

Greater estradiol exposure is associated with greater Alzheimer disease plasma biomarkers in postmenopausal APOE ε4 carriers.

APOE genotype modifies associations between estradiol exposure and plasma Alzheimer disease biomarkers in postmenopausal females

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Background & Method

**What we know:**

- Females have approximately twice the lifetime risk of Alzheimer disease (AD) compared to males<sup>1</sup>.
- APOE ε4 is a major genetic risk factor for AD<sup>2</sup>.
- Menopause-related estradiol (E2) decline and shorter lifetime exposure to endogenous E2 (LEE2) may contribute to AD pathology<sup>3,4</sup>.
- Supplementation of E2 with menopause hormone therapy (MHT) is inconsistently associated with AD risk<sup>5</sup>.

**What we don't know:**

Whether the associations of E2 exposure with AD pathology differ by APOE ε4 status.

**Participants:** 301 postmenopausal females across the neurocognitive continuum from COMPASS-ND.

| Estradiol (pmol/L) M±SD | LEE2 (years) M±SD | MHT Use n(%)                   | Age M±SD | Education M±SD | Race (White) n(%) |
|-------------------------|-------------------|--------------------------------|----------|----------------|-------------------|
| 39.5±52.3               | 36.1±7.5          | Past: 87(29)<br>Current: 12(4) | 71.4±6.8 | 15.3(3.4)      | 280(93)           |

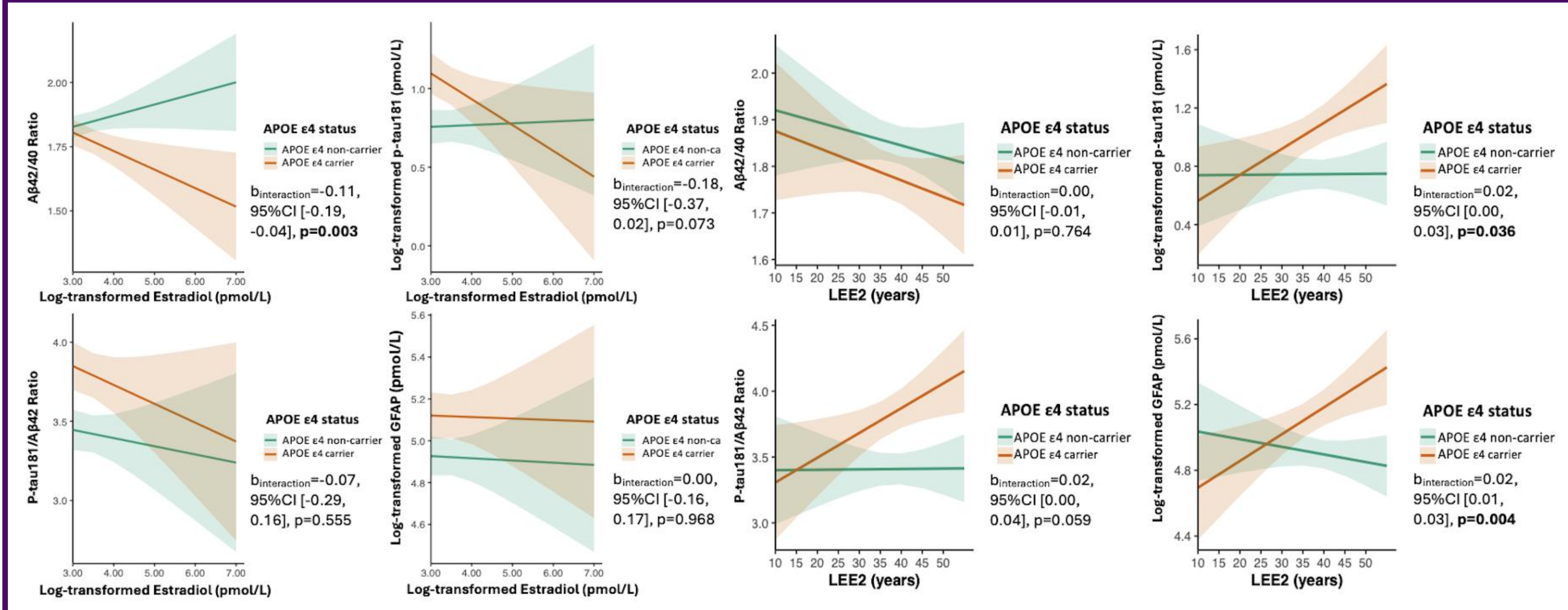
**Measures:**

- Circulating E2: Plasma E2 quantified using SiMOA.
- LEE2: Menopause age – menarche age.
- AD biomarkers: Aβ42/40, p-tau181, p-tau181/Aβ42, and glial fibrillary acidic protein (GFAP).
- APOE status: ε4 carriers (ε2/ε4, ε3/ε4, ε4/ε4) vs non-carriers (ε2/ε2, ε2/ε3, ε3/ε3).

**Analysis:**

- Adjusted linear regression models.
- Covariates: age, education, race, menopause type, and MHT use.

Result



Conclusion

**Estradiol-biomarker associations in postmenopausal females varied by APOE ε4 status, with patterns among ε4 carriers consistent with greater AD-related pathology.**

- Higher circulating E2** associated with lower plasma Aβ42/40 ratios among ε4 carriers ( $b = -0.07$ , 95% CI [-0.13, -0.02],  $p = 0.012$ ).
- Longer LEE2** duration associated with higher p-tau181 and GFAP levels among ε4 carriers (p-tau181:  $b = 0.02$ , 95%CI [0.00, 0.03],  $p = 0.008$ ; GFAP:  $b = 0.02$ , 95%CI [0.01, 0.03],  $p = 0.005$ ).
- Relationships between E2 exposures and AD biomarkers **did not reach significance among non-carriers**.

References & Contact



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