

Occipital amyloid-PET deposition across the Alzheimer's disease spectrum: A multi-cohort study

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Background

- In vivo amyloid- β (A β) PET assessment is typically done in the frontal, temporal, and parietal cortices¹
- Emerging evidence shows A β can also accumulate in the Occipital lobe, a region currently excluded from standard quantification and visual reads²
- Investigating regions beyond typical accumulation sites may help explain, in part, the heterogeneity observed in AD through distinct disease subtypes²⁻⁶
- The extent to which Occipital A β deposition influences clinical progression and trial eligibility in preclinical stages remains poorly understood

Aim

To investigate the prevalence and clinical impact of A β deposition in the Occipital lobe with and without A β in the rest of the neocortex

Methods

- We included 21,976 individuals from 16 different cohorts, covering the whole AD spectrum and all A β PET tracers⁷⁻²⁴
- The Centiloid scale was used to standardize A β quantification across tracers and centers²⁵
- The Occipital composite standardized uptake value ratio (SUVR) was computed using the Desikan-Killany atlas by volume-weighted averaging of four regions from both hemispheres: lateral occipital, cuneus, lingual, and pericalcarine; using the whole cerebellum as reference region
- Participants were classified into four groups based on Global and Occipital A β status: 1) Global and Occipital negative (G+/O+), 2) Global negative and Occipital positive (G-/O+), 3) Global positive and Occipital negative (G+/O-), and 4) Global and Occipital positive (G+/O+)
- For Global positivity, a standard threshold of 30 Centiloids was applied
- For Occipital positivity, the threshold was derived using Gaussian mixture modelling on the composite SUVR in subjects with global Centiloid > 30. The cutoff was set at the mean + 2SD from the normal curve. All cut-offs were derived separated by tracer and cohort
- Cross-sectional group differences were assessed using linear or logistic regression models, with age, sex, and cohort as covariates (unless when they were main predictors)

Conclusions

- Occipital A β deposition occurs alongside widespread cortical positivity
- Among Global-positive individuals, additional Occipital A β positivity likely reflects a more advanced disease stage
- Isolated Occipital deposition, even though it is very rare, might represent an intermediate stage or an atypical accumulation trajectory
- Further longitudinal research is needed to clarify the clinical implications on disease progression

References: 1. Klunk WE et al.,(2015) Alzheimer's Dement.; 2. Collij LE, et al.,(2022) Neurology; 3. Vogel JW et al.,(2021) Nat Med; 4. Murray ME et al.,(2013) Lancet Neurol; 5. Sperling R et al.,(2014) Neuron; 6. Sims JR et al.,(2023) JAMA; 7. Sperling RA et al.,(2014) Sci Transl Med; 8. de Wilde A et al.,(2017) Alzheimer's Dement.; 9. Molinuevo JL et al.,(2016) Alzheimer's Dement.; 10. Frisoni, GB et al.,(2019) Alzheimer's Dement.; 11. Albert M et al.,(2014) Curr Alzheimer Res; 12. Dagley et al.,(2017) Neuroimage; 13. Petersen ME et al.,(2025) Alzheimer's Dement.; 14. Mumma SA et al.,(2016) J Med Internet Res; 15. LaMontagne PJ et al.,(2019) medRxiv; 16. Tremblay-Mercier et al.,(2021) Neuroimage Clin; 17. Alcolea D et al.,(2019) Alzheimer's Dement.; 18. Lopes Alves I et al.,(2020) Alzheimer's Dement.; 19. Carrillo MC et al.,(2025) Alzheimer's Dement.; 20. Rabinovici GD et al.,(2019) JAMA; 21. Harrison T et al.,(2024) Alzheimer's Dement.; 22. Videla L et al.,(2025) Alzheimer's Dement.; 23. Li Want et al.,(2023) Nat Prot; 24. Yue Sun et al.,(2023) Nat Comm; 25. Klunk WE et al.,(2015) Alzheimer's Dement.

Results

- Most individuals were negative in both regions (G-/O- = 55,3%) followed by only Global positivity (G+/O- = 27,5%). Occipital positivity was present in 17.2% of the total sample (n = 3,787)
- Global A β -PET load significantly increased stepwise across the four groups (**Figure 1**), with Global negative / Occipital positive (G-/O+) and Global / Occipital positive (G+/O+) showing higher global A β load than their Occipital negative counterparts (p < 0.001, **Figure 1**)
- Occipital positive groups were older than their negative counterparts (p < 0.001, **Figure 2**)
- The G+/O+ group had a higher proportion of women (p < 0.001, **Figure 3**)
- APOE- ϵ 4* carriers were more prevalent in Global positive groups, and more prevalent in G-/O+ compared to G-/O- group (p < 0.01, **Figure 4**)
- Individuals with Occipital positivity showed higher plasma p-tau217 levels compared to their negative counterparts (**Figure 5**)
- Among globally A β -positive individuals, the G+/O+ group had a higher prevalence of AD-dementia and a lower prevalence of cognitive unimpairment compared to their negative counterparts (p < 0.001, **Figure 6**).
- No significant differences in diagnosis were observed between globally negative groups regardless of their Occipital status (G-/O- vs G-/O+).
- The G+/O+ group showed higher levels of white matter hyperintensities compared to the G+/O- group (p < 0.01, **Figure 7**)
- FBB was the predominant tracer across all groups (70%), except in the G-/O+ group, where FBP was the most common (42.1%) (**Table 1**)

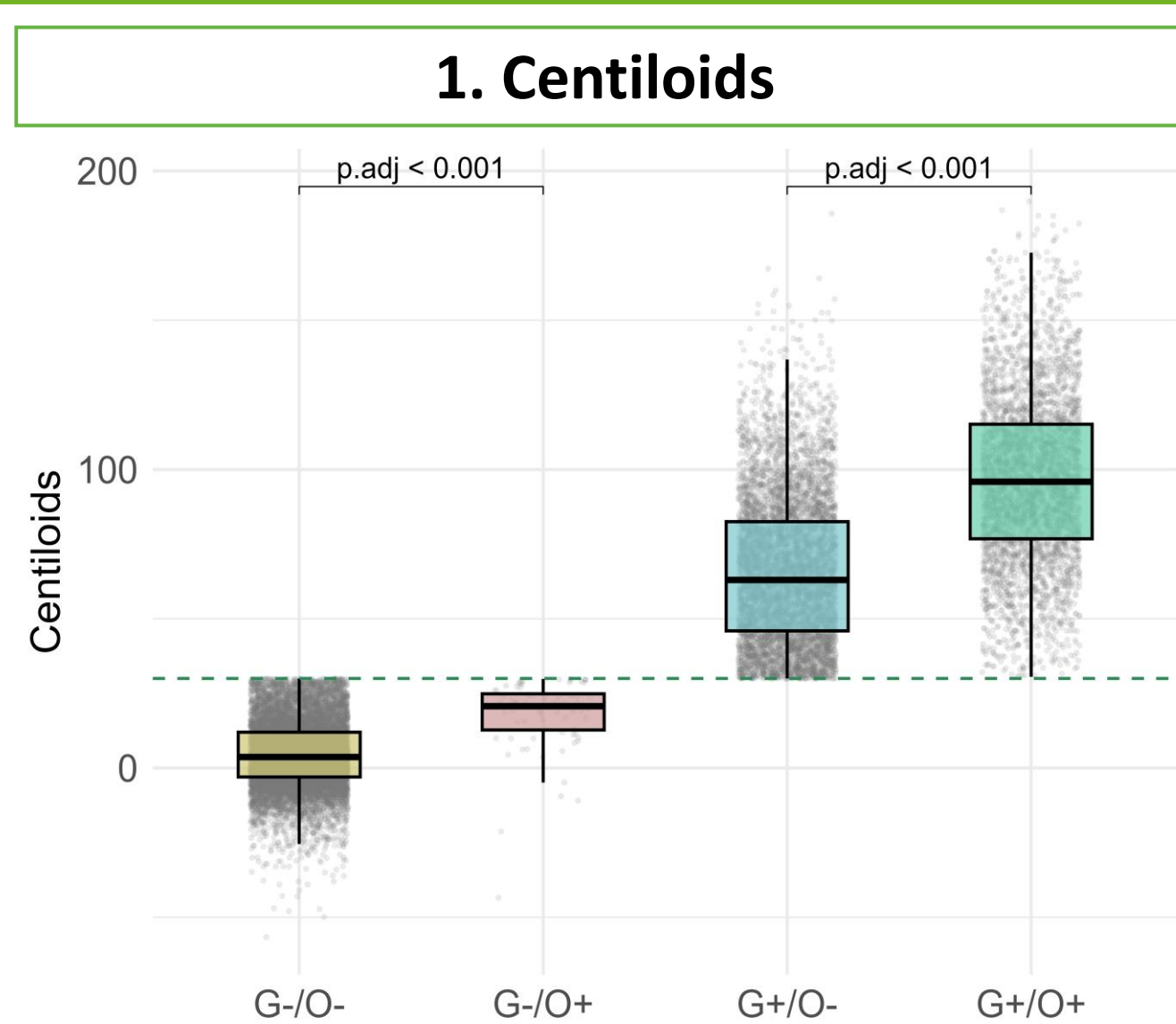


Figure 1. Centiloids difference by groups. Differences were assessed using a linear regression analysis adjusting by age, sex, and cohort. Only comparisons between O+ and O- groups are displayed

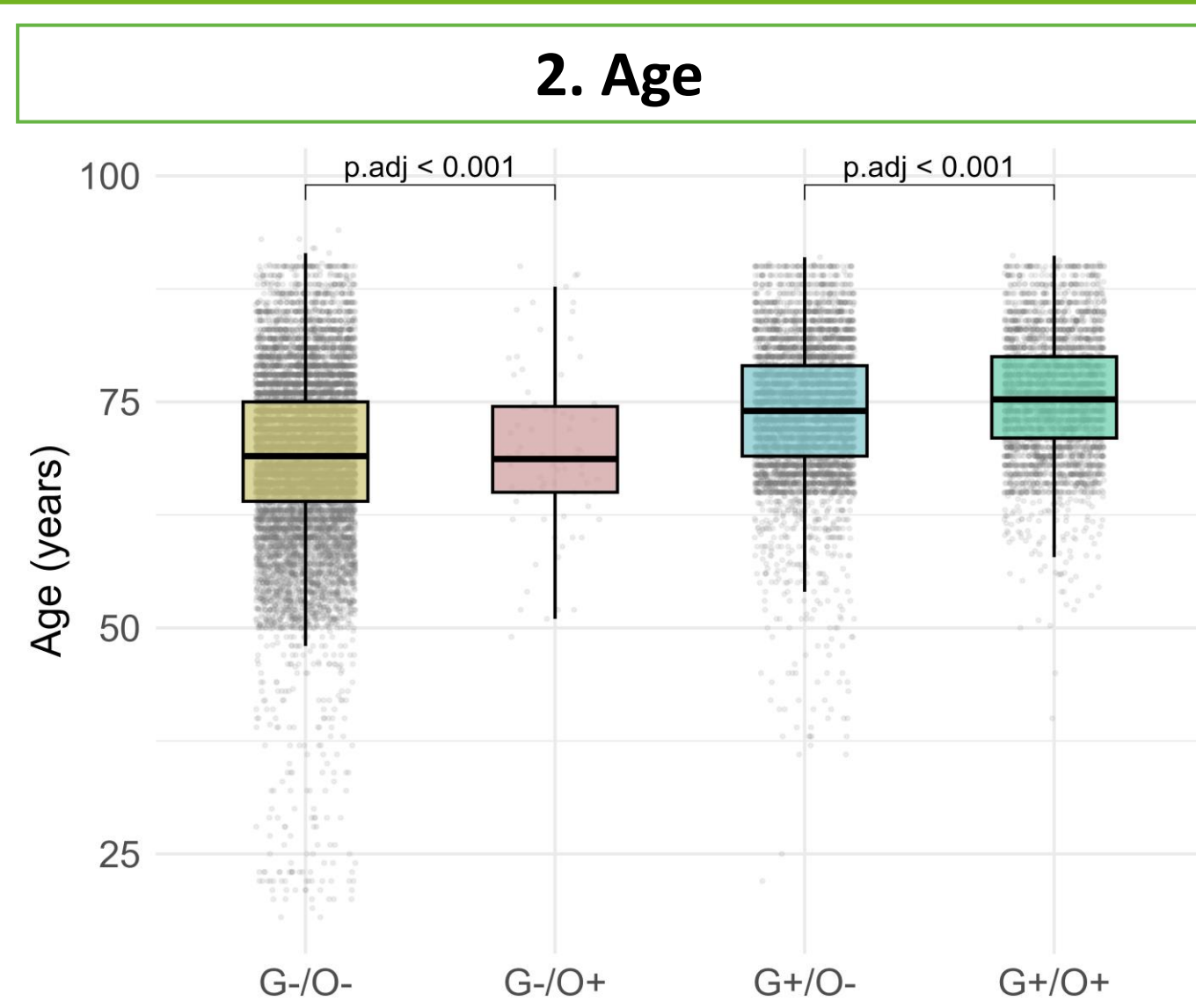


Figure 2. Age between groups. Differences were assessed using a linear regression analysis adjusting by sex and cohort. Only comparisons between O+ and O- groups are displayed

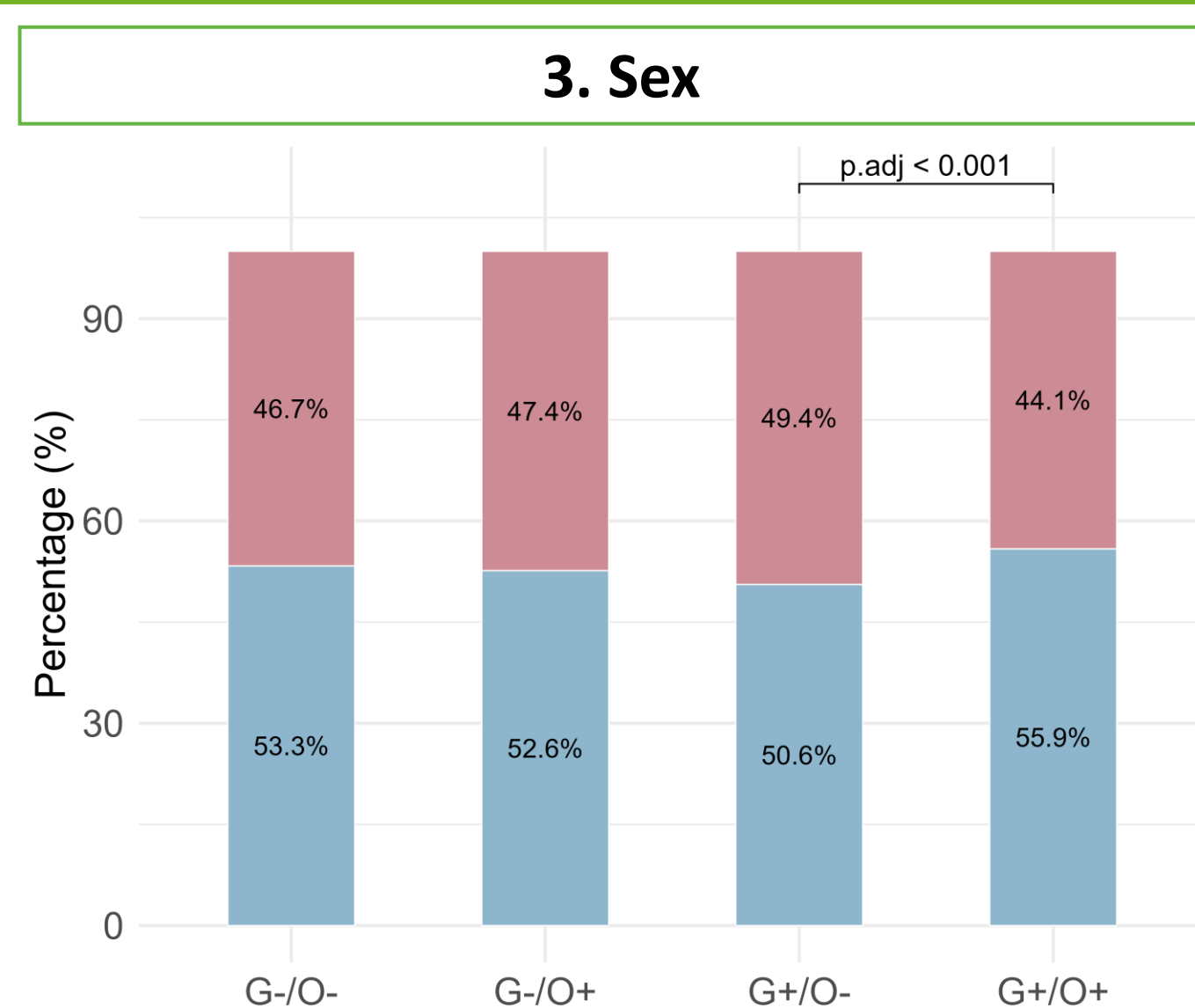


Figure 3. Differences in sex between the four groups. Differences were assessed using a linear regression analysis adjusting by age, and cohort. Only comparisons between O+ and O- groups are displayed

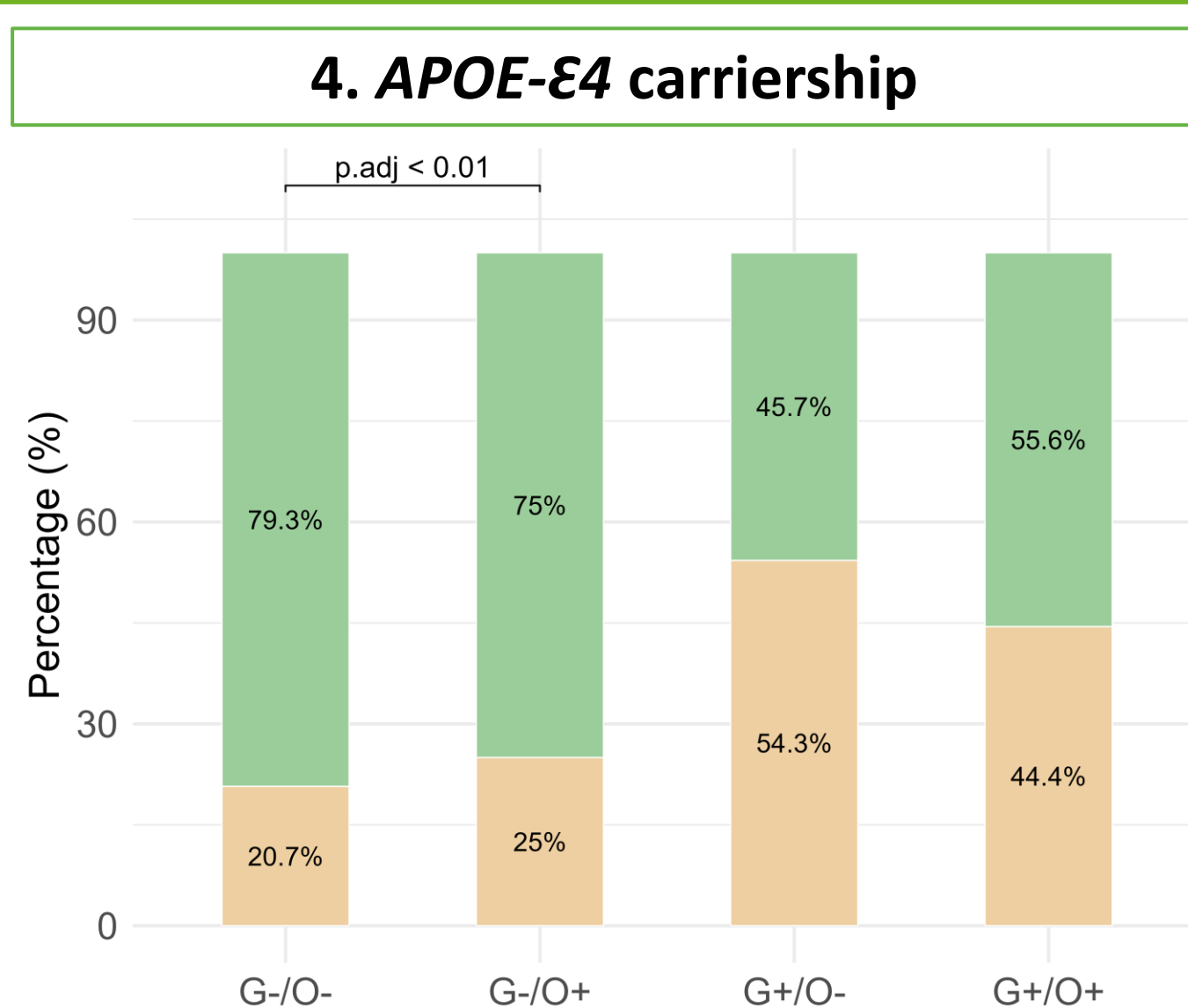


Figure 4. Differences in *APOE- ϵ 4* carriership status across the four groups. They were assessed using a linear regression model adjusted by age, sex, and cohort. Only comparisons between O+ and O- groups are displayed. N = 10,191

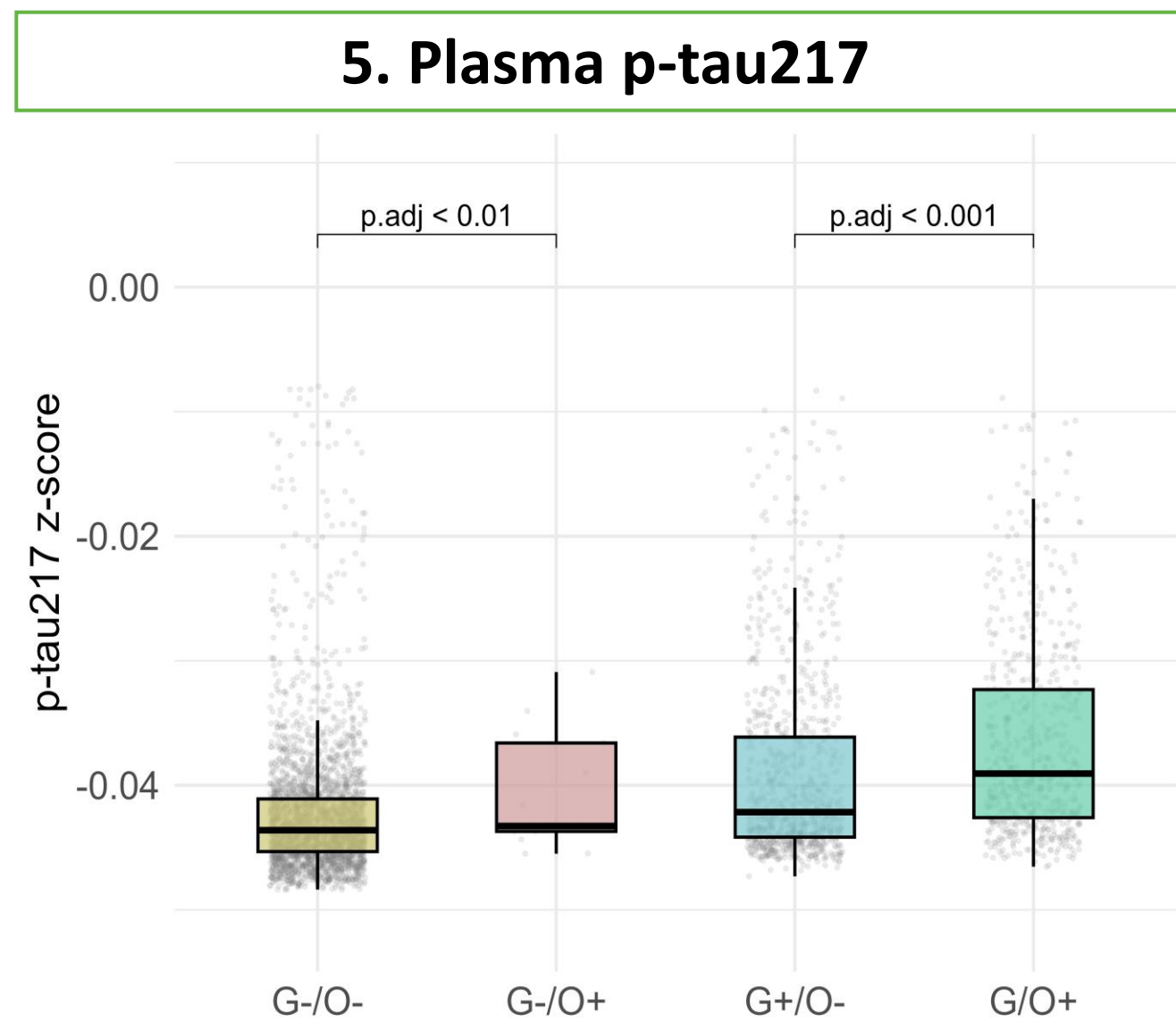


Figure 5. Differences in plasma p-tau217 levels between the four groups. Differences were assessed using a linear regression model adjusted by age, sex, and cohort. Only comparisons between O+ and O- groups are displayed. N = 4,408

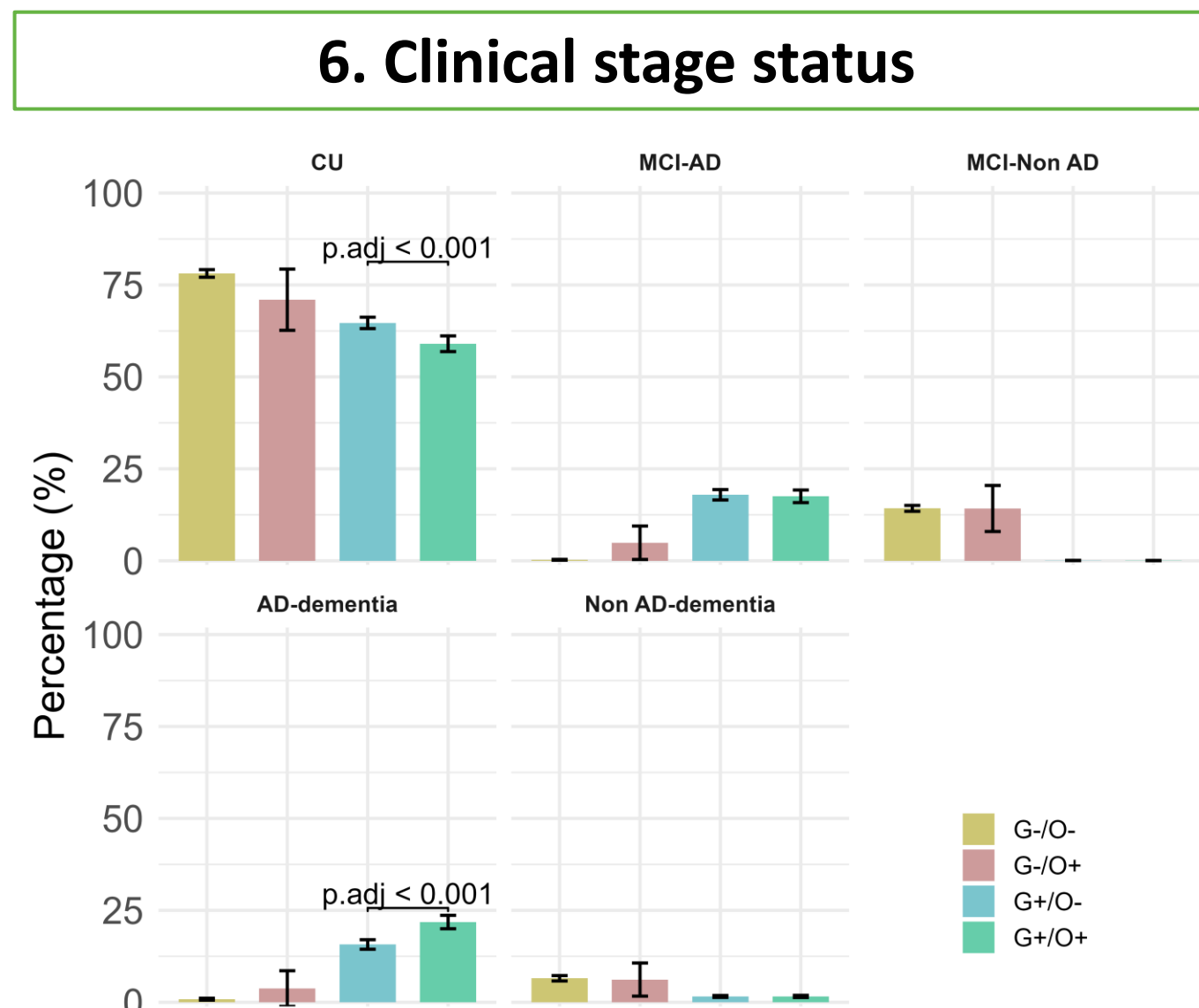


Figure 6. Differences in clinical stage status across the four groups. They were assessed using a linear regression model adjusted by age, sex, and cohort. Only comparisons between O+ and O- groups are displayed

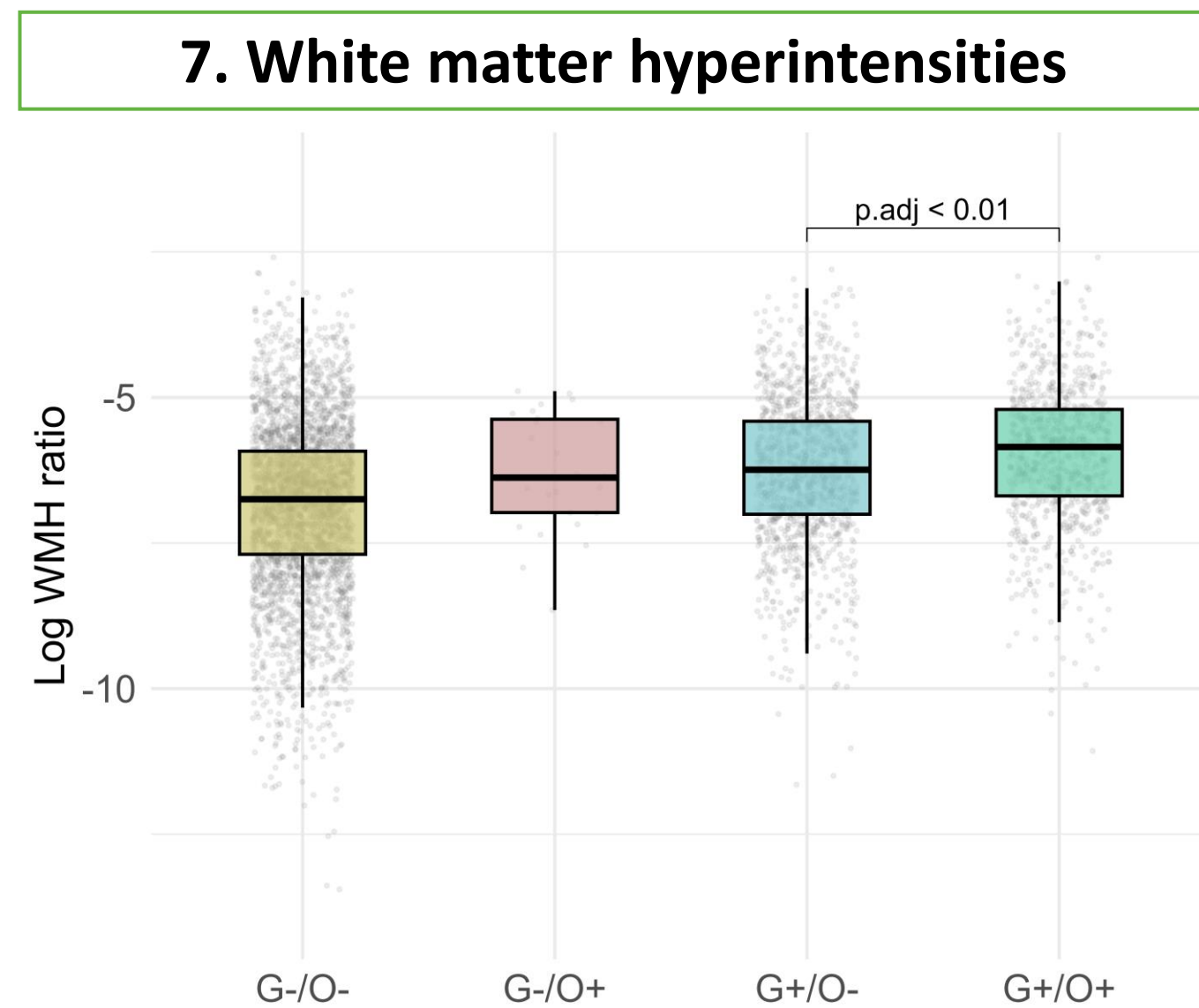


Figure 7. Differences in white matter hyperintensities (WMH) between the four groups. Differences were assessed using a linear regression analysis of the logarithmic ratio of WMH divided by the total intracranial volume and adjusting by age, sex, and cohort. Only comparisons between O+ and O- groups are displayed. N = 5,530

Demographics	Overall N = 21,976
Age, Mean (SD)	71 (9)
Sex, Female (%)	11,649 (53%)
Education, Mean (SD)	14.1 (3.6)
<i>APOE-ϵ4</i> carrier (%)	2,865 (28%)
Global Centiloids, Mean (SD)	37 (43)
PET tracer (%)	
[18F]Florbetaben	15,474 (70%)
[18F]Florbetapir	3,565 (16%)
[18F]Flutemetamol	869 (4.0%)
[18F]NAV4694	736 (3.3%)
[11C]PiB	1,332 (6.1%)
Diagnosis (%)	
CU	9,903 (41%)
MCI-AD	4,300 (20%)
MCI Non-AD	3,911 (18%)
AD dementia	2,219 (10%)
Non-AD dementia	2,453 (11%)

Table 1. Descriptive statistics of the multi-cohort sample. AD = Alzheimer's Disease, *APOE ϵ 4* = Apolipoprotein E, CU = Cognitively Unimpaired, MCI = Mild Cognitive Impairment, PiB = Pittsburgh compound B, SD = Standard Deviation. Education n = 21,556