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ALLOSTATIC LOAD AND THE RISK OF ARTERIAL AND VENOUS VASCULAR EVENTS: A PROSPECTIVE ANALYSIS FROM THE MOLI-SANI STUDY

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Background and Aims. Allostatic load (AL) reflects cumulative multisystem biological dysregulation induced by chronic exposure to stressors and has emerged as an integrative marker of chronic physiological burden. However, prospective evidence on whether AL captures long-term risk across both arterial and venous vascular outcomes remains limited. We therefore aimed to evaluate the association between AL and mortality, cardiovascular disease (CVD), and venous thromboembolism (VTE) in a large prospective cohort.

Methods. We analyzed 22,255 participants from the Moli-sani study, a population-based cohort in Italy (aged ≥ 35 years, 52% women), apparently free of cardiovascular disease (CVD) and venous thromboembolism (VTE) at baseline (2005-2010). Outcomes included all-cause and CVD mortality, as well as fatal and non-fatal CVD, coronary heart disease (CHD), stroke subtypes, and unprovoked VTE. AL was computed as the sum of standardized (z-score) biomarkers across multiple physiological systems, with inversion of protective markers and equal weighting. Variables included cardiovascular (systolic and diastolic blood pressure, heart rate), inflammatory/immune (C-reactive protein, fibrinogen, white blood cell count, albumin [inverted], glycoprotein acetyls), metabolic (HDL cholesterol [inverted], total cholesterol, triglycerides, glucose, body mass index, waist-to-hip ratio, insulin, lipoprotein(a), apolipoprotein B), respiratory (FEV1 and FVC [both inverted]) and renal markers (creatinine, cystatin C). Higher values of AL index indicated greater biological dysregulation; the index was categorized into quartiles. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for demographic, socioeconomic and lifestyle factors.

Results. Median follow-up ranged from 13 to 15 years across outcomes. During follow-up, 2,831 deaths and 1,555 incident arterial and venous vascular events were recorded, as reported in the Table. Participants in the highest global AL index quartile, compared with those in the lowest one, had an increased hazard of all-cause mortality (HR 1.43; 95% CI 1.24-1.64) and cardiovascular mortality (HR 1.80; 95% CI 1.35-2.41). A strong graded association was observed for fatal and non-fatal CVD (HR 3.14; 95% CI 2.53-3.90), with the strongest effect observed for coronary

heart disease (HR 4.54; 95% CI 3.45-5.98). Associations with overall cerebrovascular outcomes were weaker than those observed for CHD, although participants in the highest versus lowest AL index quartile still showed an almost twofold higher hazard of fatal and non-fatal ischemic stroke (HR 1.92; 95% CI 1.15-3.20). This adverse association extended beyond arterial outcomes to venous thrombotic events, with higher AL index being associated with more than a twofold higher risk of fatal and non-fatal unprovoked venous thromboembolism (HR 2.25; 95% CI 1.11-4.54).

Conclusions. In this large population-based prospective cohort, a higher global AL index was associated with an excess hazard of all-cause and cardiovascular mortality and major arterial cardiovascular events, particularly CHD. The association also extended to unprovoked VTE. A cumulative multisystem biological dysregulation may capture long-term vascular vulnerability beyond traditional arterial outcomes and may represent an integrative marker for risk stratification.

Table. Hazard ratios and 95% confidence intervals for mortality and cardiovascular outcomes according to quartiles of allostatic load in the Moli-sani study (n = 22,255).

	Quartiles of allostatic load			
	Q1	Q2	Q3	Q4
Range of AL	-29.55 to -6.17	-6.17 to -0.01	-0.01 to 5.97	5.97 to 93.69
N of participants	5,563	5,564	5,564	5,564
Total mortality, 2,831 events				
Incidence rate per 10,000 person-years	30.3	62.2	95.2	166.5
Multivariable model	(26.8-34.3)	(57.0-67.8)	(88.7-102.2)	(157.6-175.8)
Ref.		0.99 (0.85-1.15)	1.11 (0.96-1.28)	1.43 (1.24-1.64)
CVD mortality, 928 events				
Incidence rate per 10,000 person-years	6.3	19.4	30.5	60.2
Multivariable model	(4.8-8.3)	(16.6-22.7)	(26.9-34.5)	(55.0-65.9)
Ref.		1.28 (0.94-1.75)	1.35 (1.00-1.83)	1.80 (1.35-2.41)
Fatal and non-fatal CVD, 1,447 events				
Incidence rate per 10,000 person-years	14.1	38.7	60.4	98.1
Multivariable model	(11.6-17.1)	(34.4-43.6)	(54.9-66.5)	(90.9-106.0)
Ref.		1.74 (1.39-2.19)	2.25 (1.80-2.81)	3.14 (2.53-3.90)
Fatal and non-fatal CHD, 1,036 events				
Incidence rate per 10,000 person-years	8.4	26.4	44.3	71.7
Multivariable model	(6.5-10.8)	(22.8-30.4)	(39.6-49.5)	(65.5-78.4)
Ref.		2.11 (1.58-2.82)	3.08 (2.33-4.07)	4.54 (3.45-5.98)
Fatal and non-fatal stroke, 443 events				
Incidence rate per 10,000 person-years	5.8	12.6	17.3	27.3
Multivariable model	(4.3-7.8)	(10.3-15.5)	(14.5-20.7)	(23.6-31.5)
Ref.		1.17 (0.81-1.70)	1.16 (0.81-1.67)	1.34 (0.94-1.90)
Fatal and non-fatal ischemic stroke, 235 events				
Incidence rate per 10,000 person-years	2.6	6.2	8.4	16.2
Multivariable model	(1.7-4.1)	(4.7-8.4)	(6.5-10.9)	(13.4-19.5)
Ref.		1.33 (0.77-2.28)	1.33 (0.78-2.26)	1.92 (1.15-3.20)
Fatal and non-fatal haemorrhagic stroke, 126 events				
Incidence rate per 10,000 person-years	2.1	4.0	5.2	6.5
Multivariable model	(1.2-3.4)	(2.8-5.8)	(3.8-7.2)	(4.9-8.7)
Ref.		1.15 (0.61-2.17)	1.12 (0.60-2.09)	1.06 (0.57-1.99)
Fatal and non-fatal unprovoked venous thromboembolism, 108 events				
Incidence rate per 10,000 person-years	1.5	3.3	4.2	6.3
Multivariable model	(0.8-2.7)	(2.2-5.0)	(2.9-6.0)	(4.6-8.5)
Ref.		1.60 (0.78-3.31)	1.76 (0.86-3.60)	2.25 (1.11-4.54)

Multivariable model was adjusted for age, sex, education, housing, smoking, history of cancer, leisure-time physical activity, Mediterranean Diet score without alcohol consumption, energy intake and alcohol drinking patterns (categorical).