**Interaction between APOE4 and lifestyle on neuroimaging biomarkers and cognition in cognitively unimpaired older adults**

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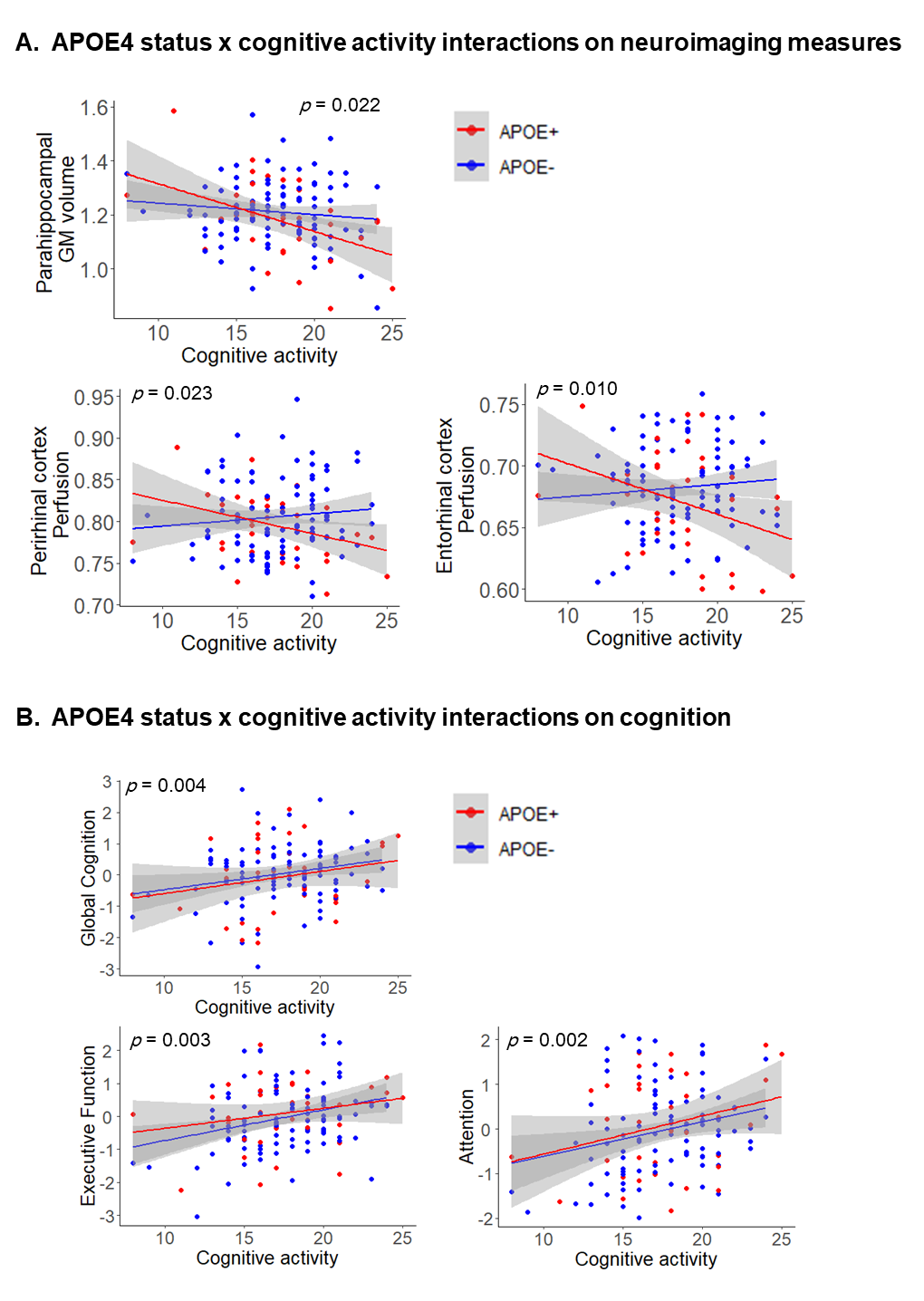
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**Background:** *APOE4* is the main genetic risk factor for Alzheimer’s disease (AD). Recent findings suggest that lifestyle factors could modulate the association between *APOE4* and cognitive impairment and/or dementia risk. However, a comprehensive assessment of the interactions between lifestyle and *APOE4* status on neuroimaging and cognitive markers of aging and AD is still missing. Our objective is to assess this question in cognitively normal elderly.

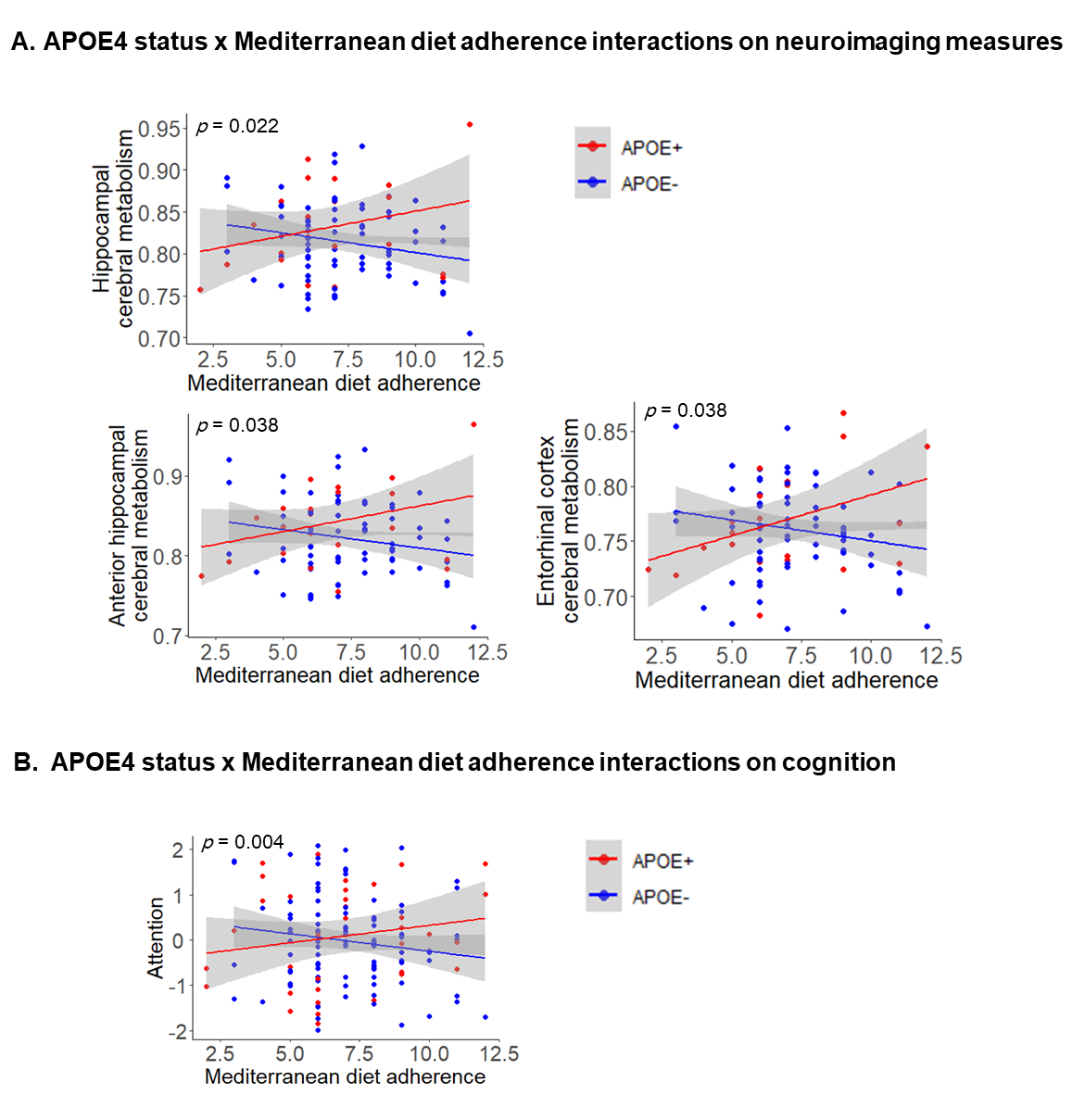
**Method:** Baseline data of 134 cognitively unimpaired older adults (mean age: 69) from the Age-Well cohort were analysed. They underwent lifestyle questionnaires (physical and cognitive activity, and diet), neuropsychological evaluation (memory, attention, executive function and global cognition) and multimodal neuroimaging (structural MRI, FDG- and Florbetapir-PET). Interactions between lifestyle and *APOE4* status on neuroimaging and cognition were assessed for each lifestyle factor separately.

**Result:** There was an interaction between *APOE4* status and cognitive activity on neuroimaging measures (ps<.04), such that higher cognitive engagement was associated with lower grey matter volume in the parahippocampus and lower brain perfusion in the entorhinal and perirhinal cortices in *APOE4* carriers only (Figure 1A). However, greater cognitive engagement was associated with increased cognitive performance (global cognition, executive function and attention, all ps<.005), and this irrespectively of *APOE4* status (i.e., no cognitive activity x *APOE4* status interaction; Figure 1B). For diet, interactions were evidenced (ps <.04) such that higher adherence to the Mediterranean diet was associated with i) higher brain glucose metabolism in the medial temporal lobe (Figure 2A) and ii) higher performance on attention tests (Figure 2B) in *APOE4* carriers only. No interactions were found for physical activity.

**Conclusion:** Our results indicate that *APOE4* carriers with higher cognitive activity had lower brain outcomes but preserved cognition, suggesting that enriched cognitive engagement promote cognitive resilience in this population. On the other hand, *APOE4* carriers with higher adherence to the Mediterranean diet had greater cerebral metabolism and greater attention capacities. Overall, this suggests that distinct lifestyle factors differentially help *APOE4* carriers to resist or cope with brain alteration and postpone cognitive decline.



**Figure 1 Interactive effects of cognitive activity and *APOE4* status on neuroimaging measures (A) and cognition (B).** Adjusted *p-values* are indicated for the significant interactive effects and were obtained using general linear models controlling, for age, sex, and education. Raw data (i.e., unadjusted) are plotted. Solid lines represent estimated regression lines and shaded areas represent 95% confidence intervals. Abbreviations: APOE+ = APOE4 carriers, APOE- = APOE4 non-carriers, GM = gray matter,

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**Figure 2 Interaction of APOE and adherence to the Mediterranean diet on neuroimaging measures (A) and cognition (B).** Adjusted *p-values* are indicated for the significant interactive effects and were obtained using general linear models controlling for age, sex, and education. Raw data (i.e., unadjusted) are plotted. Solid lines represent estimated regression lines and shaded areas represent 95% confidence intervals. Abbreviations: APOE+ = APOE4 carriers, APOE- = APOE4 non-carriers, GM = gray matter.