Supplementary Information

P-values are reported before and after false discovery rate (FDR)-correction.

1. Correction for ICD-10 diagnoses

To evaluate whether disorders known to affect the brain could drive the observed effects, all the main analyses were rerun after excluding participants with the following main and secondary ICD-10 diagnoses: F (Mental and behavioral disorder, n = 84), G (Diseases of the nervous system, n = 211) and I60-I69 (Cerebrovascular diseases, n = 42). Five women had the same or overlapping diagnoses for both main and secondary ICD-10 diagnosis.

In summary, the main results were not influenced by excluding participants with ICD-10 diagnoses. The corrected associations with apparent brain aging were as follows: *ICEE*: $\beta = 0.035, SE = 0.014, t = 2.481, p = 0.013, p_{corr} = 0.022$, n = 8,701; *HRT status*: $\beta = 0.169, SE = 0.055, t = 3.043, p = 0.002, p_{corr} = 0.012$, n = 16,358, user = 5450, never-user = 10908; *age started HRT*: $\beta = 0.022, SE = 0.009, t = 2.476, p = 0.013, p_{corr} = 0.022$, n = 5,077; *duration of HRT use*: $\beta = 0.004, SE = 0.005, t = 0.755, p = 0.450, p_{corr} = 0.563$, n = 5,077; and *OC status*: $\beta = 0.031, SE = 0.067, t = 0.464, p = 0.643, p_{corr} = 0.643$, n users = 14,333, never-users = 2,168. The interaction of *APOE e4 status* × *estradiol levels* also yielded equivalent results:$\beta = 0.008, SE = 0.002, t = 3.580, p = 4.062 \times 10^{-4}, p_{corr} = 0.001$, n = 289, covariates: current HRT use, ever used HRT, length since menopause, number of births, age at first birth, education, BMI and hypertensive status). The same was true for the main effect of estradiol levels on brain age in APOE e4 carriers $\beta = 0.006, SE = 0.002, t = 3.090, p = 0.003, p_{corr} = 0.004$, n = 75, and non-carriers $\beta = -0.003, SE = 0.001, t = -2.519, p = 0.013, p_{corr} = 0.013$, n = 214.

2. Correction for polygenic risk score (PRS) of Alzheimer's disease

To examine whether polygenic risk for Alzheimer's disease could drive the observed effects, all the main analyses were rerun while accounting for individual PRS scores. Individual PRS were calculated using PRSice version 1.25 (Euesden et al., 2014) at a p-value threshold of 0.05, using PRSice default settings. This includes the removal of the major histocompatibility complex (MHC; chromosome 6, 26-33Mb) and thinning of SNPs based on linkage disequilibrium (LD) and p-value. We based the PRS on Lambert and colleagues work (Lambert et al., 2013). No associations were found between PRS and apparent brain aging ($\beta = 330.873, SE = 192.759, t = 330.873, p = 0.086, p_{corr} = 0.129$).

The main results were not influenced by PGRS scores. The corrected associations with apparent brain aging were as follows: *ICEE*: $\beta = 0.040, SE = 0.014, t = 2.795, p = 0.005, p_{corr} = 0.016$, n = 8,618; *HRT status*: $\beta = 0.167, SE = 0.056, t = 3.003, p = 0.003, p_{corr} = 0.016$, n = 16,177, user = 5,368, never-user = 10,809; *age started HRT*: $\beta = 0.022, SE = 0.009, t = 2.423, p = 0.015, p_{corr} = 0.031$, n = 5,000; *duration of HRT use*: $\beta = 0.004, SE = 0.005, t = 0.812, p = 0.418, p_{corr} = 0.500$, n

= 5,000; and *OC status*: $\beta = -0.007, SE = 0.067, t = -0.098, p = 0.922, p_{corr} = 0.922$, n = 16,314, user = 14,165, never-user = 2,148.

3. Reproductive span

Reproductive span was calculated as (age at menopause − age at menarche). 9,188 menopausal women had data on both variables and were included in the analysis. A multiple linear regression including number of births, ever used HRT, ever used OC, and age as covariates showed a trend towards a positive association between reproductive span and apparent brain aging, but the effect did not survive FDR correction ($\beta = 0.012, SE = 1.872, t = 1.872, p = 0.061, p_{corr} = 0.209$).

4. Age at menarche

A multiple linear regression including number of births and age showed a negative association between age at menarche and apparent brain aging in pre- and menopausal women ($\beta = -0.039, SE = 0.014, t = -2.751, p = 5.955 \times 10^{-3}, p_{corr} = 0.054$, n = 16,435), indicating more apparent brain aging with earlier age at menarche. However, when including age at first birth, education, BMI and hypertensive status as additional covariates, the association did not persist ($\beta = -0.035, SE = 0.019, t = -1.814, p = 0.070, p_{corr} = 0.209$, n = 9,107).

5. Age at menopause

When accounting for a history of hysterectomy and/or oophorectomy, number of births and age, we found no relationship between age at menopause and apparent brain aging in menopausal women ($\beta = 0.007, SE = 0.007, t = 0.976, p = 0.329, p_{corr} = 0.429$, n = 9,346).

6. Surgical vs. natural menopause

Surgical menopause is defined by women transitioning to menopause through removal of both ovaries (bilateral oophorectomy) rather than natural reproductive aging. Functioning ovaries can also be removed at time of hysterectomy to reduce the risk of ovarian cancer. We stratified menopausal women according to (1) natural menopause (n = 7,888) defined by absence of hysterectomy and/or oophorectomy, and (2) surgical menopause (n = 422) characterized by age at hysterectomy and/or oophorectomy coinciding with age at menopause. A linear regression including number of births, age, ever used HRT and time since menopause showed no association between type of menopause and apparent brain aging ($\beta = -0.150, SE = 0.155, t = -0.967, p = 0.334, p_{corr} = 0.429$).

References

Euesden, J., Lewis, C. M., & O'Reilly, P. F. (2014). Prsice: polygenic risk score software. *Bioinformatics*, *31*, 1466–1468.

Lambert, J.-C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., Jun, G., DeStefano, A. L., Bis, J. C., Beecham, G. W. et al. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for alzheimer's disease. *Nature genetics*, *45*, 1452.