	0.1454	2.2	1.1	1.4	0.2407	3.3	1.6	2.3	0.0978
Body weight	2	4.8	2.4	3.2	0.0414	0.8	0.4	0.5	0.5776	2.2	1.1	1.6	0.2084
Years of education	2	0.1	0	0.1	0.944	1.1	0.6	0.7	0.4783	1.3	0.7	0.9	0.3939
Employment	3	3.7	1.2	1.6	0.1845	3.9	1.3	1.7	0.1584	4	1.3	1.9	0.1287
Income	2	2.1	1	1.4	0.2515	0.7	0.3	0.5	0.6322	1.2	0.6	0.8	0.441
Marital status	3	3.8	1.3	1.7	0.1734	6.5	2.2	2.9	0.0356	5.5	1.8	2.6	0.0521
Smoking status	2	7.2	3.6	4.8	0.0086	9.4	4.7	6.2	0.0021	13.4	6.7	9.5	< 0.0001
Alcohol consumption	2	3.3	1.6	2.2	0.1166	4.1	2.1	2.7	0.0658	4.1	2	2.9	0.0555
LVMl	2	3.3	1.6	2.2	0.1161	2.5	1.3	1.7	0.1851	2.9	1.5	2.1	0.1251
Diabetes	1					3.9	3.9	5.2	0.0232	3.7	3.7	5.2	0.0224
Hypertension	1					0.1	0.1	0.1	0.7315	0.6	0.6	0.9	0.338
Waist to height ratio	2					0.2	0.1	0.1	0.8704	1.7	0.8	1.2	0.301
Cholesterol ratio	4					5.5	1.4	1.8	0.1217	6.9	1.7	2.4	0.0458
Intake of lipidlowering drugs	3					7.8	2.6	3.5	0.0162	11	3.7	5.2	0.0014
Intake of antihypertensive drugs	5					0.9	0.2	0.2	0.9514	0.7	0.1	0.2	0.962
Pulse pressure	4					4.2	1	1.4	0.235	4.6	1.2	1.6	0.163
Diastolic BP	4					5.1	1.3	1.7	0.1492	5.4	1.3	1.9	0.1067
Cholesterol ratio * Intake of antihypertensives drugs	2					4.2	2.1	2.8	0.0629	6.5	3.3	4.6	0.01
Pulse pressure * Intake of antihypertensive drugs	2					0.3	0.1	0.2	0.8327	0.1	0.1	0.1	0.9042
Diastolic BP * Antihypertensives	2					0.7	0.3	0.4	0.643	0.3	0.1	0.2	0.8089
E/é	2									6.6	3.3	4.7	0.0092
E/A	2									0	0	0	0.9858
LAI	2									7.8	3.9	5.5	0.0041
Total	55	15048.7	485.4	641.9	< 0.0001	14376.3	293.4	389.3	< 0.0001	14186.3	257.9	366.8	< 0.0001
Error	748	615.6	0.8			598.4	0.8			526	0.7		

Supplementary Table 13: Analyses of variance of model 1, 2, and 3 of white matter hyperintensities volume (complete case analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 14 – Global Cortical Thickness (Complete Case Analysis)

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	0.0009	0.0004	0.3	0.7095	0.0015	0.0008	0.6	0.5402	0.0041	0.0021	1.8	0.1665
Baseline value of outcome	2	5.9711	2.9855	2329.3	< 0.0001	5.14	2.57	2084.6	< 0.0001	5.5916	2.7958	2430.2	< 0.0001
Age	4	0.0651	0.0163	12.7	< 0.0001	0.0492	0.0123	10	< 0.0001	0.0424	0.0106	9.2	< 0.0001
Sex	3	0.0035	0.0012	0.9	0.439	0.0063	0.0021	1.7	0.1645	0.0206	0.0069	6	0.0005
Age * Sex	2	0.0016	0.0008	0.6	0.5388	0.0042	0.0021	1.7	0.1796	0.0141	0.007	6.1	0.0023
Intracranial Volume	2	0.0034	0.0017	1.3	0.2662	0.0035	0.0017	1.4	0.2434	0.005	0.0025	2.2	0.1143
Body height	2	0.0054	0.0027	2.1	0.1217	0.0021	0.001	0.8	0.4344	0.0054	0.0027	2.4	0.095
Body weight	2	0.0012	0.0006	0.5	0.616	0.0018	0.0009	0.7	0.4792	0.0008	0.0004	0.4	0.6993
Years of education	2	0.0046	0.0023	1.8	0.1679	0.003	0.0015	1.2	0.2938	0.002	0.001	0.9	0.4166
Employment	3	0.0015	0.0005	0.4	0.7566	0.0042	0.0014	1.1	0.3356	0.0027	0.0009	0.8	0.5025
Income	2	0.0001	0.0001	0.1	0.9456	0.0009	0.0005	0.4	0.6891	0.0001	0	0	0.9662
Marital status	3	0.0121	0.004	3.1	0.0247	0.0061	0.002	1.6	0.1775	0.0112	0.0037	3.2	0.0218
Smoking status	2	0.0071	0.0036	2.8	0.0628	0.0071	0.0036	2.9	0.0558	0.0066	0.0033	2.9	0.0579
Alcohol consumption	2	0.0101	0.005	3.9	0.0199	0.0062	0.0031	2.5	0.0813	0.01	0.005	4.3	0.0133
LVMl	2	0.0203	0.0101	7.9	0.0004	0.0178	0.0089	7.2	0.0008	0.015	0.0075	6.5	0.0016
Diabetes	1					0.007	0.007	5.7	0.0175	0.0132	0.0132	11.5	0.0007
Hypertension	1					0.0026	0.0026	2.1	0.1505	0.0035	0.0035	3.1	0.0805
Waist to height ratio	2					0.0126	0.0063	5.1	0.0062	0.0075	0.0037	3.3	0.039
Cholesterol ratio	4					0.004	0.001	0.8	0.5151	0.0079	0.002	1.7	0.1464
Intake of lipidlowering drugs	3					0.0013	0.0004	0.4	0.7795	0.0048	0.0016	1.4	0.2415
Intake of antihypertensive drugs	5					0.0037	0.0007	0.6	0.6985	0.0016	0.0003	0.3	0.9293
Pulse pressure	4					0.0019	0.0005	0.4	0.8224	0.0055	0.0014	1.2	0.3121
Diastolic BP	4					0.0029	0.0007	0.6	0.6729	0.0011	0.0003	0.2	0.9215
Cholesterol ratio * Intake of antihypertensives drugs	2					0.0006	0.0003	0.2	0.7796	0.0038	0.0019	1.7	0.1913
Pulse pressure * Intake of antihypertensive drugs	2					0.0005	0.0002	0.2	0.832	0.0006	0.0003	0.2	0.7858
Diastolic BP * Antihypertensives	2					0.0029	0.0014	1.2	0.3134	0.0008	0.0004	0.4	0.6995
E/é	2									0.0034	0.0017	1.5	0.2322
E/A	2									0.001	0.0005	0.4	0.6498
LAI	2									0.0011	0.0005	0.5	0.622
Total	55	24.6651	0.7956	620.8	< 0.0001	23.9489	0.4888	396.4	< 0.0001	29.2233	0.5313	461.9	< 0.0001
Error	749	1.0549	0.0013			0.9801	0.0012			0.8617	0.0012		

Supplementary Table 14: Analyses of variance of model 1, 2, and 3 of global cortical thickness (complete case analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 15 – Cortical Brain Age (Complete Case Analysis)

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	184.7	92.4	3.2	0.043	438.9	219.4	7.8	0.0005	258.4	129.2	4.6	0.0104
Baseline value of outcome	2	57838.8	28919.4	988.8	< 0.0001	60301	30150.5	1066.8	< 0.0001	57610.5	28805.2	1023.4	< 0.0001
Age	4	1212.6	303.2	10.4	< 0.0001	928.6	232.2	8.2	< 0.0001	775	193.7	6.9	< 0.0001
Sex	3	700	233.3	8	< 0.0001	709.3	236.4	8.4	< 0.0001	600.4	200.1	7.1	0.0001
Age * Sex	2	663.2	331.6	11.3	< 0.0001	686.3	343.1	12.1	< 0.0001	583.6	291.8	10.4	< 0.0001
Intracranial Volume	2	167.7	83.9	2.9	0.0574	260.9	130.4	4.6	0.0102	65.3	32.6	1.2	0.3143
Body height	2	4.8	2.4	0.1	0.9206	8.2	4.1	0.1	0.865	16	8	0.3	0.7524
Body weight	2	25.8	12.9	0.4	0.6434	29.8	14.9	0.5	0.5907	12.6	6.3	0.2	0.7999
Years of education	2	29.5	14.7	0.5	0.6045	66.8	33.4	1.2	0.3074	16.6	8.3	0.3	0.7454
Employment	3	76.2	25.4	0.9	0.4568	66.3	22.1	0.8	0.5042	33.7	11.2	0.4	0.7541
Income	2	13.8	6.9	0.2	0.7895	11.1	5.6	0.2	0.8217	17.2	8.6	0.3	0.7371
Marital status	3	130.2	43.4	1.5	0.2176	80.2	26.7	0.9	0.4178	103.5	34.5	1.2	0.2993
Smoking status	2	553.8	276.9	9.5	< 0.0001	334.7	167.4	5.9	0.0028	450	225	8	0.0004
Alcohol consumption	2	117.7	58.9	2	0.1343	158.4	79.2	2.8	0.0612	156.1	78	2.8	0.0631
LVMl	2	446.5	223.2	7.6	0.0005	699.5	349.8	12.4	< 0.0001	579	289.5	10.3	< 0.0001
Diabetes	1					278.5	278.5	9.9	0.0018	286.8	286.8	10.2	0.0015
Hypertension	1					11.5	11.5	0.4	0.5234	13.4	13.4	0.5	0.4908
Waist to height ratio	2					140.9	70.5	2.5	0.0833	55.6	27.8	1	0.3731
Cholesterol ratio	4					495.5	123.9	4.4	0.0016	341.8	85.5	3	0.0169
Intake of lipid-lowering drugs	3					104.4	34.8	1.2	0.2971	49.5	16.5	0.6	0.6241
Intake of antihypertensive drugs	5					776	155.2	5.5	< 0.0001	827.1	165.4	5.9	< 0.0001
Pulse pressure	4					823.3	205.8	7.3	< 0.0001	850.1	212.5	7.6	< 0.0001
Diastolic BP	4					169.8	42.5	1.5	0.1996	122.7	30.7	1.1	0.3603
Cholesterol ratio * Intake of lipid-lowering drugs	2					102.4	51.2	1.8	0.1641	47.7	23.9	0.8	0.4289
Pulse pressure * Intake of antihypertensive drugs	2					598.8	299.4	10.6	< 0.0001	689.3	344.6	12.2	< 0.0001
Diastolic BP * Intake of antihypertensive drugs	2					39.9	19.9	0.7	0.4943	15.7	7.9	0.3	0.7563
E/é	2					0	0			10.2	5.1	0.2	0.8343
E/A	2					0	0			63.2	31.6	1.1	0.3259
LAI	2					0	0			15.4	7.7	0.3	0.7608
Total	55	373088.7	12035.1	411.5	< 0.0001	521847	10649.9	376.8	< 0.0001	496751.9	9031.9	320.9	< 0.0001
Error	746	23544.8	29.2			22326.8	28.3			20998.3	28.1		

Supplementary Table 15: Analyses of variance of model 1, 2, and 3 of cortical brain age (complete case analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 16 – Subcortical Brain Age (Complete Case Analysis)

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	365.3	182.6	9.3	0.0001	344.8	172.4	8.7	0.0002	426.7	213.4	10.9	< 0.0001
Baseline value of outcome	2	97568.8	48784.4	2474.9	< 0.0001	92358	46179	2340.4	< 0.0001	86311.2	43155.6	2200.2	< 0.0001
Age	4	1582.3	395.6	20.1	< 0.0001	1590.9	397.7	20.2	< 0.0001	1098.3	274.6	14	< 0.0001
Sex	3	213.7	71.2	3.6	0.013	96.9	32.3	1.6	0.1794	72.5	24.2	1.2	0.297
Age * Sex	2	40.2	20.1	1	0.361	13.1	6.5	0.3	0.7179	18.1	9.1	0.5	0.6299
Intracranial Volume	2	314.5	157.3	8	0.0004	261.4	130.7	6.6	0.0014	299.7	149.8	7.6	0.0005
Body height	2	30	15	0.8	0.468	52.6	26.3	1.3	0.264	52.4	26.2	1.3	0.2636
Body weight	2	25.3	12.7	0.6	0.526	12.9	6.5	0.3	0.7209	13.7	6.9	0.4	0.7047
Years of education	2	20.6	10.3	0.5	0.5939	31.5	15.7	0.8	0.4506	14.9	7.5	0.4	0.6838
Employment	3	51.2	17.1	0.9	0.4587	123.7	41.2	2.1	0.1002	159.1	53	2.7	0.0445
Income	2	15	7.5	0.4	0.6834	27.1	13.6	0.7	0.5035	11.8	5.9	0.3	0.7399
Marital status	3	376.1	125.4	6.4	0.0003	78.6	26.2	1.3	0.2639	199.1	66.4	3.4	0.0178
Smoking status	2	82	41	2.1	0.1257	125.6	62.8	3.2	0.042	141.2	70.6	3.6	0.0278
Alcohol consumption	2	144.9	72.5	3.7	0.0257	157.1	78.5	4	0.0191	199.1	99.5	5.1	0.0065
LVMl	2	35.7	17.9	0.9	0.4043	28.4	14.2	0.7	0.4876	31.7	15.8	0.8	0.4462
Diabetes	1					0.1	0.1	0	0.9323	0.1	0.1	0	0.9575
Hypertension	1					2.5	2.5	0.1	0.7213	0.5	0.5	0	0.872
Waist to height ratio	2					34.6	17.3	0.9	0.4168	29.6	14.8	0.8	0.47
Cholesterol ratio	4					54.7	13.7	0.7	0.5966	50.7	12.7	0.6	0.6296
Intake of lipid-lowering drugs	3					17.7	5.9	0.3	0.8259	18.7	6.2	0.3	0.8119
Intake of antihypertensive drugs	5					138.4	27.7	1.4	0.2211	114.3	22.9	1.2	0.3243
Pulse pressure	4					63.8	16	0.8	0.5198	104.2	26.1	1.3	0.2576
Diastolic BP	4					260.4	65.1	3.3	0.0108	203.3	50.8	2.6	0.0355
Cholesterol ratio * Intake of lipid-lowering drugs	2					15.7	7.9	0.4	0.6712	18	9	0.5	0.6326
Pulse pressure * Intake of antihypertensive drugs	2					45.8	22.9	1.2	0.3142	53.3	26.6	1.4	0.2578
Diastolic BP * Intake of antihypertensive drugs	2					71.7	35.8	1.8	0.1634	40.5	20.3	1	0.3564
E/é	2					0	0			114.1	57.1	2.9	0.0552
E/A	2					0	0			2.4	1.2	0.1	0.9405
LAI	2					0	0			8	4	0.2	0.816
Total	55	550920.1	17771.6	901.6	< 0.0001	569771.4	11628	589.3	< 0.0001	597688.8	10867.1	554	< 0.0001
Error	748	15966.3	19.7			15568.1	19.7			14671.4	19.6		

Supplementary Table 16: Analyses of variance of model 1, 2, and 3 of subcortical brain age (complete case analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.

Supplementary Table 17 – Brain Age (Complete Case Analysis)

Variable	df	model 1				model 2				model 3			
		SS	MS	F	P	SS	MS	F	P	SS	MS	F	P
Time interval	2	116	58	6.3	0.0018	72.8	36.4	4	0.0183	87.5	43.7	5.2	0.0059
Baseline value of outcome	2	18005.2	9002.6	985.3	< 0.0001	17653.6	8826.8	974.3	< 0.0001	16989.2	8494.6	1002.5	< 0.0001
Age	4	497.2	124.3	13.6	< 0.0001	380	95	10.5	< 0.0001	380.2	95.1	11.2	< 0.0001
Sex	3	59.4	19.8	2.2	0.0903	81.5	27.2	3	0.0299	135.4	45.1	5.3	0.0012
Age * Sex	2	58.5	29.3	3.2	0.0411	81.1	40.6	4.5	0.0117	128	64	7.6	0.0006
Intracranial Volume	2	38.4	19.2	2.1	0.123	75.2	37.6	4.2	0.0161	46	23	2.7	0.0668
Body height	2	3.2	1.6	0.2	0.8416	2.3	1.2	0.1	0.879	7.7	3.8	0.5	0.6355
Body weight	2	4.3	2.1	0.2	0.7918	18.6	9.3	1	0.3586	6.5	3.2	0.4	0.682
Years of education	2	73.7	36.8	4	0.0181	77.9	39	4.3	0.0139	18.5	9.2	1.1	0.337
Employment	3	27.7	9.2	1	0.3875	15.2	5.1	0.6	0.6427	42.1	14	1.7	0.1752
Income	2	11.7	5.9	0.6	0.5264	5.4	2.7	0.3	0.7415	9.3	4.6	0.5	0.578
Marital status	3	90.2	30.1	3.3	0.0201	70.4	23.5	2.6	0.0517	27.5	9.2	1.1	0.3566
Smoking status	2	100	50	5.5	0.0044	158.2	79.1	8.7	0.0002	179.4	89.7	10.6	< 0.0001
Alcohol consumption	2	5.3	2.6	0.3	0.7497	44.4	22.2	2.5	0.0868	66.6	33.3	3.9	0.02
LVMl	2	64.7	32.4	3.5	0.0294	50.9	25.5	2.8	0.0607	56.2	28.1	3.3	0.0368
Diabetes	1					0.9	0.9	0.1	0.7563	9.9	9.9	1.2	0.279
Hypertension	1					0.2	0.2	0	0.8784	0.4	0.4	0.1	0.8231
Waist to height ratio	2					1.5	0.7	0.1	0.9224	27.4	13.7	1.6	0.1995
Cholesterol ratio	4					34.1	8.5	0.9	0.4389	30.2	7.5	0.9	0.469
Intake of lipid-lowering drugs	3					0.3	0.1	0	0.9982	9.4	3.1	0.4	0.7755
Intake of antihypertensive drugs	5					146.3	29.3	3.2	0.0068	95.2	19	2.2	0.048
Pulse pressure	4					257.1	64.3	7.1	< 0.0001	143.8	36	4.2	0.0021
Diastolic BP	4					89.1	22.3	2.5	0.0442	45.8	11.5	1.4	0.2488
Cholesterol ratio * Intake of lipid-lowering drugs	2					0.2	0.1	0	0.9914	9.3	4.7	0.6	0.5768
Pulse pressure * Intake of antihypertensive drugs	2					133.1	66.6	7.3	0.0007	91.8	45.9	5.4	0.0046
Diastolic BP * Intake of antihypertensive drugs	2					6.1	3	0.3	0.7145	3.4	1.7	0.2	0.8174
E/é	2					0	0			66.5	33.3	3.9	0.0202
E/A	2					0	0			54.8	27.4	3.2	0.0401
LAI	2					0	0			53.2	26.6	3.1	0.044
Total	55	232205.3	7490.5	819.8	< 0.0001	259642.7	5298.8	584.9	< 0.0001	259068.5	4710.3	555.9	< 0.0001
Error	747	7409.7	9.1			7184.3	9.1			6329.8	8.5		

Supplementary Table 17: Analyses of variance of model 1, 2, and 3 of brain age (complete case analyses). Tests included all interaction terms of the corresponding factor. E/A - ratio of early and late mitral inflow velocities in diastole. E/e' - ratio of early mitral inflow velocity and early mitral annular velocity in diastole.