

Allostatic Load and Systemic Inflammation as Interconnected Pathways Linking Chronic Stress to Brain Aging and Alzheimer’s Disease Risk

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Background

Chronic stress and **systemic inflammation** accumulate across the lifespan and are central features of aging^{1,2}. These processes have been associated with **brain aging** and increased **vulnerability to Alzheimer’s disease (AD)**³⁻⁵. However, their interrelationships remain insufficiently characterized.

Allostatic Load (AL) is a composite index of multisystem physiological dysregulation reflecting cumulative biological burden associated with chronic stress across the lifespan⁶.

Objective

This exploratory study aims to examine cross-sectional relationships between **AL**, **inflammatory and immune biomarkers**, **brain integrity**, and **AD vulnerability** in aging.

Methods

111 cognitively unimpaired older adults from the Age-Well trial⁷

	Mean (± SD)	Range
Demographics		
Age (years)	68,9 (± 3,8)	65 – 83
Sex (% women)	63	-
Education level	13,2 (± 3,2)	7 – 22
Allostatic Load (non z-scored)	0 (± 0,51)	-1,19 – 1,45



Allostatic load

z-score of 5 categories :

- Cardiorespiratory**: Systolic and diastolic BP, pulse pressure, ECG measures (SDNN, RMSSD)
- Immune**: IL-6, hsCRP
- Anthropometric**: BMI, Waist-to-hip ratio
- Neuroendocrine**: Cortisol, DHEA-S, epinephrin, norepinephrin
- Metabolic**: Insulin, triglycerides, HDL, LDL, creatinine



Blood-based biomarkers

AD-related and neurodegeneration biomarkers: Aβ42/Aβ40, p-Tau 181, NfL, GFAP, sTREM2

Inflammatory and immune biomarkers : blood cell counts and levels of cytokines, chemokines, and adhesion and vascular factors



Multimodal neuroimaging

T1, FLAIR and **DKI MRI**

Early- and late-AV45 and **¹⁸F-FDG PET**



AD risk factors

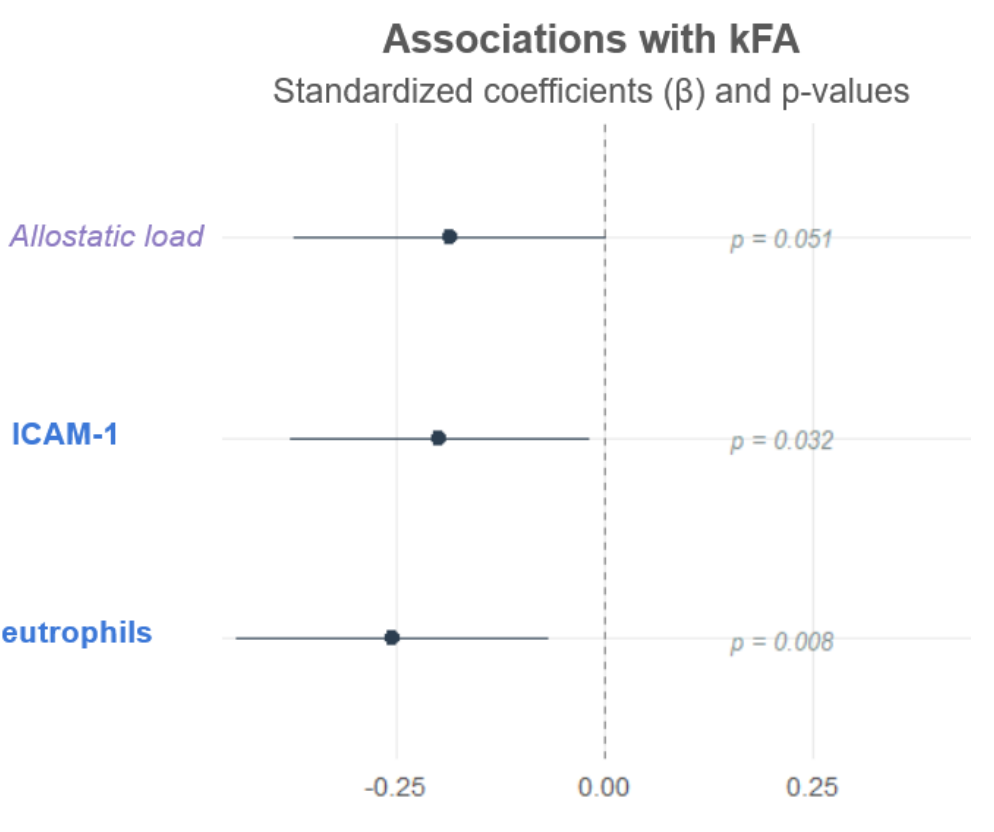
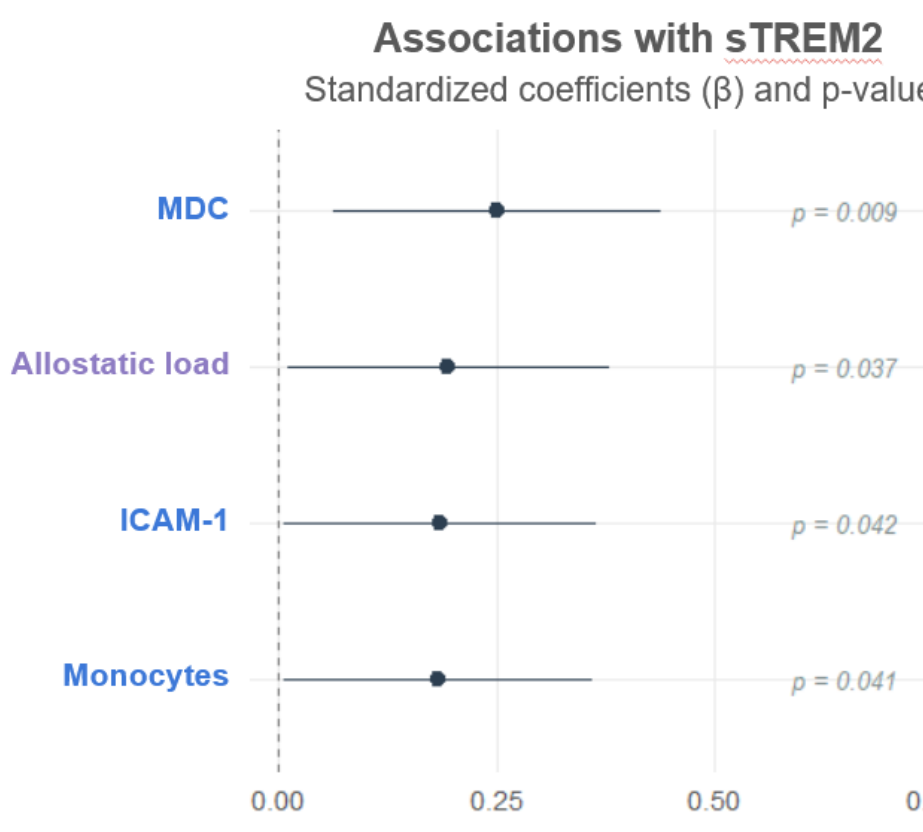
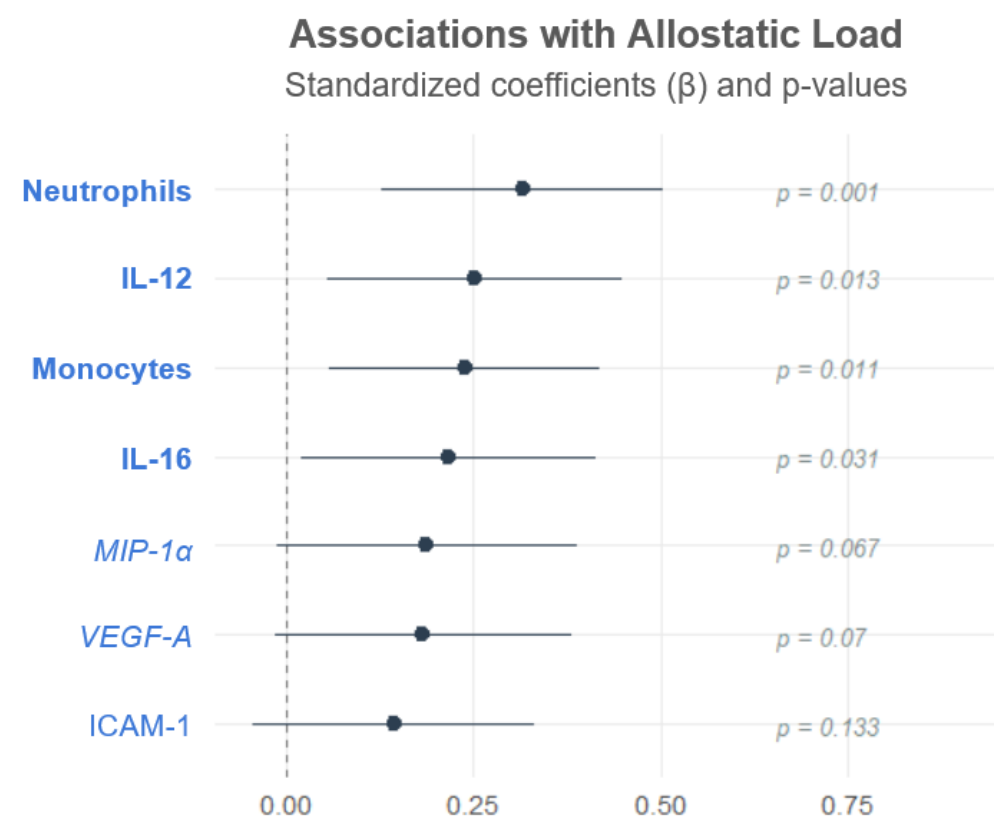
ApoE genotype

AD polygenic risk scores (PGS)

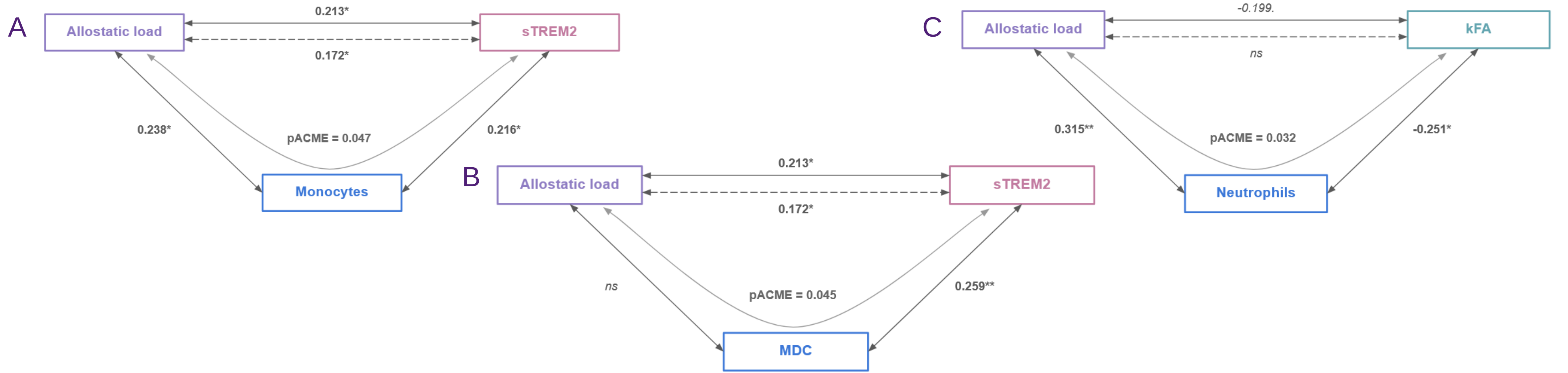
Results were obtained from **linear regression** and **interaction models** as well as **causal mediation analysis**. All models were adjusted for **age**, **sex**, **education level**, **smoking status** and **current medication use**.

Results

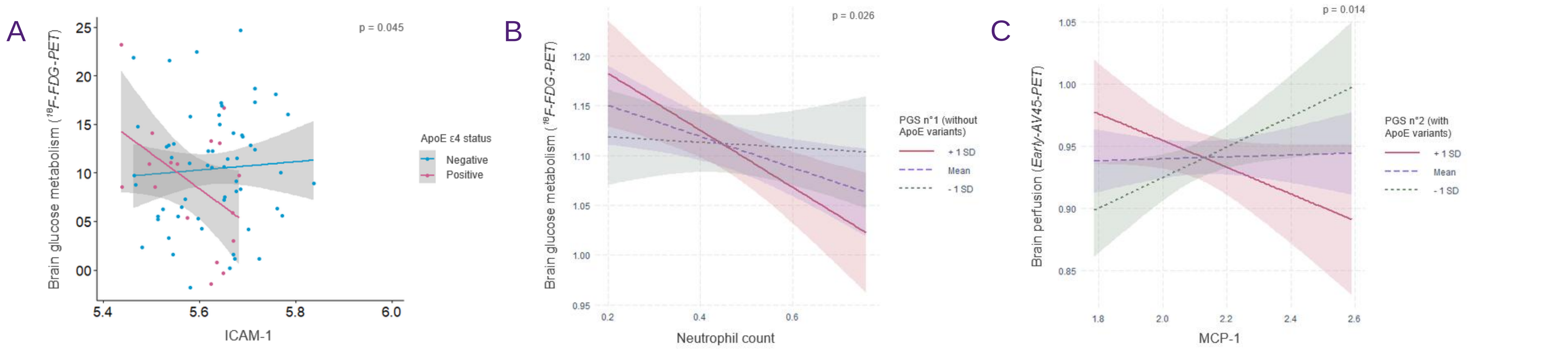
- 1 **Higher AL** is associated with **systemic physiological and inflammatory dysregulation**
- 2 Both **AL** and **inflammatory and immune biomarkers** are associated with **neuroinflammation (sTREM2)** and **white matter tracts alterations (DKI MRI)**



- 3 **Inflammatory and immune biomarkers mediate** the associations between **AL** and **neuroinflammation (A/B)** and **white matter integrity (C)**



- 4 **ApoE ε4 status (A)** and **AD PGS (B/C)** modulate the associations between **inflammatory and immune biomarkers** and **brain glucose metabolism (¹⁸F-FDG-PET) and perfusion (Early-AV45-PET)**



Conclusions

- Higher allostatic load is associated with a **systemic inflammatory profile** in physiological aging
- Stress-related inflammatory processes** may contribute to increased vulnerability of the aging brain, notably by amplifying **neuroinflammation** and weakening **white matter tracts**
- Modulation by **AD genetic risk factors** may suggest a **specific role** for inflammation in **AD physiopathology**
- AL** is an integrative marker of physiological dysregulation linked to **brain aging** and **neuroinflammatory signatures**

References

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