Supplementary Material

One-Year Aerobic Exercise Increases Cerebral Blood Flow in Cognitively Normal Older Adults

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Running Title: Aerobic Exercise and Cerebral Hemodynamics

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Table S1. Volumetric blood flow, vessel diameter, and mean blood flow velocity by groups

	Stretching-and-Toning		Aerobic Exercise Training		Effect p-values		
	Baseline	12-month	Baseline	12-month	Time	Group	Time × Group
Volumetric blood flow (mL/min)							
R ICA	232 ± 48	236 ± 43	226 ± 32	237 ± 52	0.238	0.800	0.622
L ICA	209 ± 41	199 ± 42	206 ± 58	217 ± 45	0.964	0.499	0.118
R VA	80 ± 38	77 ± 34	73 ± 27	77 ± 32	0.855	0.691	0.180
L VA	80 ± 31	88 ± 34	79 ± 34	81 ± 36	0.075	0.689	0.278
Vessel diameter (mm)							
R ICA	4.5 ± 2.6	4.7 ± 2.7	4.6 ± 2.9	4.5 ± 2.6	0.494	0.826	0.113
L ICA	4.3 ± 1.9	4.3 ± 1.8	4.3 ± 2.3	4.4 ± 2.2	0.212	0.614	0.296
R VA	3.4 ± 2.0	3.5 ± 2.2	3.4 ± 1.8	3.4 ± 1.8	0.386	0.924	0.433
L VA	3.4 ± 2.0	3.5 ± 2.0	3.5 ± 2.1	3.5 ± 2.3	0.286	0.751	0.974
Blood flow velocity (cm/sec)							
R ICA	25.7 ± 6.4	24.5 ± 6.7	25.2 ± 7.3	25.7 ± 5.7	0.676	0.808	0.346
L ICA	24.4 ± 5.5	22.8 ± 4.7	24.4 ± 8.2	24.5 ± 6.9	0.446	0.576	0.378
R VA	14.3 ± 3.4	13.7 ± 2.7	13.2 ± 3.4	13.5 ± 3.2	0.787	0.364	0.314
L VA	14.5 ± 3.4	15.7 ± 4.3	14.2 ± 3.7	14.1 ± 4.4	0.219	0.309	0.205

Data are mean ± standard deviation. ICA, internal carotid artery; L, left; R, right; VA, vertebral artery.

Table S2. Pearson's product-moment correlation coefficients and (p-value) illustrate the associations between the one-year changes (Δ) in carotid and cerebral hemodynamic variables

	Carotid hemodynamics					*Cerebral hemodynamics*				
	ΔcSBP	ΔcPP	Δβstiffness	ΔcfPWV	ΔCIMT	ΔnCBF	ΔnCVR	ΔmCBFV	ΔCVRi	ΔPI
Stretching-and-toning										
ΔcSBP		**0.869**	0.181	-0.034	0.052	-0.342	**0.785**	0.129	0.372	0.037
ΔcPP	**(0.001)**		**0.469**	-0.171	-0.077	-0.365	**0.466**	-0.004	0.161	0.322
Δβ-stiffness	(0.367)	**(0.016)**		-0.319	-0.021	0.327	-0.247	-0.291	0.085	**0.428**
ΔcfPWV	(0.868)	(0.403)	(0.104)		0.169	-0.078	0.141	0.058	-0.085	-0.240
ΔCIMT	(0.797)	(0.709)	(0.918)	(0.399)		-0.110	0.164	-0.094	0.161	0.115
ΔnCBF	(0.094)	(0.079)	(0.111)	(0.709)	(0.601)		**-0.546**	-0.221	0.143	0.047
ΔnCVR	**(0.001)**	**(0.022)**	(0.233)	(0.501)	(0.434)	**(0.005)**		0.161	0.358	-0.301
ΔmCBFV	(0.587)	(0.986)	(0.213)	(0.809)	(0.695)	(0.363)	(0.509)		**-0.715**	-0.095
ΔCVRi	(0.107)	(0.496)	(0.722)	(0.721)	(0.497)	(0.560)	(0.133)	**(0.001)**		-0.102
ΔPI	(0.871)	(0.144)	**(0.047)**	(0.282)	(0.609)	(0.841)	(0.184)	(0.690)	(0.669)	
Aerobic Exercise Training										
ΔcSBP		**0.878**	0.275	0.095	0.187	-0.051	**0.742**	-0.269	**0.753**	0.090
ΔcPP	**(0.001)**		0.196	-0.021	0.254	0.011	**0.494**	0.060	0.257	-0.194
Δβ-stiffness	(0.157)	(0.328)		0.045	0.063	**-0.506**	**0.510**	-0.284	0.230	**0.622**
ΔcfPWV	(0.629)	(0.919)	(0.822)		-0.240	0.329	-0.161	-0.013	0.097	0.041
ΔCIMT	(0.342)	(0.202)	(0.750)	(0.219)		-0.120	0.161	-0.138	0.352	0.195
ΔnCBF	(0.799)	(0.957)	**(0.007)**	(0.094)	(0.550)		**-0.629**	**0.630**	-0.347	**-0.484**
ΔnCVR	**(0.001)**	**(0.010)**	**(0.007)**	(0.421)	(0.422)	**(0.001)**		**-0.681**	**0.814**	**0.484**
ΔmCBFV	(0.251)	(0.803)	(0.225)	(0.956)	(0.561)	**(0.004)**	**(0.001)**		**-0.746**	**-0.559**
ΔCVRi	**(0.001)**	(0.274)	(0.329)	(0.683)	(0.128)	(0.145)	**(0.001)**	**(0.001)**		**0.486**
ΔPI	(0.707)	(0.412)	**(0.003)**	(0.864)	(0.409)	**(0.036)**	**(0.036)**	**(0.010)**	**(0.030)**	

cSBP, carotid systolic blood pressure; cPP, carotid pulse pressure; β-stiffness, carotid β-stiffness index; cfPWV, carotid-femoral pulse wave velocity; CIMT, carotid intima-media thickness; nCBF, normalized cerebral blood flow; nCVR, normalized cerebrovascular resistance; mCBFV, mean cerebral blood flow velocity; CVRi, cerebrovascular index; PI, pulsatility index. Bold values represent $p < 0.05$. Data of mCBFV, CVRi, and PI were measured at the middle cerebral artery and are available 22 in SAT and 21 in AET.

Table S3. Correlation between one-year changes (Δ) in neurocognitive performance and hemodynamic variables

	ΔcSBP	ΔcPP	Δβstiffness	ΔcfPWV	ΔCIMT	ΔnCBF	ΔnCVR	ΔmCBFV	ΔCVRi	ΔPI
Stretching-and-toning										
ΔETS Letter Sets	-0.204 (0.339)	-0.191 (0.382)	-0.153 (0.474)	0.005 (0.982)	-0.106 (0.621)	0.265 (0.211)	-0.186 (0.385)	-0.128 (0.601)	0.034 (0.891)	-0.105 (0.660)
ΔRPM accuracies	-0.120 (0.576)	0.071 (0.746)	0.109 (0.611)	-0.087 (0.685)	0.053 (0.806)	**0.436 (0.033)**	-0.344 (0.100)	-0.218 (0.371)	0.077 (0.754)	0.086 (0.718)
ΔLM Immediate recalls	-0.171 (0.425)	-0.219 (0.316)	0.110 (0.61)	**-0.445 (0.029)**	-0.164 (0.444)	0.345 (0.099)	-0.128 (0.552)	0.049 (0.843)	-0.033 (0.894)	0.276 (0.238)
ΔLM Delayed recalls	-0.355 (0.088)	-0.253 (0.245)	-0.001 (0.997)	-0.176 (0.410)	-0.110 (0.610)	-0.017 (0.937)	-0.246 (0.246)	0.122 (0.618)	-0.222 (0.360)	0.222 (0.346)
ΔWJ Immediate recalls	-0.074 (0.729)	0.011 (0.959)	-0.009 (0.966)	0.197 (0.355)	-0.155 (0.468)	0.106 (0.622)	-0.228 (0.283)	0.370 (0.118)	-0.251 (0.301)	0.002 (0.994)
ΔWJ Delayed recalls	-0.280 (0.185)	-0.334 (0.119)	-0.027 (0.901)	0.224 (0.292)	-0.076 (0.724)	0.129 (0.548)	-0.202 (0.343)	0.278 (0.249)	-0.121 (0.623)	0.128 (0.591)
ΔDigit Comparison	-0.203 (0.342)	-0.075 (0.732)	-0.119 (0.579)	0.054 (0.803)	-0.095 (0.660)	-0.264 (0.213)	-0.184 (0.390)	0.019 (0.938)	-0.250 (0.302)	0.162 (0.496)
ΔLetter Number Sequencing	-0.291 (0.168)	-0.183 (0.402)	-0.188 (0.379)	-0.082 (0.702)	-0.193 (0.367)	-0.233 (0.274)	-0.214 (0.316)	0.408 (0.083)	**-0.595 (0.007)**	0.350 (0.13)
ΔOperation Span	0.063 (0.769)	0.066 (0.763)	0.043 (0.843)	0.249 (0.240)	0.111 (0.607)	0.12 (0.576)	0.057 (0.79)	-0.018 (0.941)	0.071 (0.771)	**-0.455 (0.044)**
ΔCOWAT-FAS	0.017 (0.937)	-0.121 (0.581)	-0.132 (0.540)	-0.229 (0.281)	-0.026 (0.902)	0.100 (0.643)	0.093 (0.664)	0.312 (0.194)	-0.045 (0.856)	-0.138 (0.561)
ΔETS Vocabulary	0.230 (0.279)	0.156 (0.476)	-0.351 (0.093)	**0.514 (0.010)**	0.034 (0.873)	**-0.447 (0.028)**	0.256 (0.228)	0.205 (0.400)	-0.152 (0.534)	-0.016 (0.945)

cSBP, carotid systolic blood pressure; cPP, carotid pulse pressure; β-stiffness, carotid β-stiffness index; cfPWV, carotid-femoral pulse wave velocity; CIMT, carotid intima-media thickness; nCBF and nCVR, normalized cerebral blood flow and cerebrovascular resistance by total brain tissue mass measured by magnetic resonance imaging; mCBFV, mean cerebral blood flow velocity; CVRi, cerebrovascular index; PI, pulsatility index; ETS, educational testing service; RPM, Raven's Progressive Matrices; LM, logical memory; WJ, Woodcock-Johnson, COWAT-FAS, COWAT-FAS, Controlled Word Association FAS. Data of mCBFV, CVRi, and PI were measured at the middle cerebral artery and are available 22 in SAT. Bold values represent $p < 0.05$.

Table S3 (Cont.). Correlation between one-year changes (Δ) in neurocognitive performance and hemodynamic variables

	ΔcSBP	ΔcPP	Δβstiffness	ΔcfPWV	ΔCIMT	ΔnCBF	ΔnCVR	ΔmCBFV	ΔCVRi	ΔPI
Aerobic Exercise Training										
ΔETS Letter Sets	-0.157 (0.436)	-0.249 (0.220)	0.128 (0.524)	0.262 (0.187)	0.345 (0.078)	0.186 (0.364)	-0.236 (0.245)	-0.041 (0.866)	0.127 (0.604)	0.275 (0.255)
ΔRPM accuracies	0.039 (0.847)	0.361 (0.070)	-0.218 (0.275)	-0.337 (0.085)	0.027 (0.894)	-0.032 (0.876)	-0.099 (0.632)	0.348 (0.144)	**-0.594 (0.007)**	-0.396 (0.093)
ΔLM Immediate recalls	**-0.473 (0.013)**	-0.325 (0.106)	-0.178 (0.374)	-0.053 (0.791)	-0.152 (0.45)	0.048 (0.818)	**-0.423 (0.031)**	0.205 (0.400)	**-0.516 (0.024)**	-0.163 (0.505)
ΔLM Delayed recalls	-0.265 (0.182)	-0.301 (0.136)	-0.171 (0.393)	-0.055 (0.786)	-0.137 (0.496)	-0.034 (0.870)	-0.020 (0.924)	0.158 (0.519)	-0.179 (0.464)	-0.207 (0.395)
ΔWJ Immediate recalls	**-0.394 (0.042)**	-0.300 (0.136)	**-0.498 (0.008)**	-0.097 (0.629)	-0.062 (0.761)	0.290 (0.151)	**-0.483 (0.012)**	0.147 (0.547)	-0.329 (0.169)	-0.449 (0.054)
ΔWJ Delayed recalls	-0.182 (0.364)	-0.221 (0.278)	-0.058 (0.775)	0.014 (0.945)	-0.290 (0.143)	0.189 (0.354)	-0.206 (0.312)	-0.034 (0.891)	-0.115 (0.640)	-0.047 (0.849)
ΔDigit Comparison	0.172 (0.390)	0.169 (0.410)	0.227 (0.255)	0.215 (0.281)	0.052 (0.795)	-0.069 (0.737)	0.205 (0.316)	-0.451 (0.053)	0.298 (0.216)	0.238 (0.326)
ΔLetter Number Sequencing	0.050 (0.805)	0.102 (0.619)	-0.036 (0.859)	0.060 (0.765)	0.216 (0.278)	-0.118 (0.564)	0.109 (0.596)	0.042 (0.864)	-0.041 (0.869)	-0.082 (0.739)
ΔOperation Span	-0.033 (0.868)	0.149 (0.467)	-0.070 (0.730)	**-0.473 (0.013)**	**0.417 (0.030)**	0.057 (0.782)	-0.082 (0.690)	0.307 (0.202)	-0.193 (0.428)	-0.066 (0.789)
ΔCOWAT-FAS	0.163 (0.416)	0.119 (0.562)	0.210 (0.292)	0.104 (0.604)	0.115 (0.568)	0.212 (0.300)	-0.122 (0.552)	0.062 (0.802)	0.323 (0.177)	0.268 (0.267)
ΔETS Vocabulary	0.103 (0.609)	0.218 (0.284)	-0.101 (0.615)	0.010 (0.959)	0.194 (0.333)	0.119 (0.562)	-0.121 (0.556)	0.319 (0.183)	-0.207 (0.395)	-0.008 (0.973)

cSBP, carotid systolic blood pressure; cPP, carotid pulse pressure; β-stiffness, carotid β-stiffness index; cfPWV, carotid-femoral pulse wave velocity; CIMT, carotid intima-media thickness; nCBF and nCVR, normalized cerebral blood flow and cerebrovascular resistance by total brain tissue mass measured by magnetic resonance imaging; mCBFV, mean cerebral blood flow velocity; CVRi, cerebrovascular index; PI, pulsatility index; ETS, educational testing service; RPM, Raven's Progressive Matrices; LM, logical memory; WJ, Woodcock-Johnson, COWAT-FAS, COWAT-FAS, Controlled Word Association FAS. Data of mCBFV, CVRi, and PI were measured at the middle cerebral artery and are available 21 in AET. Bold values represent $p < 0.05$.

Table S4: Test-retest reliability estimates compared between the baseline and 12-month follow-up measurements

		n	ICC	(95% CI)			p-value
Peak oxygen consumption	mL/min	54	0.952	0.917	to	0.972	**<0.001**
	mL/kg/min	54	0.899	0.826	to	0.942	**<0.001**
Carotid hemodynamics parameters							
Systolic blood pressure		55	0.617	0.343	to	0.777	**<0.001**
Pulse pressure		55	0.681	0.453	to	0.814	**<0.001**
β-stiffness index		55	0.825	0.701	to	0.898	**<0.001**
carotid-femoral pulse wave velocity		55	0.790	0.640	to	0.877	**<0.001**
Intima-media thickness		55	0.836	0.719	to	0.905	**<0.001**
Cerebral hemodynamics parameters							
Total CBF		55	0.898	0.825	to	0.940	**<0.001**
Internal carotid artery blood flow		55	0.880	0.794	to	0.930	**<0.001**
Vertebral artery blood flow		55	0.904	0.835	to	0.944	**<0.001**
Normalized CBF		55	0.884	0.797	to	0.933	**<0.001**
CVR		55	0.780	0.622	to	0.871	**<0.001**
Normalized CVR		55	0.843	0.726	to	0.910	**<0.001**
CBF velocity		43	0.955	0.914	to	0.976	**<0.001**
CVR index		43	0.925	0.859	to	0.961	**<0.001**
Pulsatility index		43	0.902	0.819	to	0.947	**<0.001**

Intraclass correlations (ICC) and 95% confidence interval (CI) were calculated by the two-way mixed, average measures. *n* is the number of observations included in the analysis. CBF, cerebral blood flow; CVR, cerebrovascular resistance.

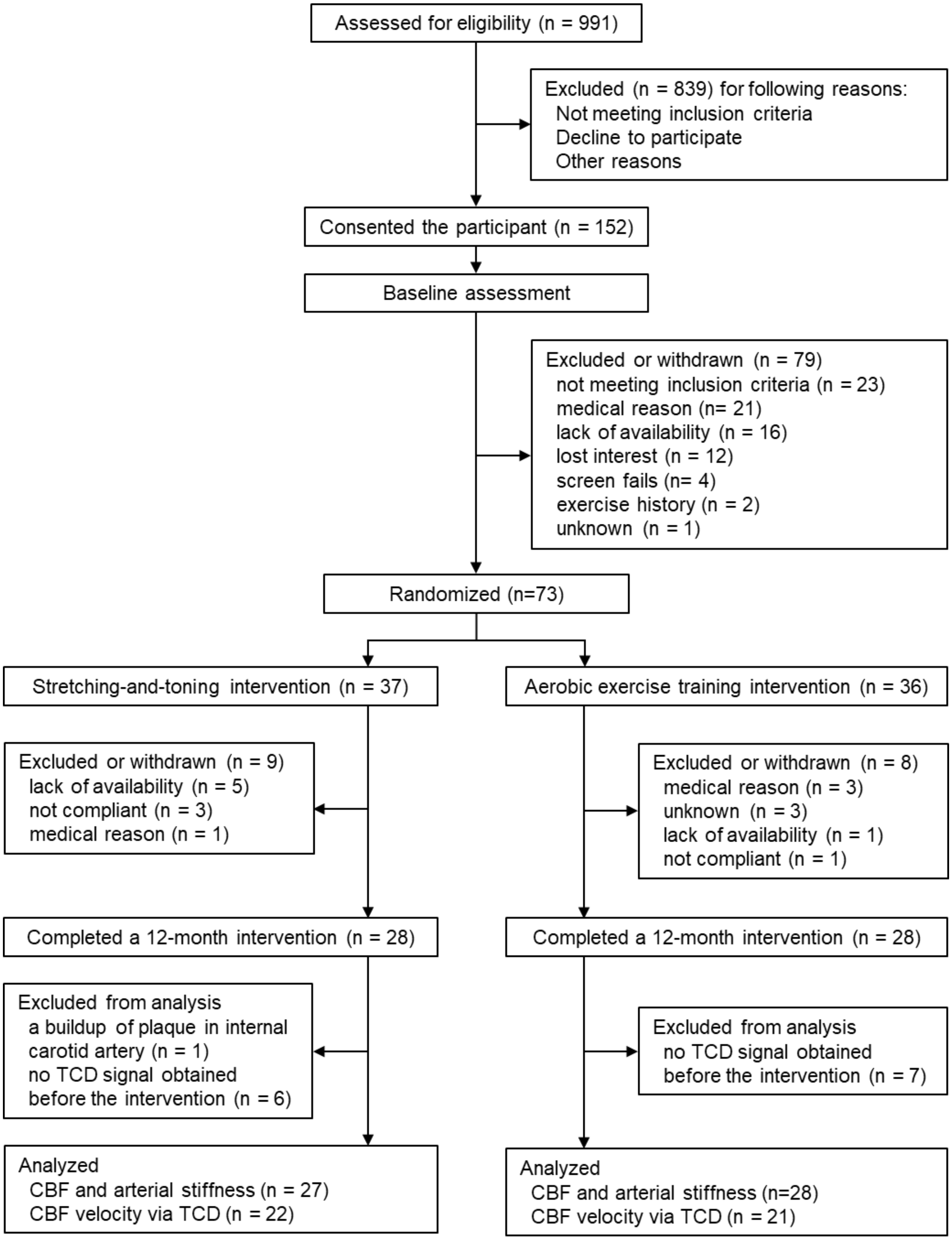
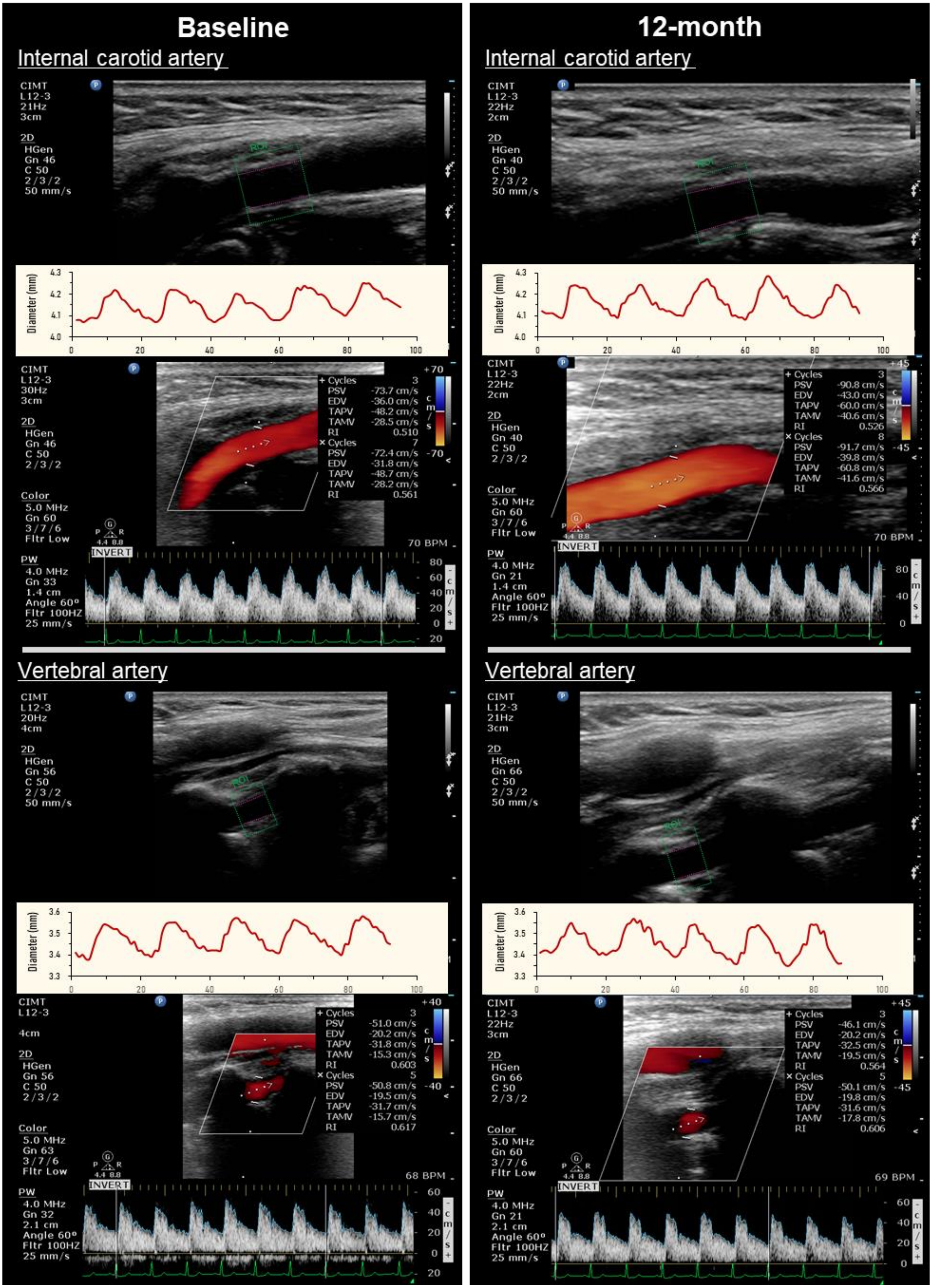


Figure S1: Participant flowchart. Participants were randomized into 12-months of aerobic exercise training or stretching-and-toning programs. Statistical analysis was performed in 55 participants (27 in stretching-and-toning and 28 in aerobic exercise training) who completed the training and had cerebral blood flow (CBF) and arterial stiffness measurements. Among the 55 participants, 43 (22 in stretching-and-toning and 21 in aerobic exercise training) had CBF velocity measurements via transcranial Doppler (TCD).



Baseline
12-month
Internal carotid artery
CIMT
L12-3
21Hz
3cm
2D
HGen
Gn 46
C 50
2/3/2
50 mm/s
ROI
Diameter (mm)
+ Cycles 3
PSV -73.7 cm/s
EDV -36.0 cm/s
TAPV -48.2 cm/s
TAMV -28.5 cm/s
RI 0.510
× Cycles 7
PSV -72.4 cm/s
EDV -31.8 cm/s
TAPV -48.7 cm/s
TAMV -28.2 cm/s
RI 0.561
70 BPM
INVERT
PW
4.0 MHz
Gn 33
1.4 cm
Angle 60°
Fltr 100HZ
25 mm/s
CIMT
L12-3
22Hz
2cm
2D
HGen
Gn 40
C 50
2/3/2
50 mm/s
+ Cycles 3
PSV -90.8 cm/s
EDV -43.0 cm/s
TAPV -60.0 cm/s
TAMV -40.6 cm/s
RI 0.526
× Cycles 8
PSV -91.7 cm/s
EDV -39.8 cm/s
TAPV -60.8 cm/s
TAMV -41.6 cm/s
RI 0.566
70 BPM
PW
4.0 MHz
Gn 21
1.4 cm
Angle 60°
Fltr 100HZ
25 mm/s
Vertebral artery
CIMT
L12-3
20Hz
4cm
2D
HGen
Gn 56
C 50
2/3/2
50 mm/s
+ Cycles 3
PSV -51.0 cm/s
EDV -20.2 cm/s
TAPV -31.8 cm/s
TAMV -15.3 cm/s
RI 0.603
× Cycles 5
PSV -50.8 cm/s
EDV -19.5 cm/s
TAPV -31.7 cm/s
TAMV -15.7 cm/s
RI 0.617
Color
5.0 MHz
Gn 63
3/7/6
Fltr Low
68 BPM
PW
4.0 MHz
Gn 32
2.1 cm
Angle 60°
Fltr 100HZ
25 mm/s
CIMT
L12-3
21Hz
3cm
2D
HGen
Gn 66
C 50
2/3/2
50 mm/s
+ Cycles 3
PSV -46.1 cm/s
EDV -20.2 cm/s
TAPV -32.5 cm/s
TAMV -19.5 cm/s
RI 0.564
× Cycles 5
PSV -50.1 cm/s
EDV -19.8 cm/s
TAPV -31.6 cm/s
TAMV -17.8 cm/s
RI 0.606
Color
5.0 MHz
Gn 60
3/7/6
Fltr Low
69 BPM
PW
4.0 MHz
Gn 21
2.1 cm
Angle 60°
Fltr 100HZ
25 mm/s

Figure S2: Representation of ultrasonography image of measurement of blood flow in the right internal carotid artery (ICA: upper panel) and the right vertebral artery (VA: lower panel) with color-coded duplex ultrasonogram at baseline (left side) and 12-month (right side) from one subject in the aerobic exercise training group. High-resolution B-mode image of the ICA and VA. Regions of interest, represented by the green rectangles are manually selected to cover a segment of the ICA or VA, the double pink lines are the detected vessel inner walls used to track the wall movements and to measure beat-by-beat pulsatile changes of vessel diameter for the ICA and VA. Beat-by-beat recordings of blood flow velocity at the sites of diameter measurements are presented for the ICA and VA.

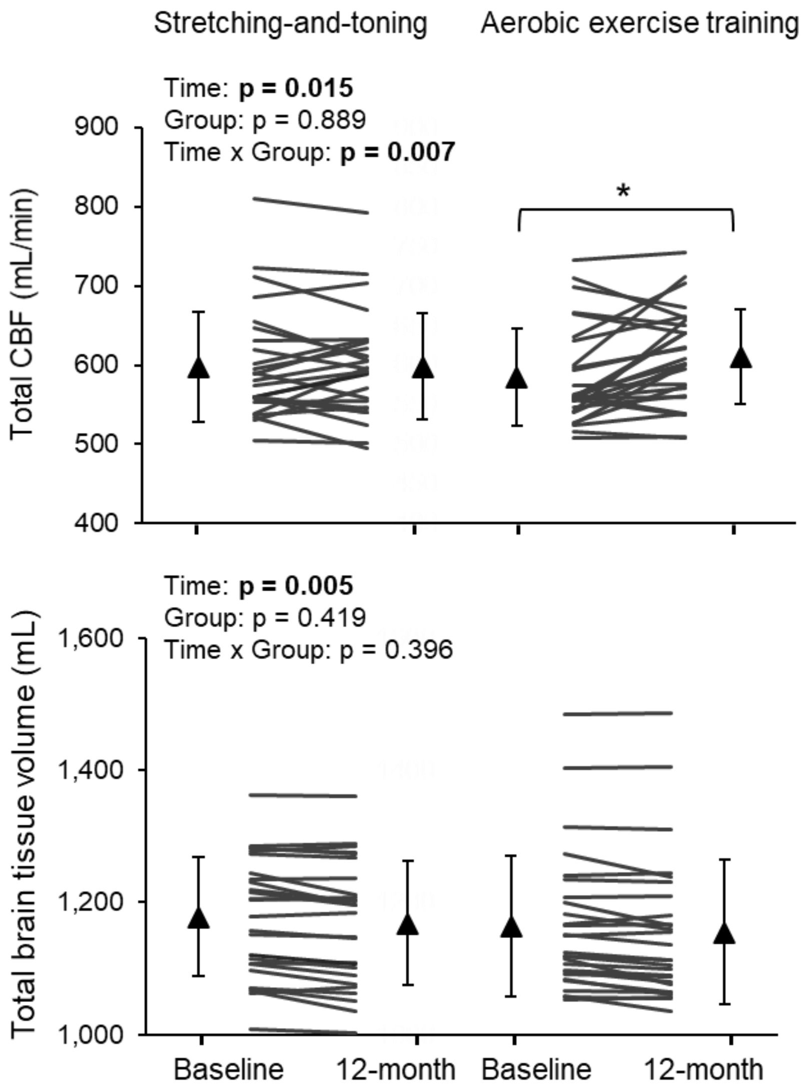


Figure S3: Changes in total cerebral blood flow (CBF) (upper panel) and total brain tissue volume (lower panel) after one-year stretching-and-toning or aerobic exercise training. Thin lines represent individual changes. Triangles show mean values and the error bars represent standard deviations. ∗ $p < 0.05$ compared with baseline after Bonferroni correction.

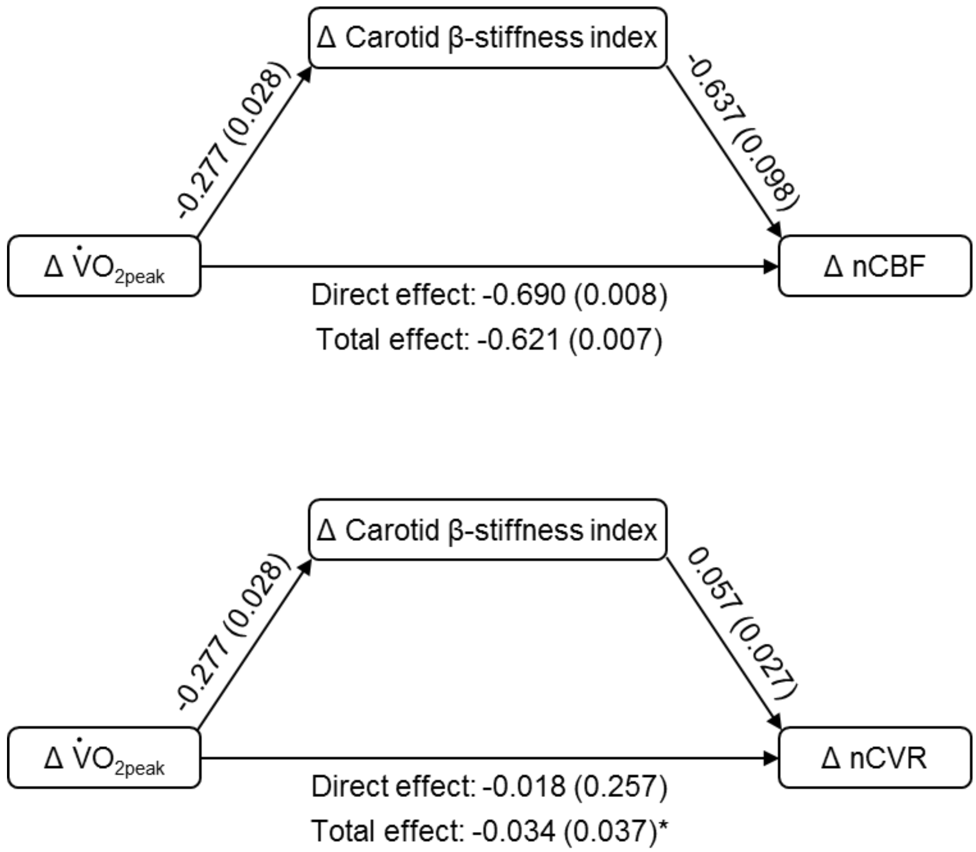


Figure S4: Mediation model to assess the relationship between changes in peak oxygen consumption ($\dot{V}O_{2peak}$) and normalized cerebral blood flow (nCBF: upper panel) or cerebrovascular resistance (nCVR: lower panel) with carotid β-arterial stiffness as a mediator in the aerobic exercise training group. Data are unstandardized regression coefficient (p-value). Changes in carotid β-arterial stiffness attenuated the negative association between $\dot{V}O_{2peak}$ and nCVR. * This result was further confirmed by a bootstrapping assessment, which demonstrated significant indirect effects of carotid β-arterial stiffness on nCVR (95% confidence interval: -0.005 to -0.037). A data set of n = 28 was used for modeling.