

**Comprehensive allostatic load risk index is associated with increased frontal and left parietal white matter hyperintensities in mid-life healthy cognitively adults.**

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# Supplementary Material

- **Supplementary Table S1.** Statistical comparisons between males and females for age
- **Supplementary Table S2.** Multinomial Logistic Regression for Comprehensive AL scoring (ALSC) risk categories and demographic covariates
- **Supplementary Table S3.** Intracranial and brain volumes before and after eICV or eTIV correction method
- **Supplementary Table S4.** Multiple comparison test of associated MRI measurements between ALCS risk categories
- **Supplementary Table S5.** Model fit comparison between ALCS and ALES algorithms in selected MRI measurements
- **Supplementary Table S6.** Univariate regression analysis of strongly associated WMHV and AL risk categories derived from a non-cardiovascular index.
- **Supplementary Table S7.** Cut-off thresholds for Allostatic Load scorings

**Supplementary Table S1. Statistical comparisons between males and females**

		<b>Mean ± SD</b>	<b>Normality<sup>a</sup></b>	<b>Independent samples test<sup>b</sup></b>
<b>Age</b>	Males	51.71 ± 5.56	W=0.931, p<0.001	U=41731.5, p=0.07
	Females	50.97 ± 5.41	W=0.951, p<0.001	
<b>Years Education</b>	Males	16.35 ± 3.2	W=0.959, p<0.001	U=47973, p=0.287
	Females	16.75 ± 3.68	W=0.957, p<0.001	
<b>ALCS score</b>	Males	6.88 ± 3.99	W=0.939, p<0.001	U=38615.5, p=0.001
	Females	5.79 ± 3.83	W=0.945, p<0.001	
<b>ALES score</b>	Males	4.22 ± 2.73	W=0.942, p<0.001	U=41374.5, p=0.047
	Females	3.77 ± 2.64	W=0.939, p<0.001	

<sup>a</sup> Shapiro-Wilk test  
<sup>b</sup> 2-sided Mann-Whitney test ( $\alpha=0.05$ )

**Supplementary Table S2. MLR for ALCS risk categories and demographic covariates  
(No-risk category set as reference category)**

	Low risk		Medium risk		High risk		Overall likelihood ratio test	
	aOR	95% CI	aOR	95% CI	aOR	95% CI	$\chi^2$ (3)	p
<b>Age</b>	1.1	[0.98, 1.23]	1.16 **	[1.04, 1.29]	1.2 **	[1.07, 1.34]	24.66	<0.001
<b>Sex</b>	0.11 *	[0.01, 0.86]	0.11 *	[0.01, 0.84]	0.13	[0.02, 1.08]	9.05	0.029
<b>Educational level</b>	0.76	[0.44, 1.31]	0.72	[0.42, 1.24]	0.58	[0.33, 1]	9.89	0.019
<b>Employment</b>	0.92	[0.1, 8.24]	0.7	[0.08, 6.12]	0.78	[0.09, 6.9]	0.84	0.84
<b>Smoking history</b>	0.61	[0.25, 1.5]	0.49	[0.2, 1.2]	0.7	[0.29, 1.73]	6.03	0.11
<b>Parent dementia history</b>	5.51	[0.66, 45.99]	5.44	[0.65, 45.53]	3.52	[0.42, 29.72]	7.24	0.065
<b>Direct relative AD</b>	0.14	[0.01, 1.37]	0.17	[0.02, 1.64]	0.22	[0.02, 2.12]	4.98	0.173
<b>APOE<math>\epsilon</math>4 carriers</b>	0.8	[0.25, 2.62]	0.9	[0.28, 2.93]	1.08	[0.33, 3.56]	1.79	0.618
<b>Subjective memory complaint</b>	0.76	[0.21, 2.76]	0.67	[0.18, 2.42]	0.7	[0.19, 2.56]	0.59	0.898

aOR: adjusted odds ratio. AD: Alzheimer's disease.  
\*p<0.05, \*\*p<0.01, \*\*\* p<0.001

**Supplementary Table S3. Intracranial and brain volumes before and after eICV or eTIV correction method**

	<b>Total Sample (n=571)</b>	<b>Males (n=227)</b>	<b>Females (n=344)</b>	<b>p</b>
<b>eICV (SD)</b>	1492077.4 (162263.66)	1608918.24 (134196.86)	1414976.03 (129968.82)	<0.001
<b>WM (SD)</b>	467785.8 (58412.4)	507380.56 (55512.14)	441657.86 (43788.77)	<0.001
<b>GM (SD)</b>	647551.3 (58440.87)	692394.57 (48926.21)	617959.96 (43466.64)	<0.001
<b>SCG (SD)</b>	57160.59 (5161.1)	60592.4 (4562.33)	54896 (4196.8)	<0.001
<b>IHC (SD)</b>	4018.53 (405.21)	4219.14 (410.02)	3886.15 (343.33)	<0.001
<b>rHC (SD)</b>	4136.03 (434.92)	4338.52 (436.41)	4002.41 (379.22)	<0.001
<b>adj WM (SD)</b>	467785.8 (34491.36)	473379.87 (36422.7)	464094.36 (32687.99)	0.002
<b>adj GM (SD)</b>	647551.3 (35613.36)	658978.09 (33597.12)	640010.95 (34935.93)	<0.001
<b>adj SC Grey (SD)</b>	57160.59 (3531.69)	57905.06 (3491.43)	56669.33 (3476.58)	<0.001
<b>adj IHC (SD)</b>	4018.53 (326.37)	3985.46 (341.85)	4040.36 (314.34)	0.049
<b>adj rHC (SD)</b>	4136.03 (348.46)	4104.83 (361.8)	4156.62 (338.33)	0.082
	<b>Total Sample (n=481)</b>	<b>Males (n=190)</b>	<b>Females (n=291)</b>	<b>p</b>
<b>eTIV (SD)</b>	1496126.75 (150288.05)	1605755.79 (129132.38)	1424547.65 (116195.93)	<0.001
<b>CA1</b>	1371.22 (150.02)	1442.63 (153.47)	1324.6 (127.99)	<0.001
<b>adj CA1</b>	1371.22 (134.51)	1333 (133.53)	1396.18 (129.39)	<0.001

p<0.05, statistically significant after 2-tailed unpaired t-test between sex. SD - Standard-deviation.

eICV: estimated intracranial volume; WM: white matter volume GM: grey matter volume; SCG: subcortical grey matter volume; IHC: left Hippocampal volume; rHC: right hippocampal volume; eTIV: estimated total intracranial volume (for CA1 correction); CA1: Hippocampal CA1 subregion volume; adj: volume after residual correction method.

**Supplementary Table S4. Multiple comparison test of associated MRI measurements between ALCS risk categories**

Kruskal-Wallis test				Dunn's test for multiple comparisons <sup>a</sup>			
	H(3)	p	AL category	Mean ± SEM	vs. Low	vs. Medium	vs. High
<b>PV WMHV<sup>c</sup></b>	H(3) = 18.86	<0.001	No risk	1.44 ± 0.84	Q= 1.25; p= 1.000	Q= 1.95; p= 0.308	Q= 2.64; <b>p= 0.049</b>
			Low risk	1.2 ± 0.12			Q= 3.87; <b>p= 0.001</b>
			Medium risk	1.45 ± 0.13			Q= 2.03; p= 0.253
			High risk	2.12 ± 0.28			
<b>LF WMHV<sup>c</sup></b>	H(3) = 16.65	<0.001	No risk	0.27 ± 0.07	Q= 0.75; p= 1.000	Q= 1.42; p= 0.938	Q= 2.12; p= 0.202
			Low risk	0.39 ± 0.04			Q= 3.82; <b>p= 0.001</b>
			Medium risk	0.54 ± 0.06			Q= 2.06; p= 0.238
			High risk	0.8 ± 0.11			
<b>RF WMHV<sup>c</sup></b>	H(3) = 16.33	<0.001	No risk	0.37 ± 0.12	Q= 0.81; p= 1.000	Q= 1.66; p= 0.586	Q= 2.12; p= 0.202
			Low risk	0.45 ± 0.04			Q= 3.66; <b>p= 0.001</b>
			Medium risk	0.69 ± 0.12			Q= 1.38; p= 1.000
			High risk	0.83 ± 0.1			
<b>LP WMHV<sup>c</sup></b>	H(3) = 10.05	0.018	No risk	0.05 ± 0.03	Q= 0.11; p= 1.000	Q= 0.73; p= 1.000	Q= 1.23; p= 1.000
			Low risk	0.12 ± 0.03			Q= 3.08; <b>p= 0.012</b>
			Medium risk	0.15 ± 0.03			Q= 1.45; p= 0.89
			High risk	0.23 ± 0.06			
<b>LT WMHV<sup>c</sup></b>	H(3) = 6.11	0.106	No risk	0.04 ± 0.03			
			Low risk	0.08 ± 0.01			
			Medium risk	0.1 ± 0.02			
			High risk	0.13 ± 0.03			

SCGM: subcortical grey matter volume; WMHV: white matter hyperintensity volume; PV: peri-ventricular; LF: left-frontal; RF: right-frontal; LP: left-parietal; LT: left-temporal.

<sup>a</sup> p values adjusted by Bonferroni correction.

<sup>b</sup> Adjusted to eICV by residual correction method.

<sup>c</sup> Normalized to SPM12 total intracranial volume (TIV).

**Supplementary Table S5. Model fit comparison between ALCS and ALES algorithms in selected MRI measurements<sup>a</sup>**

		<b>F(1,565)</b>	<b>R<sup>2</sup></b>	<b>ΔR<sup>2</sup></b>	<b>BIC</b>	<b>ΔBIC</b>
<b>Total WMHV</b>	ALCS	7.68**	0.013	0.001	-61.6553	-0.6929
	ALES	6.99**	0.012	REF	-60.9624	REF
<b>PV WMHV</b>	ALCS	10.54**	0.018	0.003	-616.0605	-2.048
	ALES	8.46**	0.015	REF	-614.0125	REF
<b>LF WMHV</b>	ALCS	17.06***	0.029	0.009	-1712.238	-5.3112
	ALES	11.44**	0.02	REF	-1706.927	REF
<b>RF WMHV</b>	ALCS	8.04**	0.014	0.002	-1373.027	-1.366
	ALES	6.66*	0.012	REF	-1371.661	REF
<b>LP WMHV</b>	ALCS	4.2*	0.007	-0.001	-2323.829	0
	ALES	4.32*	0.008	REF	-2323.829	REF
<b>LT WMHV</b>	ALCS	3.97*	0.007	0	-3048.837	0
	ALES	3.72	0.007	REF	-3048.837	REF

WMHV: white matter hyperintensity volume, PV: peri-ventricular; LF: left-frontal; RF: right-frontal; LP: left-parietal; LT: left-temporal.

<sup>a</sup> MRI measurements selected for showing strong associations when regressed on ALCS univariate model.  
\* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001

**Supplementary Table S6. Univariate regression analysis of strongly associated WMHV and AL risk categories derived from a non-cardiovascular index<sup>a</sup>**

	<b>F(1,565)</b>	<b>β<sup>b</sup></b>	<b>p</b>
<b>Total WMHV</b>	2.58	0.067	0.109
<b>PV WMHV</b>	3.5	0.079	0.062
<b>LF WMHV</b>	5.49	0.098	0.019*
<b>RF WMHV</b>	3.23	0.75	0.073
<b>LP WMHV</b>	1.33	0.049	0.249
<b>LT WMHV</b>	1.39	0.05	0.239

WMHV: white matter hyperintensity volume, PV: peri-ventricular; LF: left-frontal; RF: right-frontal; LP: left-parietal; LT: left-temporal.

<sup>a</sup> MRI measurements selected for showing strong associations when regressed on ALCS univariate model.

<sup>b</sup> Standardized regression coefficients reported.

\* p < 0.05



Supplementary Table S7. Cut-off thresholds for Allostatic Load (AL) scorings									
System	Biomarker	Gender	Clinical thresholds	p75 (p25*)	Comprehensive Score			Empirical Score	
					No-risk	At-risk	High-risk	No-risk	At-Risk
Immune	Creatinine [μmol/L]	Male	59 - 104	88.00	≤87.99	≥88 - ≤104	≥104.01	<88	≥87.99
		Female	45 - 84	69.00	≤68.99	≥69 - ≤84	≥84.01	<69	≥68.99
	Albumin* [gr/L]	Male	35 - 50	40.00	≥40.01	≤35 - ≥40	≤34.99	>40	≤40.01
		Female	same as Male	38.00	≥38.01	≤35 - ≥38	≤34.99	>38	≤38.01
	C-reactive protein (CRP) [mg/L]	Male	<5	3.65	≤3.64	≥3.65 - ≤4.99	≥5	<3.65	≥3.64
		Female	same as Male	4.00	≤3.99	≥4 - ≤4.99	≥5	<4	≥3.99
	Fibrinogen [gr/L]	Male	1.7 – 4.98	3.10	≤3.09	≥3.1 - ≤4.98	≥4.99	<3.1	≥3.09
Female		same as Male	3.38	≤3.37	≥3.38 - ≤4.98	≥4.99	<3.38	≥3.37	
Metabolic	Total Cholesterol [mmol/L]	Male	0 - 5.0	5.94	≤5	≥5.01 - ≤5.94	≥5.95	<5.94	≥5.93
		Female	same as Male	6.19	≤5	≥5.01 - ≤6.19	≥6.2	<6.19	≥6.18
	HDL Cholesterol* [mmol/L]	Male	1.0 – 3.0	1.17	≥1.18	≥1 - ≤1.17	≥0.99	>1.17	≤1.18
		Female	same as Male	1.48	≥1.49	≤1 - ≥1.48	≤0.99	>1.48	≤1.49
	LDL Cholesterol [mmol/L]	Male	1.0 – 3.0	3.8	≤3	≤3.01 - ≥3.8	≤3.81	<3.8	≥3.79
		Female	same as Male	3.83	≤3	≥3.01 - ≤3.83	≥3.84	<3.83	≥3.82
	Triglycerides [mmol/L]	Male	0 – 1.7	1.6	≤1.59	≥1.6 - ≤1.7	≥1.71	<1.6	≥1.59
Female		same as Male	1.2	≤1.19	≥1.2 - ≤1.7	≥1.71	<1.2	≥1.19	
Glycemia [mmol/L]	Male	5.5 - 6.9	5.4	≤5.39	≥5.4 - ≤6.9	≥6.91	<5.4	≥5.39	
	Female	same as Male	5.2	≤5.19	≥5.2 - ≤6.9	≥6.91	<5.2	≥5.19	
Body mass index (BMI) [kg/m2]	Male	25 - 29.9	30.33	≤24.99	≥25 - ≤29.99	≥30	<30.33	≥30.32	
	Female	same as Male	30.22	≤24.99	≥25 - ≤29.99	≥30	<30.22	≥30.21	
Cardiovascular	Systolic blood pressure (SBP) [mmHg]	Male	120 - 149	140.5	≤140.49	≥140.5 - ≤149	≥149.01	<140.5	≥140.49
		Female	same as Male	127.67	≤127.66	≥127.67 - ≤149	≥149.01	<127.67	≥127.66
	Diastolic blood pressure (DBP) [mmHg]	Male	80 - 89	86.17	≤86.16	≥86.17 - ≤89	≥89.01	<86.17	≥86.16
		Female	same as Male	79	≤78.99	≥79 - ≤89	≥89.01	<79	≥78.99
	Waist-to-hip ratio (WHR)	Male	no-risk ≤0.95, risk: 0.96-0.99, high-risk ≥1	0.98	≤95.99	≥96 - ≤0.99	≥1	<0.98	≥0.97
		Female	no-risk ≤0.80, risk: 0.81-0.84, high-risk ≥85	0.87	≤80.99	≥0.81 - ≤0.84	≥85	<0.87	≥0.86
	Resting heart rate (RHR) [BPM]	Age ≤45	Male	average: <76, below average: 76-82, poor:>82	69.67	≤75.99	≥76 - ≤82	≥82.01	<69.67
Female			average: <79, below average: 79-84, poor:>84	69.83	≤78.99	≥79 - ≤84	≥84.01	<69.83	≥69.83
Age 46 - 55		Male	average: <77, below average: 77-83, poor:>83	67	≤76.99	≥77 - ≤83	≥83.01	<67	≥67

Age 56 - 65	Female	average: <78, below average: 78- 83, poor:>83	69.67	≤77.99	≥78 - ≤83	≥83.01	<69.67	≥69.67
	Male	average: <76, below average: 76- 81, poor:>81	67	≤75.99	≥76 - ≤81	≥81.01	<68	≥68
	Female	average: <78, below average: 78- 83, poor:>83	69.67	≤77.99	≥78 - ≤83	≥83.01	<68.67	≥68.67
* Reverse scorings (p25 or low clinical thresholds used for risk)								