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Effect of parity and APOE-ε4 on hippocampal volume in postmenopausal women

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Background



- Being biologically female is one of the main risk factors of AD¹. Females who develop AD show a worse cognitive trajectory after mild cognitive impairment (MCI) diagnosis² and a faster atrophy rate in the hippocampus³
- Pregnancy causes major hormonal changes which impact immune⁴, cardiovascular⁵ and endocrine systems⁶.
- Epidemiological studies looking at parity and AD risk yield mixed results^{7,8}
- Evidence from rodents tells us that APOE-ε4 carrierhip may affect the long-term effects of parity on neuroanatomical changes over the lifespan, but this has not been studied in humans⁹.

Aim

To test whether parity interacts with APOE-ε4 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 ε4 carriers
 - Enriched in AD genetic risk factors



- Aβ+ = Aβ42/40 < 0.071 pg/mL
- Hippocampal volume (ASHS)
- Preclinical Alzheimer's cognitive composite
- Number of biological children (only normotensive gestations)

- Primary analysis:
HV ~ **parity** * **time** * **APOE-ε4** + covariates + (1|subject)
HV ~ **parity** * **time** * **APOE-ε4** + covariates + Aβ status (1|subject)
HV ~ **parity** * **time** * **APOE-ε4** + covariates (1|subject) in Aβ- only (n=121)

- Secondary analysis :
mPACC ~ **parity** * **time** * **APOE-ε4** + covariates + (1|subject)

Results

Our sample

- N = 188 women**
- 2 visits spaced by ~3 years
 - Post-menopausal
 - No history of preeclampsia or gestational diabetes

- 61.1 yo (4.6)
- 13 years of education (3.6)
- 53% APOE-ε4 carriers
- 34% Aβ+
- 0 kids = 15.4%, 1 kid= 20.7% , 2 kids= 48.4%, 3+ kids= 15.4%

Parity interacts with APOE-ε4 to affect cognitive change

- Parity, APOE-ε4, and time showed a significant three-way interaction for total HV ($\beta = -0.019$, 95% CI [-0.032, -0.006], $p = 0.003$), indicating that higher parity was associated with a steeper decline in HV among APOE-ε4 carriers (Figure 1).
- Stratifying by APOE-ε4 status yielded a significant interaction between parity and time in carriers only ($\beta = -0.013$, 95% CI [-0.021, -0.006], $p < 0.001$).

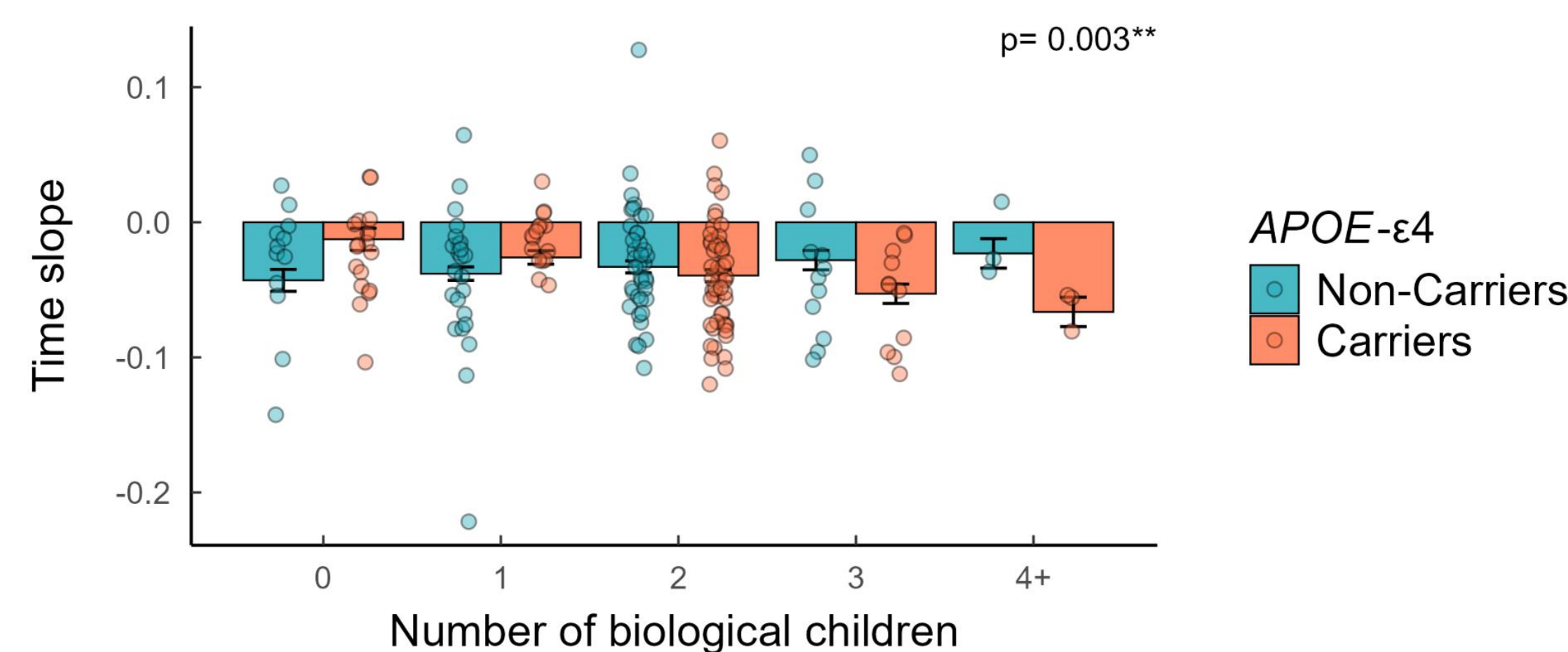


Figure 1. Effect of parity on HV change depending on APOE-ε4 status. A) Bars represent estimated HV slope by number of biological children over one year. Error bars represent 95% confidence intervals. Each point represents a subject slope. Significant value refers to the 3-way interaction outcome in the longitudinal model: parity x APOE-ε4 status x time covaried by age, education, HMT and TIV.

Genetic contributions independent from amyloid accumulation

- ε4 carriers were significantly more likely to have an Aβ+ status. However, the effect was reproduced when adjusting for Aβ status and when carrying the analysis in Aβ- only women.

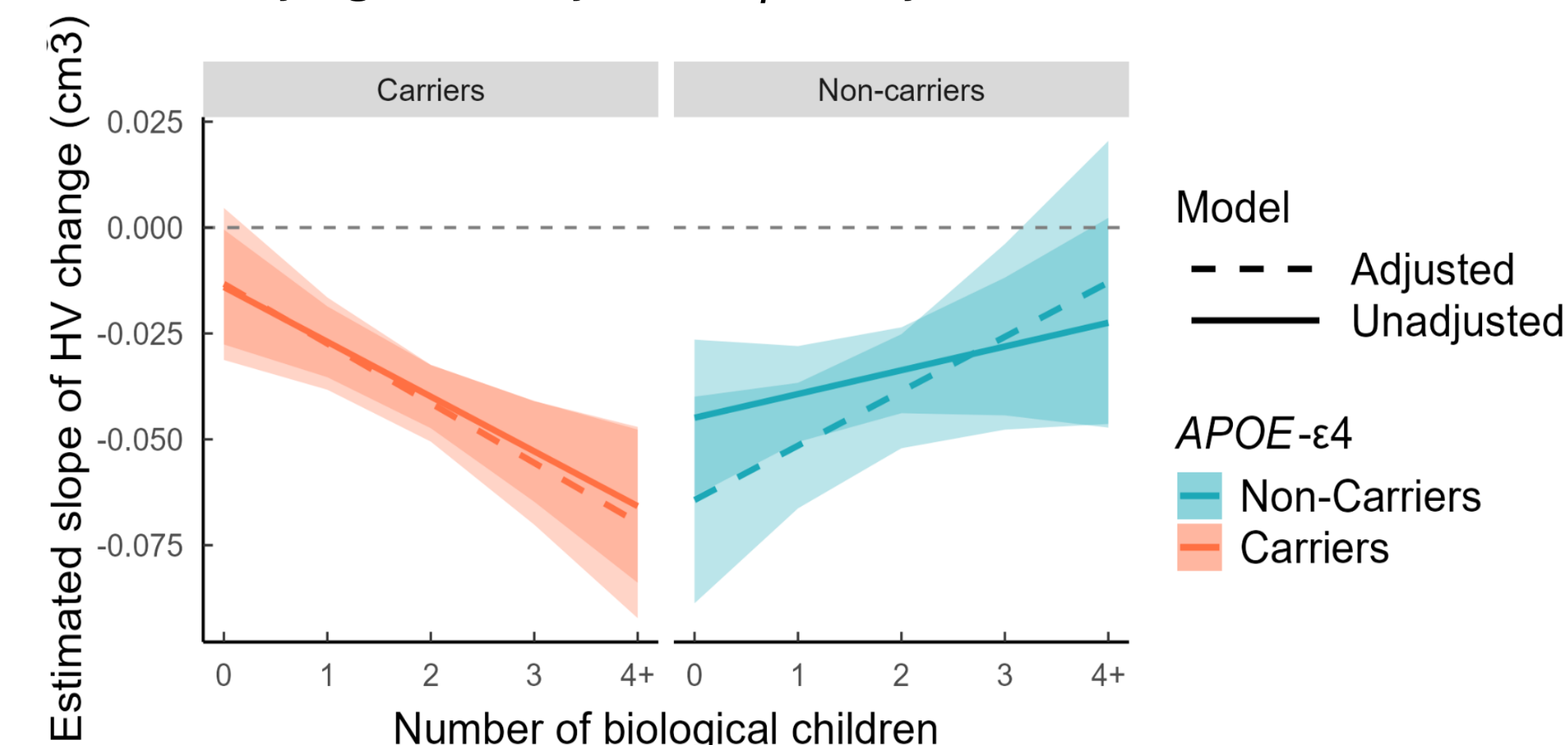


Figure 2. Effect of parity on HV change adjusted for Aβ status. Estimated values of HV change by number of biological children, stratified by APOE-ε4 status. Continuous lines represents the main models, dashed line represents the model adjusted by continuous CSF Ab42/40 levels. Shaded areas represent the 95% confidence interval.

Exploratory analysis of hippocampal subfields

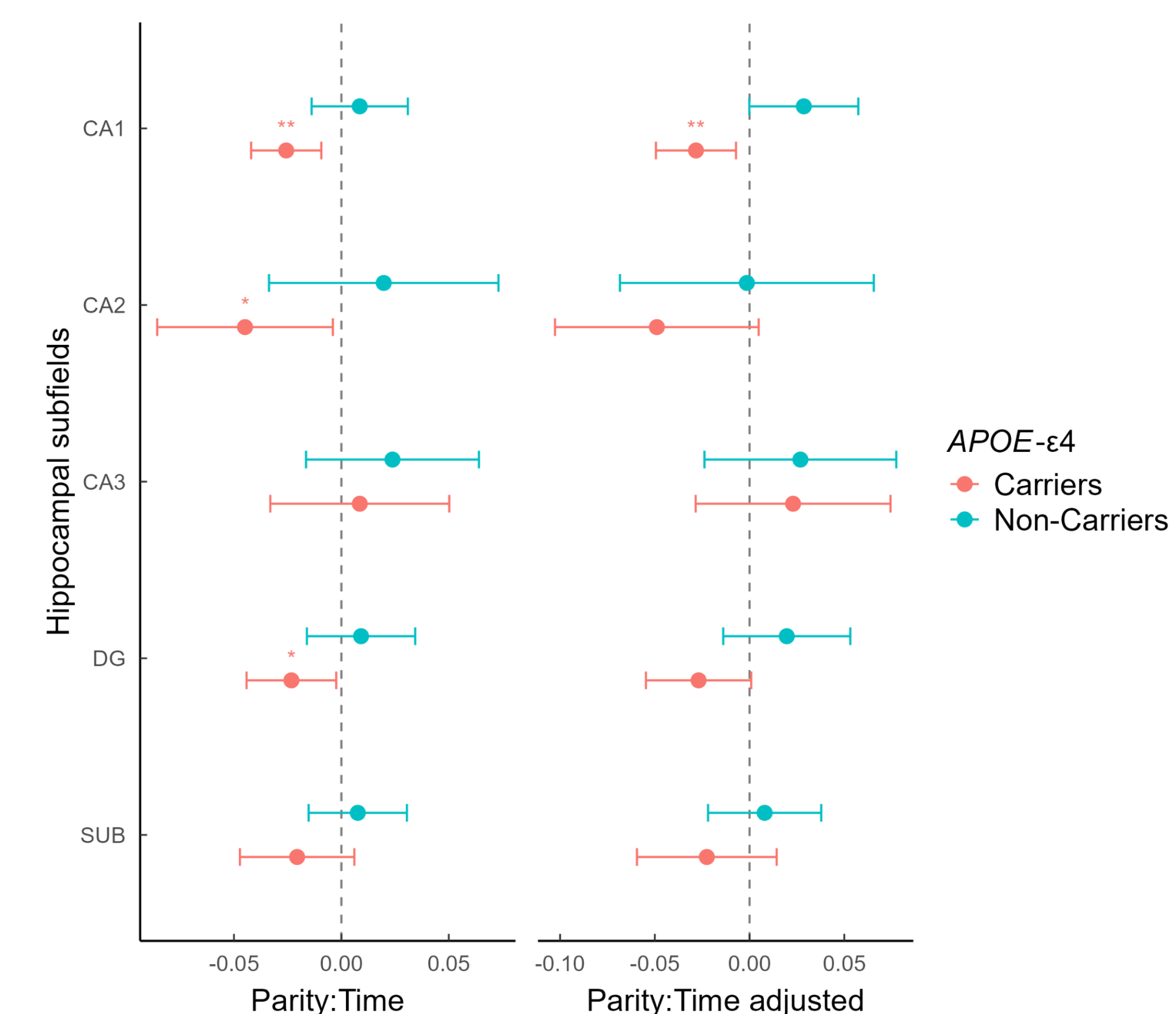


Figure 3. Effect of parity on hippocampal subfield volume change depending on APOE-ε4 status. Error bars represent the estimate of parity and time interaction in models stratified by APOE-ε4 status and covaried by age, education, HMT and TIV, with 95% confidence interval. The left plot shows the model with no amyloid load adjustment, and the right plot shows the model with amyloid adjustment. Subfield volumes were standardized for comparison.

Conclusions

This research shows preliminary evidence that parity is associated with HV trajectory in postmenopausal women depending on their AD genetic risk profile.

Our results underscore the importance of incorporating reproductive history into models of neurodegeneration in women.

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