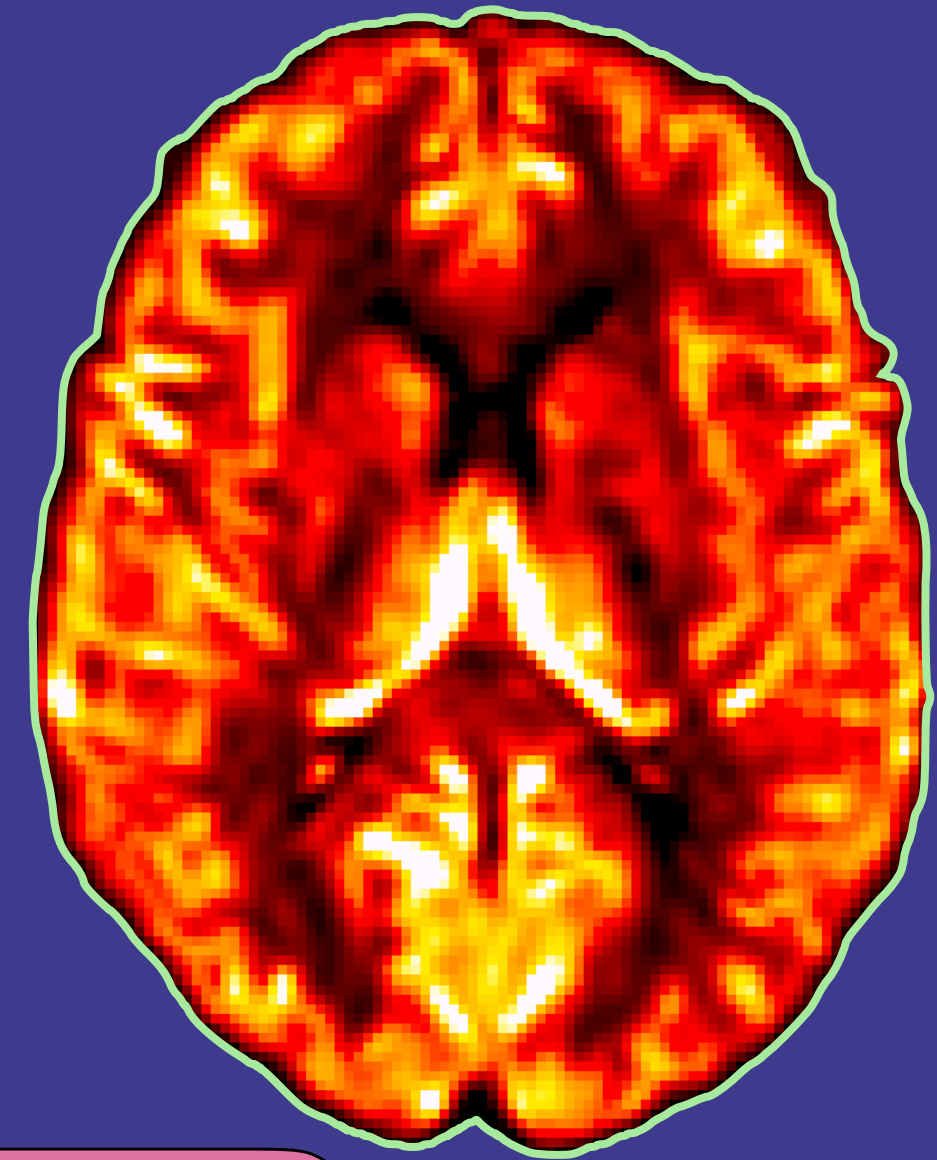


APOE ε4 And Cognitive Status Moderate The Association Between Midlife Physical Activity And Cerebral Perfusion During Older Adulthood

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BACKGROUND

- Cerebrovascular dysfunction, including reduced regional cerebral perfusion is increasingly recognised as an early contributor to Alzheimer’s Disease (AD).¹
- Midlife physical activity (PA) is associated with reduced dementia risk², potentially through preserving cerebrovascular function.³
- RCTs have demonstrated cerebral perfusion increases following aerobic exercise in healthy older adults⁴⁻⁵, though effects appear less consistent in cognitively impaired populations.⁶⁻⁷
- Emerging evidence suggests apolipoprotein E ε4 (APOE ε4) carriage may modulate the beneficial effects of PA on cerebrovascular health,⁸ including cerebral perfusion.⁹

We tested whether APOE ε4 carriage and cognitive status together moderated the association between midlife PA and cerebral perfusion in regions implicated in exercise and cognitive decline.

METHODS

174 participants ($M = 68.72$ years, $SD = 7.80$) from the New Zealand Dementia Prevention Research Clinics¹⁰ were assigned to a cognitively unimpaired group (healthy controls and subjective cognitive decline) or an amnesic mild cognitive impairment group (aMCI) (Table 1).

Midlife PA was derived as continuous composite score of self-reported PA frequency and intensity during ages 30–65 years using the Lifetime Experiences Questionnaire, and was square root-transformed prior to analysis.

Cerebral perfusion was measured as CBF (mL/100g/min) from pseudo-continuous ASL MRI, processed using ExploreASL¹¹, across seven a priori ROIs implicated in exercise and cognitive decline, and the whole brain.

Eight pre-specified **linear regression models** tested the three-way interaction between midlife PA, cognitive status, and APOE ε4 carriage, adjusting for age and sex. Simple slopes were probed for interactions significant at the uncorrected level.

DEMOGRAPHICS

Table 1 Participant Demographics

Variable	Cognitively Unimpaired	Amnesic Mild Cognitive Impairment	p
n	86	88	
Age (years)	67.79 (8.40)	69.61(7.09)	.125
Female (%)	55/86 (64%)	44/88 (50%)	.088
Education (years)	15.16 (3.30)	15.18 (3.03)	.968
ACE-III score	93.05 (5.28)	85.72 (7.07)	<.001***
APOE ε4 (%)	28/86 (32.6%)	59/88 (67.0%)	<.001***
Midlife PA	5.10 (1.71)	5.18 (2.16)	.771
CBF (mL/100g/min)	61.42 (15.17)	57.19 (12.36)	.046*

Note. Group differences were assessed using independent samples t-tests for continuous variables and chi-square tests for categorical variables. ACE-III = Addenbrooke’s Cognitive Examination-III.

RESULTS

Three-way interactions between midlife PA, APOE ε4 carriage and cognitive status were significant for CBF in the posterior cingulate cortex, precuneus, and frontal lobe (Table 2).

Table 2 Three-way interaction on cerebral perfusion by region

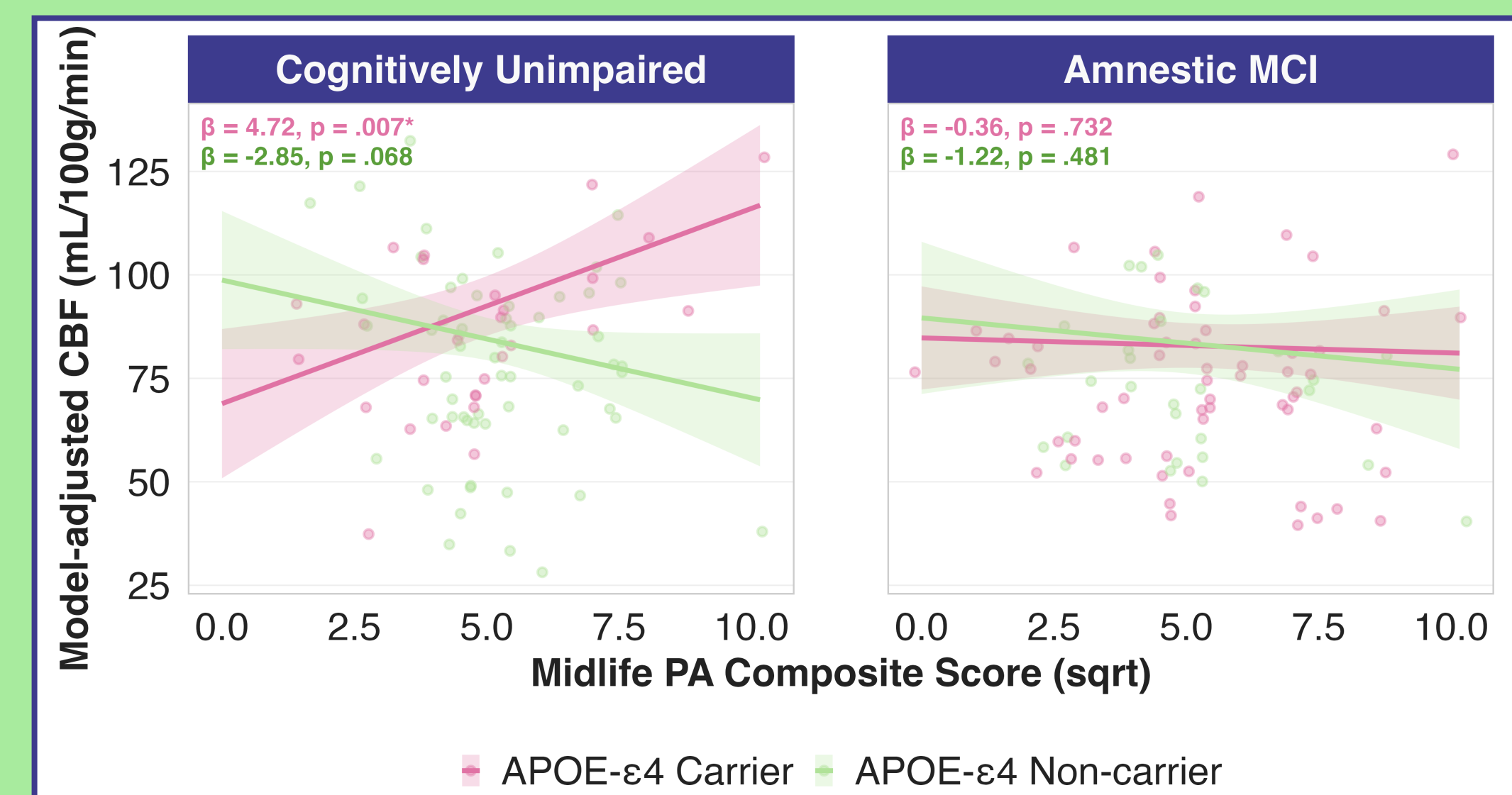
Region of Interest	β	SE	t	p
Whole Brain Gray Matter	3.37	2.03	1.66	.099
Angular Gyrus	6.94	3.95	1.76	.081
Anterior Cingulate Cortex	4.74	2.60	1.82	.070
Posterior Cingulate Cortex	6.70	3.07	2.18	.030*
Precuneus	6.74	3.16	2.13	.035*
Hippocampus	2.99	2.02	1.48	.142
Frontal Lobe	5.96	2.69	2.22	.028*
Temporal Lobe	3.39	1.93	1.76	.080

Note. β = three-way PA × group × APOE interaction term from linear regression adjusting for age and sex. *p < .05, uncorrected for multiple comparisons.

Probing the simple slopes revealed a positive association between midlife PA and CBF in cognitively unimpaired APOE ε4 carriers, with no association in other subgroups (Figure 1).

KEY FINDING

Figure 1 Simple slopes of the midlife PA-CBF association in the PCC by APOE ε4 carriage, split by cognitive status



Note. PCC shown; precuneus and frontal lobe showed comparable patterns.

CONCLUSIONS

- Our preliminary cross-sectional analysis demonstrated **cognitively unimpaired ε4 carriers showed a positive association between midlife PA and CBF in the PCC, precuneus, and frontal lobe that was not apparent in other groups.**
- APOE ε4-related cerebrovascular vulnerability may confer greater vascular responsiveness to PA^{8,9}, before clinical impairment emerges.
- Genetic risk and cognitive status may be important moderators of PA-CBF associations.
- Verification of these preliminary findings is underway in a larger sample, and longitudinal changes will be examined.

REFERENCES 1. de la Torre, *J Alzheimers Dis*, 2018; 2. Livingston et al., *Lancet*, 2024; 3. Kennedy et al., *J Alzheimers Dis*, 2017; 4. Chapman et al., *Front Aging Neurosci*, 2013; 5. Maass et al., *Mol Psychiatry*, 2015; 6. Alfini et al., *J Alzheimers Dis*, 2019; 7. Thomas et al., *J Alzheimers Dis*, 2020; 8. de Frutos-Lucas et al., *Ageing Res Rev*, 2020; 9. Zlatar et al., *J Alzheimers Dis*, 2014; 10. Tippett et al., *J R Soc NZ*, 2023; 11. Mutsaerts et al., *NeuroImage*, 2020.

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