



Plasma klotho increases correlate with less Alzheimer's Disease Pathologies and cognitive decline in *APOE*-ε4 carriers

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Background

- Klotho is a longevity-associated protein with established neuroprotective properties.
- Higher circulating Klotho levels or the *KL*-VS heterozygous genotype are associated with a reduced risk of Alzheimer's disease (AD) and better cognitive performance.
- These protective associations may be amplified in individuals carrying the *APOE*-ε4 allele.
- It is unclear how plasma Klotho levels relate to AD pathologies and cognitive performance.

Aim

Using a well-defined Chinese cohort, this study comprehensively examined the relationship between plasma Klotho levels and AD-related pathologies and cognitive outcomes across different *APOE*-ε4 statuses.

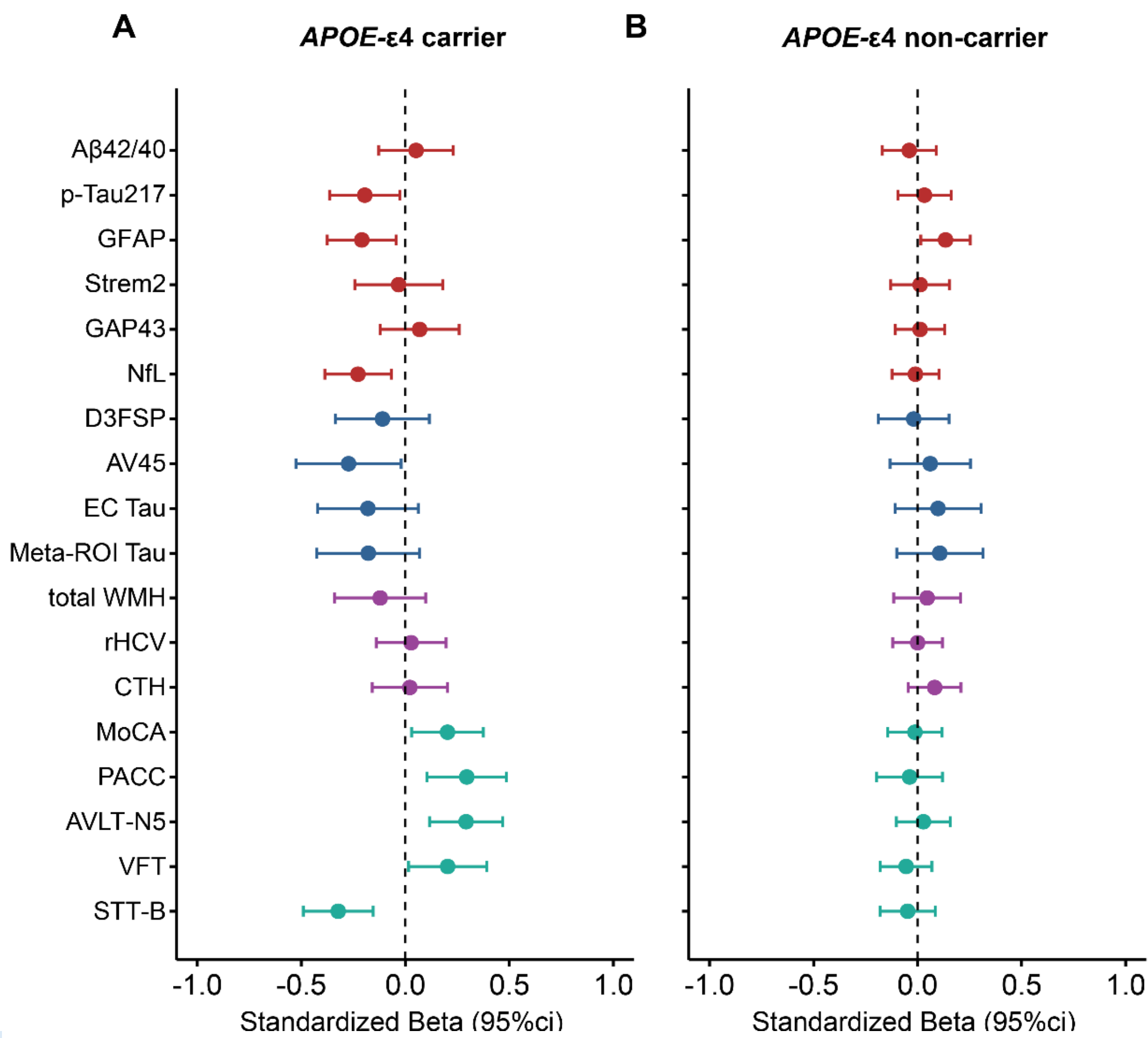
Cohort & Demographic

- **354 participants** from the Greater-Bay-Area Healthy Aging Brain Study (**GHABS**) cohort

	<i>APOE</i> ε4-	<i>APOE</i> ε4+
	n = 240	n = 114
Age, year	67.01 (62.05, 71.37)	66.93 (62.32, 70.74)
Female, No. (%)	134 (55.8)	71 (62.3)
Education, years	13.00 (10.00, 15.62)	12.00 (9.00, 15.00)
Plasma Klotho, pg/mL	776.27 (655.31, 954.24)	851.98 (745.14, 1,008.61)

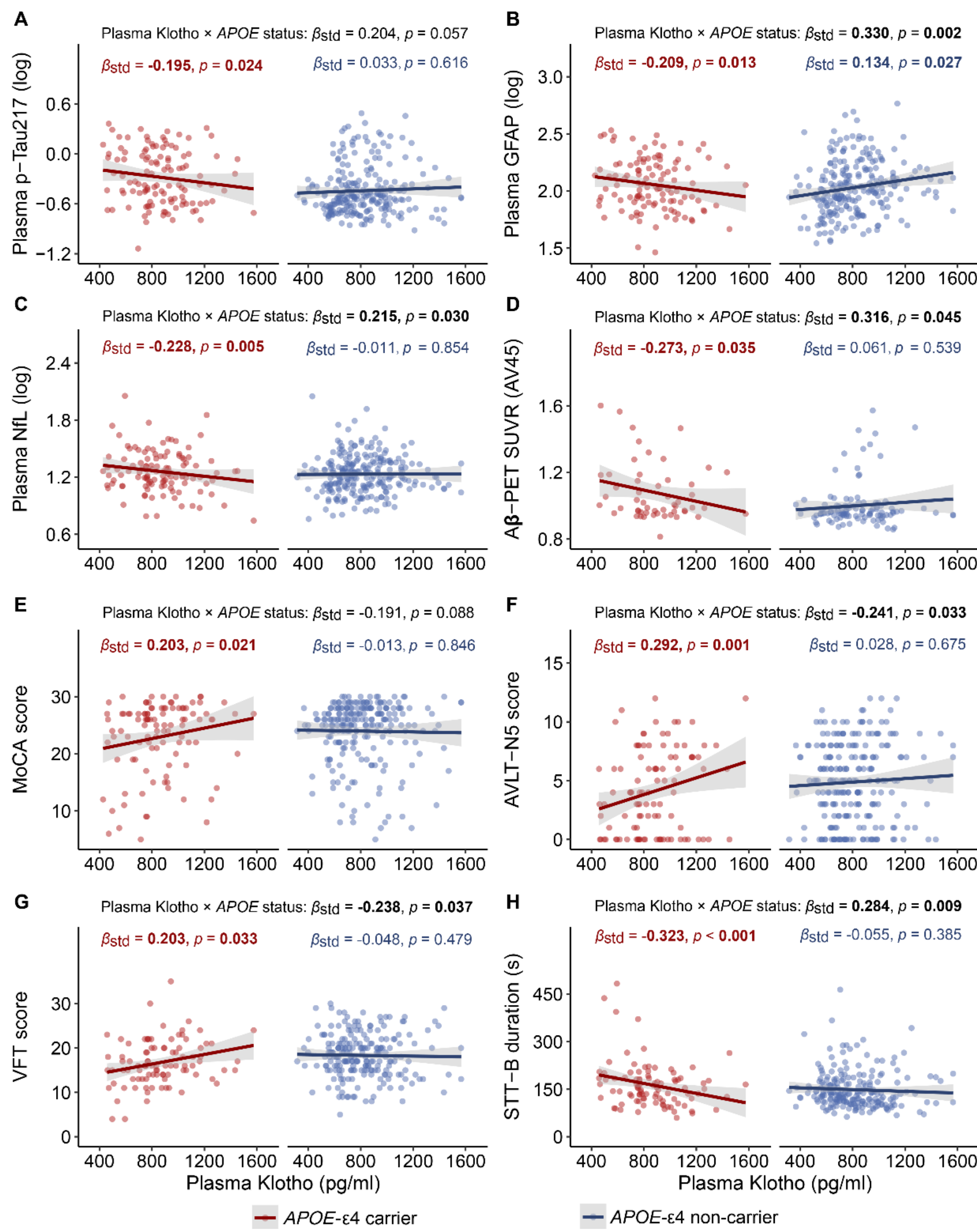
Results-1

- Higher plasma Klotho levels were associated with lower AD-related biomarkers and better cognitive performance in *APOE*-ε4 carriers.



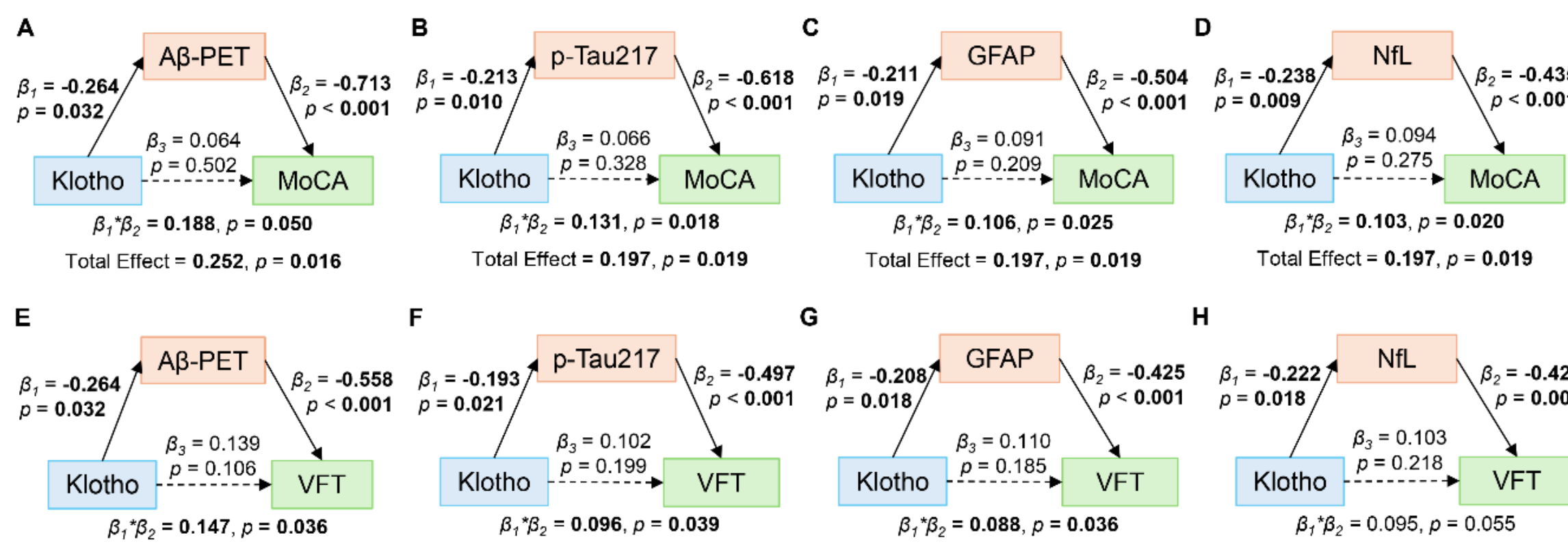
Results-2

- Significant/ marginally significant Klotho×*APOE*-ε4 interactions were observed for p-Tau217, GFAP, NfL, Aβ PET, and cognition, suggesting an *APOE*-ε4-dependent pattern.



Results-3

- In *APOE*-ε4 carriers, Aβ PET, p-Tau217, GFAP, and NfL substantially mediated the Klotho and cognition association for both MoCA (74.6%, 66.5%, 53.8%, 52.3%) and VFT (51.4%, 48.5%, 44.4%, 48.0%).



Conclusion

This study suggests that plasma Klotho is an *APOE*-ε4-dependent protective factor, which may attenuate AD-related pathology and improve cognitive performance.