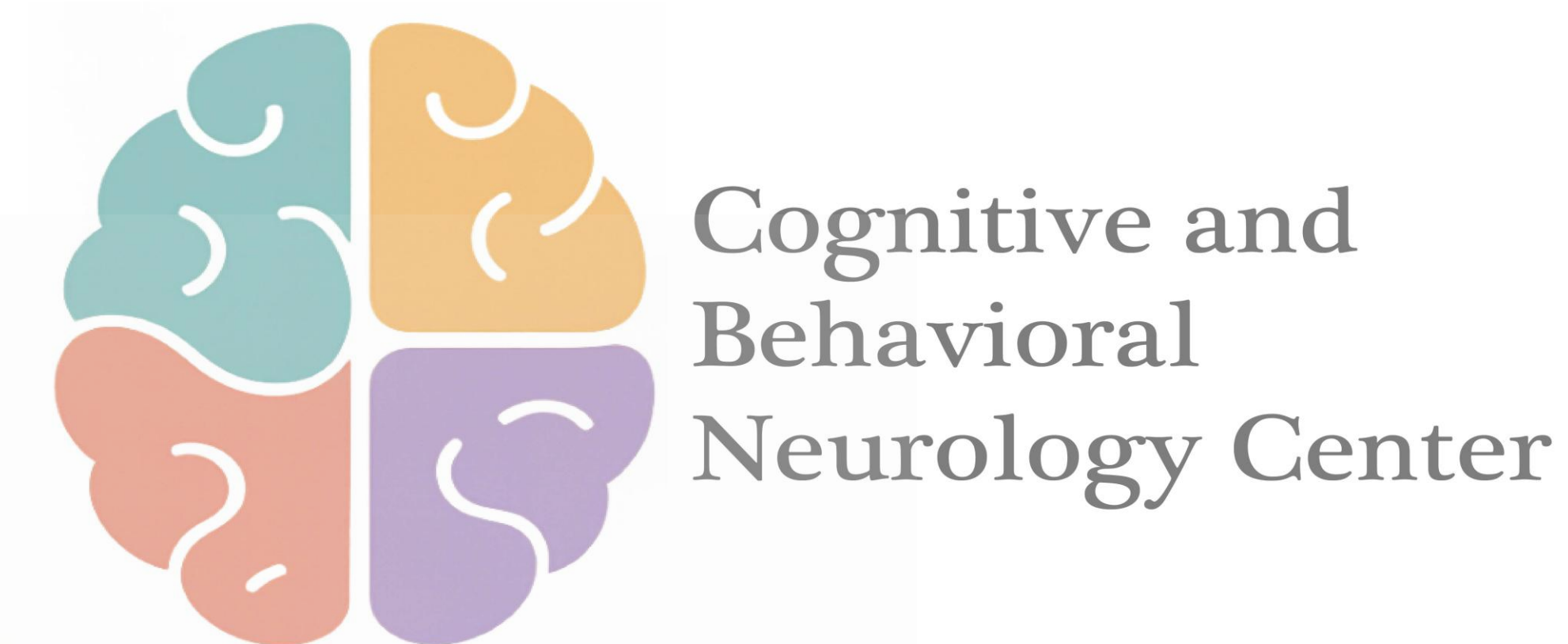


Tau phosphorylation links *APOE* ϵ 4 to informant-rated subjective cognitive decline, with biological risk groups differing selectively in age and informant perception.



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Background

Subjective cognitive decline (SCD), particularly when reported by informants, is considered a preclinical manifestation of Alzheimer's disease (AD). However, the biological pathways through which genetic vulnerability translates into early subjective symptoms remain incompletely understood. We combined causal mediation and biological risk-group stratification to investigate whether tau phosphorylation mediates *APOE* ϵ 4 effects on SCD and whether *APOE* $\times$ p-tau217 profiles capture early subjective differences in the Brazilian Subjective Cognitive Decline (BRASCODE) cohort.

Methods

In the BRASCODE cohort, we evaluated whether plasma p-tau217 mediates the association between *APOE* ϵ 4 and informant-rated SCD using linear models adjusted for age, sex, and education, with indirect (ACME), direct (ADE), and total effects estimated via 5,000 bootstrap simulations. Participants were categorized into four biomarker-defined groups (*APOE* ϵ 4-/p-tau-, *APOE* ϵ 4-/p-tau+, *APOE* ϵ 4+/p-tau-, *APOE* ϵ 4+/p-tau+), and group differences in cognition, SCD, and demographic variables were examined using Kruskal-Wallis tests.

Results

A total of 139 participants were included in the analysis. Baseline characteristics indicated a mean (SD) age of 70.25 (4.53) years, a mean (SD) educational attainment of 14.06 (5.55) years, and a predominantly White sample (93.2%). Plasma p-tau217 significantly mediated the association between *APOE* ϵ 4 and informant-rated SCD (ACME = 0.63, 95% CI 0.18-1.23, p = 0.005). The direct (ADE = -0.50, p = 0.44) and total effects were not significant, indicating that tau phosphorylation fully accounted for the *APOE*-SCD relationship.

In stratified analyses, the four biomarker-defined risk groups showed no differences in objective cognition or participant-reported SCD. Only age and informant-rated SCD differed significantly between groups, with higher-risk profiles (*APOE*-/p-tau+ and *APOE*+/p-tau+) exhibiting both greater age (Figure 1) and higher informant concern (Figure 2).

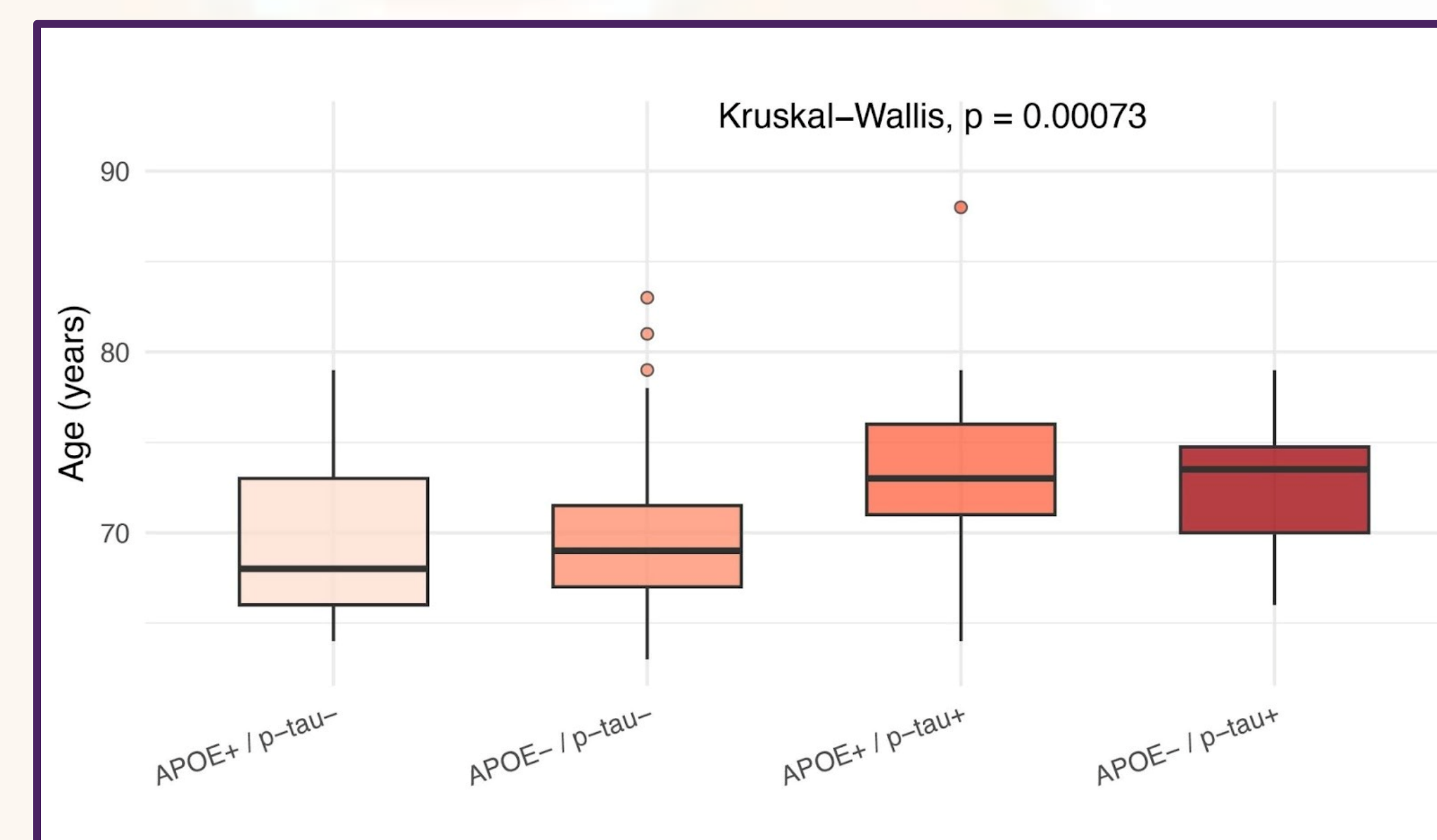
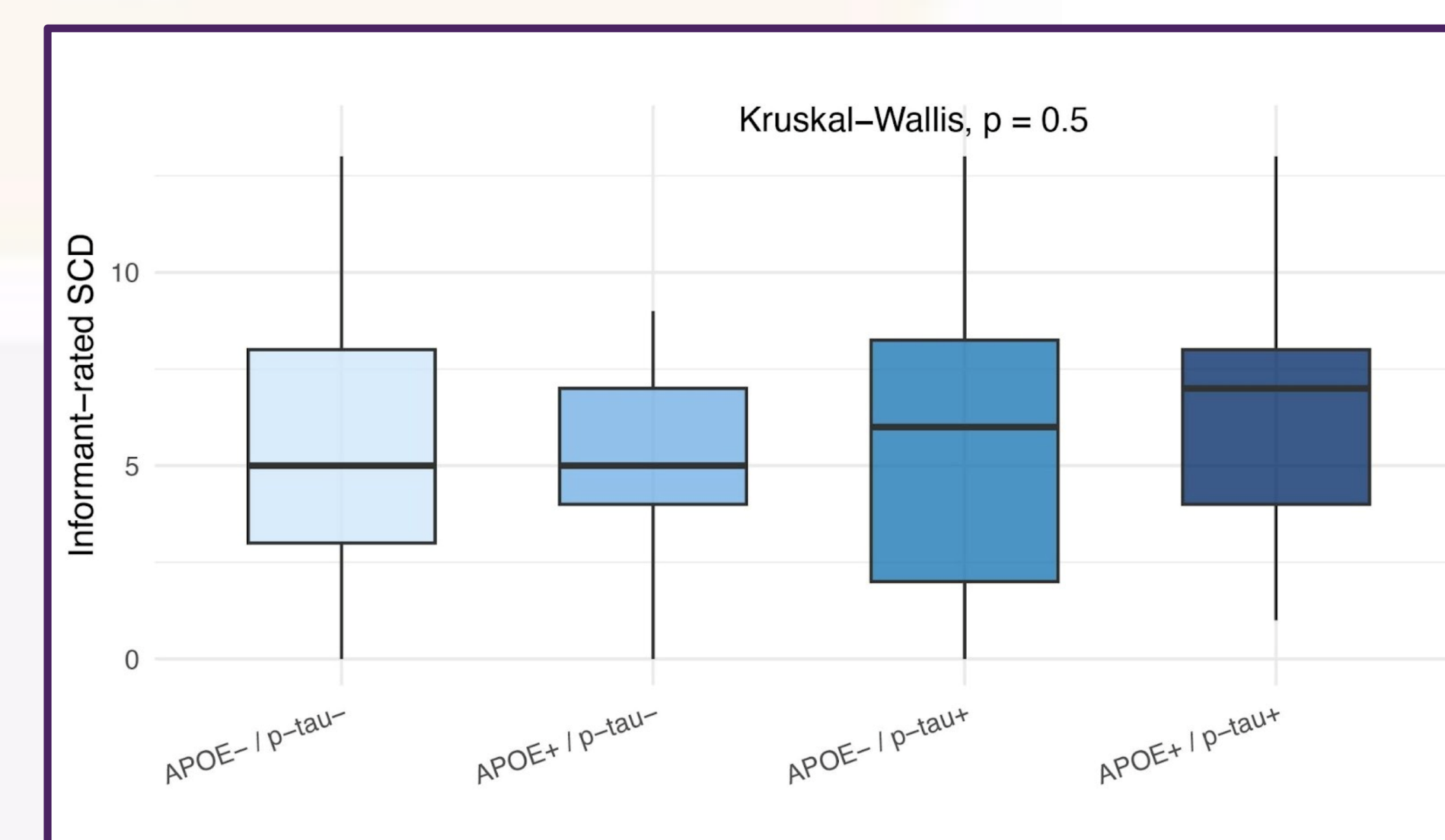


Figure 1: Age according to groups formed by the combination of ptau217 and *APOE* ϵ 4 status

Figure 2: Informant-rated SCD according to groups formed by the combination of ptau217 and *APOE* ϵ 4 status



Conclusion

These convergent findings indicate that tau phosphorylation is a key biological pathway through which *APOE* ϵ 4 influences early subjective cognitive changes detectable by informants. While cognitive performance remains preserved, informant-perceived decline (but not self-report) tracks with underlying molecular risk, reinforcing p-tau217 as a promising marker for identifying biologically meaningful SCD in the earliest stages of the AD continuum.

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