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RESEARCH ARTICLE OPEN ACCESS

## Effect of Parity and $\beta$ -Amyloid on Cognition and Hippocampal Volume in Postmenopausal Women

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### Background



- Being biologically female is one of the main risk factors of AD<sup>1</sup>. Females who develop AD show a worse cognitive trajectory after mild cognitive impairment (MCI) diagnosis<sup>2</sup> and a faster atrophy rate in the hippocampus<sup>3</sup>
- Pregnancy causes major hormonal changes which impact immune<sup>4</sup>, cardiovascular<sup>5</sup> and endocrine systems<sup>6</sup>.
- Epidemiological studies looking at parity and AD risk yield mixed results<sup>7,8</sup>
- Only 2 studies have investigated the impact of pregnancy on AD whilst including biomarkers, and their results are mixed<sup>9,10</sup>

### Aim

To test whether parity interacts with A $\beta$  load in its association with cognitive decline and HV

### Method

#### ALFA + Longitudinal study

- N = 450
- Cognitively unimpaired
- 45-75 years old at V1
- Enriched AD phenotype
  - Higher prevalence of  $\epsilon$ 4 carriers
  - Enriched in AD genetic risk factors



- A $\beta$ + = A $\beta$ 42/40 < 0.071 pg/mL
- Hippocampal volume (ASHS)
- Preclinical Alzheimer's cognitive composite
- Number of biological children (only normotensive gestations)

### Results

#### Our sample

- N = 254 women
- 30% have 1 visit
  - 70% have 2 visits spaced by ~3 years
  - Post-menopausal
  - No history of preeclampsia or gestational diabetes



60.8 yo [55.9 – 65.7]



13 years of education [12.4 - 16.6]



51% APOE- $\epsilon$ 4 carriers



34% A $\beta$ +

0 kids = 15.3%, 1 kid= 21.2% ,  
2 kids= 49.6%, 3 kids= 10.6%, 4+ kids = 3%

#### Parity interacts with amyloid status to affect cognitive change

- Parity did not predict A $\beta$  status.
- The main effect of parity did not significantly relate to mPACC changes (p=0.614).
- The 3-way interaction between parity, time, and A $\beta$  status revealed a significant effect on mPACC z-score change ( $\beta$ =-0.035, 95% CI [-0.068, -0.003], p=0.031)
- **A $\beta$ - women showed less cognitive decline with higher parity, whereas A $\beta$ + women showed steeper cognitive decline with higher parity (Figure 1)**

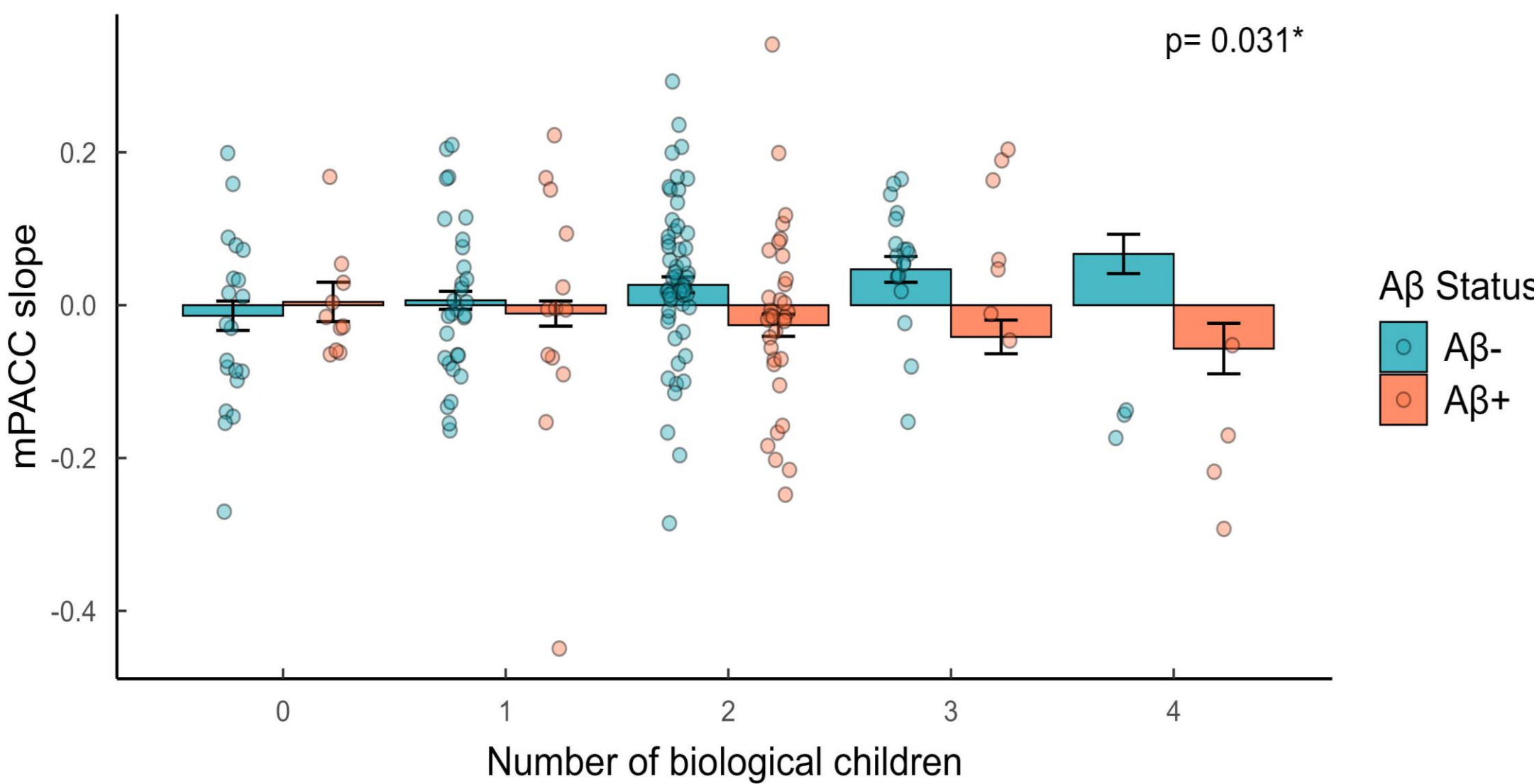


**Figure 1. Effect of parity on mPACC z-score change depending on A $\beta$  status.** Estimated mPACC score slope by number of biological children and stratified by A $\beta$  status, over one year. mPACC scale ranges from -4 to 4. Error bars represent 95% confidence intervals. Significant value refers to the 3-way interaction outcome in the longitudinal model: parity x A $\beta$  status x time.

#### Multiparity drives the effect?

- Using parity as a 3-level categorical variable reduced the estimate and the interaction was no longer significant
- However, post-hoc analysis shows significant group mean difference (Figure 2).

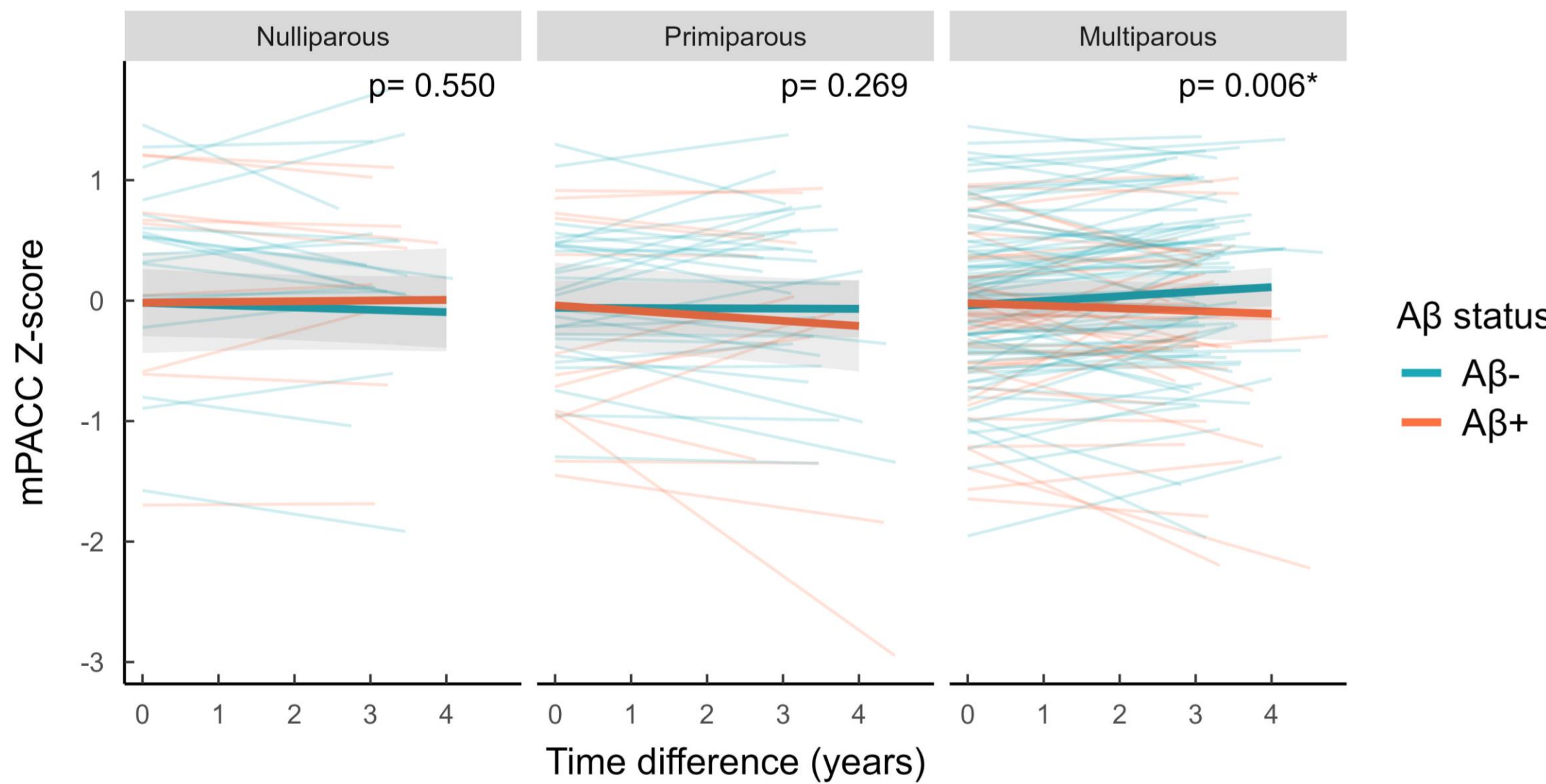


**Figure 2. Effect of parity on mPACC z-score change depending on A $\beta$  status.** Predicted values of mPACC change stratified by parity group (nulliparous [0 biological child], primiparous [1 biological child], and multiparous [2+ biological children]) and A $\beta$  status. Lines represent predicted change. Shaded areas represent 95% confidence intervals. Significant values indicate group differences in the predicted slopes, as estimated from marginal means.

#### Parity interacts with amyloid status to HV across visits

- The 3-way interaction between parity, time and HV was not significant.
- The lower-order interaction between parity and A $\beta$  status was significant ( $\beta$  = -0.134, 95% CI [-0.263, -0.005], p = 0.040)
- Higher parity in A $\beta$ + women was associated with a lower volume (Figure 3).

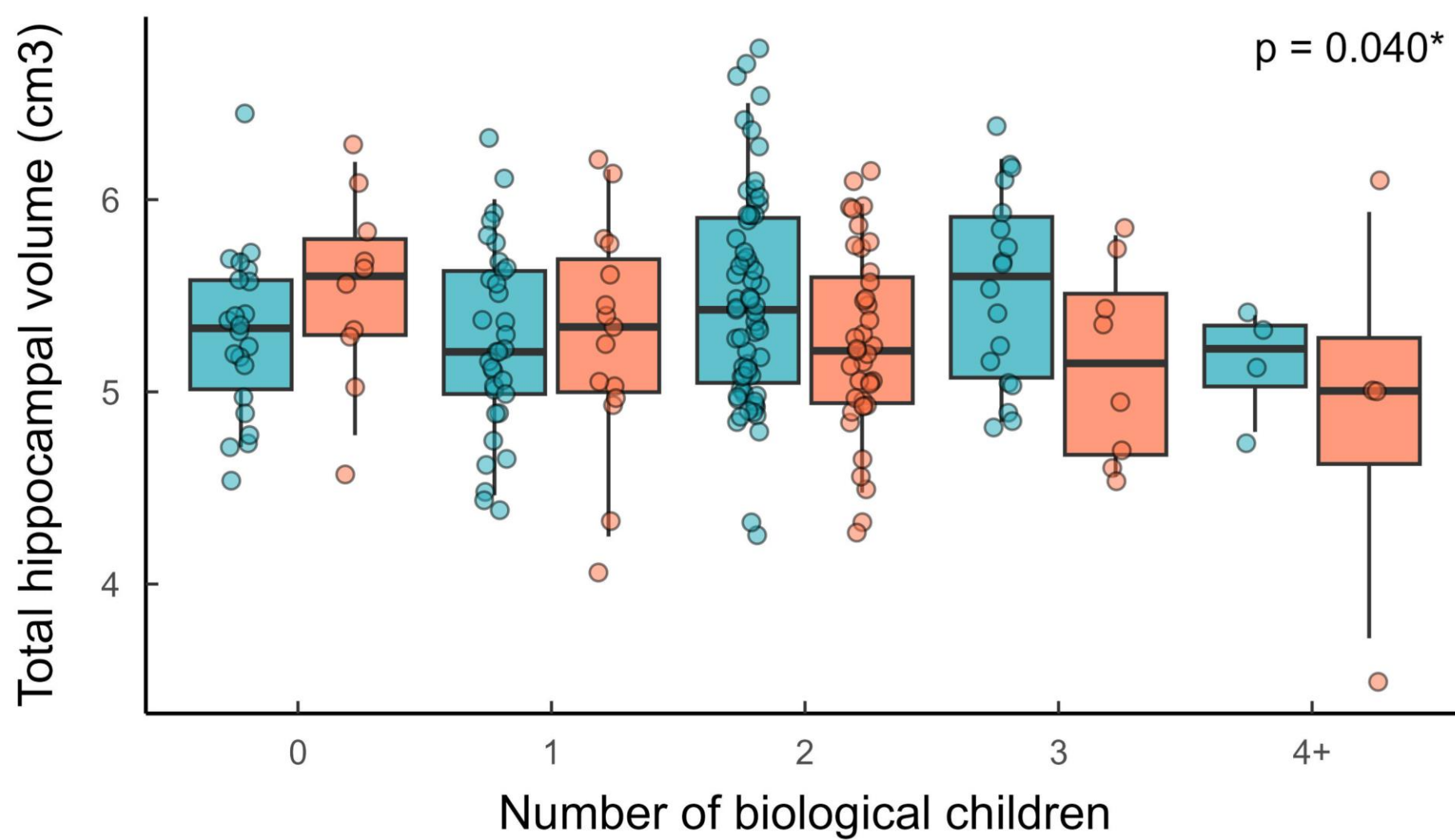


**Figure 3. Effect of parity on whole hippocampal volume by A $\beta$  status.** A) Raw HV data at baseline plotted by number of biological children and A $\beta$  status. Whiskers represent 95% confidence intervals. Significant value refers to the 2-way cross-sectional outcome of parity x A $\beta$  status.

### Conclusions

Having children does not directly influence AD pathology but may interact with it when present.

Our results may help reconcile previously inconsistent findings on the association between parity and AD risk and underscore the importance of considering female-specific biological factors in AD research.

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