

## Supplementary Information

### No Causal Links Between Estradiol and Female's Brain and Mental Health Using Mendelian Randomization

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### Supplementary Notes

#### Note 1. Exclusion Criteria for Newly run GWAS.

##### *Exclusion of Participants from Brain Age Gap Sample*

A total of  $N = 42,052$  participants in the UK Biobank (UKB) had T1-weighted imaging data and  $N = 39,028$  ( $n = 36,941$  after exclusion of missing data) had diffusion-weighted imaging data. Of these,  $n = 19,670$  females and  $n = 17,268$  males had both T1- and diffusion-weighted data. Participants were excluded if they were not White European. Furthermore, participants who had an ICD-10 diagnosis of mental and behavioral disorders (ICD field F including F00-03 for Alzheimer's disease and dementia and F06.7 for mild cognitive disorders, and excluding depressive disorders), diseases of the nervous system (ICD field G including inflammatory and neurodegenerative diseases, except G55-59), or stroke (ICD field code I64) were excluded, to prevent disorders known to cause brain changes to influence the results, following previous studies. This led to the exclusion of  $n = 5,257$  females and  $n = 3,712$  males. Of the remaining samples,  $n = 4,008$  females and  $n = 3,470$  males were scanned in Newcastle,  $n = 8,649$  females and  $n = 8,410$  males were scanned in Cheadle, and  $n = 1,756$  females and  $n = 1,676$  males were scanned in Reading. During brain age prediction,  $n = 126$  female outliers and  $n = 133$  male outliers were removed, leading to a final sample of  $N = 14,287$  females (age range: 45.13 – 81.83 years; mean = 63.56,  $SD = 7.27$ ) and  $N = 13,423$  males (age range: 46.07 – 82.18 years; mean = 64.82,  $SD = 7.57$ ).

##### *Exclusion of Participants from Estradiol Levels Sample*

A total of  $N = 502,370$  participants in the UKB had either above-threshold (1) values or missing values (coded as below-threshold; 0), with  $n = 264,719$  females. Of these,  $n = 43,320$  were excluded due to not being White British/Caucasian. Furthermore,  $n = 14,280$  were included in the brain age gap sample and thus excluded from the estradiol levels sample. This resulted in a final sample for binary estradiol levels of  $N = 207,119$  females (age range: 40.16 – 71.10 years; mean = 57.39,  $SD = 7.93$ ), with estradiol levels below (0;  $n = 165,035$ ; age range: 40.18 – 71.10 years; mean = 59.54,  $SD = 6.81$ ) or above (1;  $n = 42,084$ ; age range: 40.16 – 70.70 years; mean = 48.95,  $SD = 6.21$ ) the detection limit. The females with estradiol levels below the detection limit were significantly older than the females with estradiol levels above the detection limit (Welch two sample t-test:  $t(70,191) = 306.17$ ,  $p < .001$ ). Of the  $n = 42,084$  females with estradiol levels above the detection limit,  $n = 7,387$  females were removed due to answering “prefer not to answer” or “do not know/not sure” on one of the covariates (i.e., menopausal status (“had menopause”; [UKB Field 2724](#)), history of oral contraceptive use (“ever taken oral contraceptive pill”; [UKB Field 2784](#)), history of HRT use (“ever used HRT”;

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[UKB Field 2814](#)), history of bilateral oophorectomy (“bilateral oophorectomy (both ovaries removed)”); [UKB Field 2834](#)), and history of hysterectomy (“ever had hysterectomy (womb removed)”); [UKB Field 3591](#))). This resulted in a final sample with continuous estradiol levels of  $N = 34,697$  females.

### *Exclusion of Participants from Male-Only Depression GWAS Meta-Analysis*

In line with the female-only depression GWAS meta-analysis<sup>1</sup>, GWAS were run on males with White European ancestry from the UK Biobank (UKB)<sup>2</sup> and the Norwegian Mother and Child Cohort Study (MoBa)<sup>3</sup>. The UKB is a prospective population-based study from the United Kingdom, encompassing over 500,000 participants aged 40-69 that were recruited between 2006 and 2010<sup>3</sup>. This research has been conducted using the UKB Resource under Application Number 27412. The UKB complies with the Helsinki Declaration, with informed consent obtained from all participants. MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health<sup>3</sup>. Participants were recruited from all over Norway from 1999-2008<sup>3</sup>. The women consented to participation in 41% of the pregnancies<sup>3</sup>. The cohort includes approximately 114,500 children, 95,200 mothers, and 75,200 fathers<sup>3</sup>. MoBa is regulated by the Norwegian Health Registry Act<sup>3</sup>. The present study was approved by the Regional Committees for Medical and Health Research Ethics (2016/1226/REK).

Inclusion and exclusion criteria were chosen following previous studies<sup>1,4</sup>. Cases were defined as having a lifetime (primary or secondary for UKB; following the Norwegian Patient Registry for MoBa) diagnosis of a depressive episode or recurrent depressive episode, according to the ICD-10 (F32 or F33). Cases with a lifetime (primary or secondary) diagnosis of schizophrenia, schizotypal, or delusional disorder (F20-F29), mania or bipolar disorder (F30 or F31), or personality disorder (F40 or F61) were excluded. Further, controls with a lifetime (primary or secondary) diagnosis of any mood disorder (F30-F39), schizophrenia, schizotypal, or delusional disorder (F20-F29), or personality disorder (F40 or F61) were excluded. Finally,  $n = 9,413$  cases and  $n = 176,243$  controls were included from the UKB and  $n = 2,470$  cases and  $n = 45,628$  controls were included from MoBa. From the PGC and iPSYCH samples ( $n = 10,194$  cases and  $n = 18,799$  controls), GWAS summary statistics of diagnosed depression in males were received from the authors upon request<sup>5</sup>. The following linkage disequilibrium score (LDSC; v2.0.0) heritability<sup>6,7</sup> estimated were computed: UKB  $h^2 = 0.02$  (SE = 0.00), MoBa  $h^2 = 0.11$  (SE = 0.05), and PGC and iPSYCH  $h^2 = 0.07$  (SE = 0.02). Using LDSC genetic correlations, the UKB and MoBa GWAS correlated at  $r_g = 0.87$  (SE = 0.24,  $p = 2.00e^{-4}$ ), the

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UKB and PGC and iPSYCH GWAS correlated at  $r_g = 1.05$  ( $SE = 0.21$ ,  $p = 7.86e^{-7}$ ), and the MoBa and PGC and iPSYCh GWAS correlated at  $r_g = 0.67$  ( $SE = .31$ ,  $p = .03$ ).

### Note 2. Procedure of Male-Only Depression GWAS Meta-Analysis.

The UKB v3 imputed genetic data was used for the UKB GWAS, which has been genotyped, extensively quality controlled, and imputed by the UKB genetics team<sup>8</sup>. The imputed genetic data from the MoBaPsychGen pipeline v.1<sup>9</sup> was used for the MoBa GWAS. Both GWAS were performed using REGENIE v4.1<sup>10</sup>. For the association analysis, we retained only autosomal variants with a minor allele count  $> 20$  and an imputation information score  $> 0.80$ . Covariates included age, the first twenty genetic principal components and genotyping batch (only for MoBa). METAL (version 2020-05-05; <https://github.com/statgen/METAL>)<sup>11</sup> was used for the inverse variance-based meta-analysis of the GWAS summary statistics from the UKB, MoBa, and PGC and iPSYCH samples.

### Note 3. Selection of Instrumental Variables.

In cases where the genome-wide significance threshold of  $p < 5 \times 10^{-8}$  resulted in very few available ( $n \text{ SNPs} < 5$ ) instrumental variables after pruning, or when the outcome dataset included too few of the identified instrumental variables, the number of instrumental variables was increased, to increase statistical power, by lowering the significance threshold to  $p < 5 \times 10^{-7}$  or  $p < 5 \times 10^{-6}$  or searching for proxy variants for the main analyses.

Proxy variants were searched for using the LDProxy Tool from [LDlink](https://www.wellcomegenomeproject.org/ldproxy/). The respective instrumental variable was entered in the search using the Great British reference population (GBR). When available, resulting proxy variants with a minimum linkage disequilibrium (LD)  $R^2$  of .60 were ordered according to their  $R^2$  and the proxy variant with the highest  $R^2$  was used. During harmonization of the exposure and outcome datasets, palindromic SNPs were excluded. See Supplementary Table 4 for an overview of the thresholds used, numbers of instrumental variables, and instrument strength of each analysis.

#### A. Main Analyses

- a. **Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB).** For continuous estradiol levels in the combined pre- and postmenopausal sample, 1 and 2 significant SNPs were identified at the thresholds of  $p < 5 \times 10^{-8}$  and  $p < 5 \times 10^{-7}$ , respectively. The threshold was relaxed to  $p < 5 \times 10^{-6}$ , resulting in 18 significant SNPs. After harmonization, 16 SNPs were available for brain age gap and depression, and

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15 SNPs were available for Alzheimer's disease as outcomes. There was no indication of weak instrument bias (all  $F = 23.0$ ).

- b. **Estradiol Levels (continuous approach; postmenopausal LIFE samples).** For estradiol levels measured in the LIFE samples (Pott et al., 2019), 0 and 3 significant SNPs were identified after clumping at the thresholds of  $p < 5 \times 10^{-8}$  and  $p < 5 \times 10^{-7}$ , respectively. The threshold was relaxed to  $p < 5 \times 10^{-6}$ , resulting in 12 significant SNPs. After harmonization, 10 SNPs were available for brain age gap, depression, and Alzheimer's disease as outcomes. There was no indication of weak instrument bias ( $F = 23.3$ ).
- c. **Estradiol Levels (continuous approach; premenopausal sample from the UKB).** For estradiol levels measured in premenopausal females using the continuous approach (Haas et al., 2022), 1 and 2 significant SNPs were identified after clumping at the thresholds of  $p < 5 \times 10^{-8}$  and  $p < 5 \times 10^{-7}$ , respectively. The threshold was relaxed to  $p < 5 \times 10^{-6}$ , resulting in 14 significant SNPs. After harmonization, 13 SNPs were available for brain age gap, depression, and Alzheimer's disease. There was no indication of weak instrument bias (all  $F = 23.6$ ).
- d. **Estradiol Levels (continuous approach; postmenopausal sample from the UKB).** For estradiol levels measured in postmenopausal females using the continuous approach (Haas et al., 2022), 0 and 2 significant SNPs were identified after clumping at the thresholds of  $p < 5 \times 10^{-8}$  and  $p < 5 \times 10^{-7}$ , respectively. The threshold was relaxed to  $p < 5 \times 10^{-6}$ , resulting in 14 significant SNPs. After harmonization, 12 SNPs were available for brain age gap, depression, and Alzheimer's disease. There was no indication of weak instrument bias (brain age gap:  $F = 22.6$ ; Alzheimer's disease:  $F = 22.7$ ; depression:  $F = 23.6$ ).
- e. **Reproductive Span.** For reproductive span, 85 SNPs were identified as instrumental variables at the threshold of  $p < 5 \times 10^{-8}$ . After harmonization, 73 SNPs were available for brain age gap and depression, and 68 SNPs were available for Alzheimer's disease as an outcome. There was no indication of weak instrument bias (brain age gap and depression:  $F = 79.7$ ; Alzheimer's disease:  $F = 81.1$ ).
- f. **Age at Menarche.** For the age at menarche (ReproGen sample) dataset used with brain age gap and depression as outcomes, 68 significant SNPs were

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identified at the threshold of  $p < 5 \times 10^{-8}$ . After harmonization, 54 SNPs were available for brain age gap and depression. In the dataset used for age at menarche (UKB sample) with Alzheimer's disease, 249 SNPs were identified at the threshold of  $p < 5 \times 10^{-8}$ , of which 204 were available for the outcome. There was no indication of weak instrument bias (brain age gap and depression:  $F = 83.7$ ; Alzheimer's disease:  $F = 66.5$ ).

- g. **Age at Menopause.** For the age at natural menopause (ReproGen sample) dataset used with brain age gap and depression as outcomes, 42 significant SNPs were identified at the threshold of  $p < 5 \times 10^{-8}$ . After harmonization, 37 SNPs were available for brain age gap and 38 SNPs were available for depression. In the dataset used for age at menopause (UKB sample) with Alzheimer's disease as an outcome, 80 significant SNPs were identified at the threshold of  $p < 5 \times 10^{-8}$ , of which 68 were available for the outcome. There was no indication of weak instrument bias (brain age gap:  $F = 78.8$ ; depression:  $F = 77.6$ ; Alzheimer's disease:  $F = 77.2$ ).
- h. **Number of Childbirths.** For number of childbirths, 11 significant SNPs were identified at the threshold of  $p < 5 \times 10^{-8}$ . After harmonization, 8 SNPs were available for all outcomes, which did not exhibit weak instrument bias (all  $F = 39.6$ ).

### B. Sensitivity Analyses

- a. **Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB).** For estradiol levels in the sample of pre- and postmenopausal females using the binary approach, 10 significant SNPs were identified at the threshold of  $p < 5 \times 10^{-8}$ , of which all were available for all outcomes. There was no indication of weak instrument bias (all  $F = 52.1$ ).
- b. **Estradiol Levels (binary approach; premenopausal sample from the UKB).** For estradiol levels in premenopausal females using the binary approach (Haas et al., 2022), 5 significant SNPs were identified after clumping at the threshold of  $p < 5 \times 10^{-8}$ . After harmonization, all SNPs were available for brain age gap, Alzheimer's disease, and depression. There was no indication of weak instrument bias (all  $F = 44.9$ ).
- c. **Estradiol Levels (binary approach; postmenopausal sample from the UKB).** For estradiol levels in postmenopausal females using the binary approach (Haas et al., 2022), 9 significant SNPs were identified at the threshold



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of  $p < 5 \times 10^{-8}$ . After harmonization, 8 SNPs were available for brain age gap and depression, and 7 SNPs were available for Alzheimer's disease. There was no indication of weak instrument bias (brain age gap and depression:  $F = 48.3$ ; Alzheimer's disease:  $F = 50.2$ ).

- d. Estradiol Levels (male sample).** For estradiol levels in the male sample, 55 significant SNPs were identified at the threshold of  $p < 5 \times 10^{-8}$ . After harmonization, 44, 45, and 42 SNPs were available for the brain age gap (male sample), depression (male sample), and Alzheimer's disease (male sample) outcomes, respectively. There was no indication of weak instrument bias (brain age gap:  $F = 37.1$ ; depression:  $F = 37.3$ ; Alzheimer's disease:  $F = 37.4$ ). For the sensitivity analysis using the depression subsample excluding UKB, 6 SNPs were available ( $F = 37.5$ ).
- e. Recurrent Depression (Outcome Variable).** The following number of instrumental variables were used for each respective exposure variable with recurrent depression as an outcome: 5 (estradiol levels continuous approach; combined pre- and postmenopausal sample from the UKB), 5 (estradiol levels continuous approach; postmenopausal LIFE samples), 7 (estradiol levels continuous approach; premenopausal sample from the UKB), 6 (estradiol levels continuous approach; postmenopausal sample from the UKB), 43 (reproductive span), 136 (age at menarche; UKB sample), 42 (age at menopause; UKB sample). For number of childbirths, 3 SNPs were available for the recurrent depression analysis and 4 proxy SNPs were found. There was no indication of weak instrument bias (estradiol levels (continuous approach; combined pre- and postmenopausal sample from the UKB):  $F = 22.1$ ; estradiol levels (continuous approach; postmenopausal LIFE samples):  $F = 22.4$ ; estradiol levels (continuous approach; premenopausal sample from the UKB):  $F = 22.3$ ; estradiol levels (continuous approach; postmenopausal sample from the UKB):  $F = 22.5$ ; reproductive span:  $F = 89.6$ ; age at menarche (UKB sample):  $F = 70.4$ ; age at menopause (UKB sample):  $F = 82.3$ ), apart from number of childbirths as an exposure ( $F = 0.70$ ).
- f. Depression Subsample Excluding UKB.** The following number of instrumental variables were used for each respective exposure variable: 5 (estradiol levels continuous approach; combined pre- and postmenopausal sample from the UKB), 7 (estradiol levels continuous approach; premenopausal

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sample from the UKB), 7 (estradiol levels continuous approach; postmenopausal sample from the UKB), and 45 (reproductive span). For number of childbirths, 3 SNPs were available, and 4 proxy SNPs were found. For the sensitivity analyses, the following number of instrumental variables were used for each respective exposure variable: 5 (estradiol levels binary approach; combined pre- and postmenopausal sample from the UKB), 8 (estradiol levels binary approach; premenopausal sample from the UKB), 5 (estradiol levels binary approach; postmenopausal sample from the UKB), 12 (oral contraceptive use), 7 (HRT use), 13 (history of hysterectomy), and 5 (history of oophorectomy). There was no indication of weak instrument bias (estradiol levels (continuous approach; combined pre- and postmenopausal sample from the UKB):  $F = 22.1$ ; estradiol levels (continuous approach; premenopausal sample from the UKB):  $F = 22.3$ ; estradiol levels (continuous approach; postmenopausal sample from the UKB):  $F = 22.4$ ; reproductive span:  $F = 92.0$ ; estradiol levels (binary approach; combined pre- and postmenopausal sample from the UKB):  $F = 65.0$ ; estradiol levels (binary approach; premenopausal sample from the UKB):  $F = 32.8$ ; estradiol levels (binary approach; postmenopausal sample from the UKB):  $F = 51.7$ ); oral contraceptive use:  $F = 22.4$ ; HRT use:  $F = 47.6$ ; history of hysterectomy:  $F = 24.7$ ; history of oophorectomy:  $F = 47.0$ ), apart from number of childbirths as an exposure ( $F = 0.80$ ).

- g. Oral Contraceptive Use.** No significant SNPs were found at the  $p < 5 \times 10^{-8}$  threshold for oral contraceptive use, and 2 significant SNPs were found at the threshold of  $p < 5 \times 10^{-7}$ . The more liberal threshold of  $p < 5 \times 10^{-6}$  identified 26 SNPs as instrumental variables. 17 SNPs were available for brain age gap and 19 SNPs were available for depression and Alzheimer's disease as outcomes. There was no indication of weak instrument bias (brain age gap:  $F = 22.6$ ; depression and Alzheimer's disease:  $F = 22.5$ ).
- h. HRT Use.** For HRT use, 6 significant SNPs were identified at the  $p < 5 \times 10^{-8}$  threshold, of which 4 were available after harmonization. Thus, the more liberal threshold of  $p < 5 \times 10^{-7}$  was used, identifying 17 instrumental variables. 14 SNPs were available for brain age gap and depression, and 13 SNPs were available for Alzheimer's disease as outcomes. There was no indication of weak

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instrument bias (brain age gap and depression:  $F = 41.2$ ; Alzheimer's disease:  $F = 41.6$ ).

- i. History of Hysterectomy.** At the  $p < 5 \times 10^{-8}$  threshold, 3 significant SNPs were identified for history of hysterectomy. At the  $p < 5 \times 10^{-7}$  threshold, 5 significant SNPs were identified, of which 1 SNP was removed during harmonization. At the threshold of  $p < 5 \times 10^{-6}$  was applied, identifying 20 significant SNPs. After harmonization, 17 SNPs were available for all outcome variables. There was no indication of weak instrument bias (all  $F = 24.4$ ).
- j. History of Oophorectomy.** For history of oophorectomy, 6 significant SNPs were identified at the  $p < 5 \times 10^{-8}$  threshold. All SNPs were available for brain age gap and depression, and 5 SNPs were available for Alzheimer's disease as outcomes. There was no indication of weak instrument bias (brain age gap and depression:  $F = 44.4$ ; Alzheimer's disease:  $F = 47.0$ ).
- k. Age at Natural Menopause.** For the sensitivity analysis including age at natural menopause (ReproGen sample) as an exposure, of the 42 identified significant SNPs at the  $p < 5 \times 10^{-8}$  threshold, 38 were available after harmonization for Alzheimer's disease as an outcome. There was no indication of weak instrument bias (Alzheimer's disease:  $F = 77.6$ ).
- l. Multivariable Analysis: Estradiol Levels and BMI.** For the multivariable analyses including estradiol levels and BMI as exposures, a total of 38 and 41 SNPs were significant, respectively, for the continuous and binary estradiol levels measured in the combined pre- and postmenopausal sample. For both continuous and binary estradiol levels with BMI as exposures, all instrumental variables were available in the brain age gap and Alzheimer's disease datasets. 36 and 39 SNPs were available for depression as an outcome, for the continuous and binary estradiol levels, respectively. The instrumental variables did not exhibit weak instrument bias for BMI (estradiol levels (continuous approach; combined pre- and postmenopausal sample from the UKB) and BMI with brain age gap and Alzheimer's disease: conditional  $F = 27.97$ ; depression: 32.10; estradiol levels (binary approach; combined pre- and postmenopausal sample from the UKB) and BMI with brain age gap and Alzheimer's disease: conditional  $F = 56.66$ ; depression: conditional  $F = 57.88$ ), however, for estradiol levels the instrumental variables did indicate possible weak instrument bias (estradiol levels (continuous approach; combined pre- and postmenopausal

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sample from the UKB) and BMI with brain age gap and Alzheimer's disease: conditional  $F = 1.92$ ; depression: 1.93; estradiol levels (binary approach; combined pre- and postmenopausal sample from the UKB) and BMI with brain age gap and Alzheimer's disease: conditional  $F = 8.87$ ; depression: conditional  $F = 9.16$ ). For the sensitivity analyses using the depression subsample excluding UKB, 36 and 39 SNPs were available for the continuous (estradiol levels:  $F = 0.99$ ; BMI:  $F = 13.01$ ) and binary (estradiol levels:  $F = 8.49$ ; BMI:  $F = 58.37$ ) estradiol levels measured in the combined pre- and postmenopausal sample.

**m. Multivariable Follow-up Analysis: Age at Menarche and BMI.** For the multivariable analysis including age at menarche (ReproGen sample) and BMI as exposures, a total of 84 SNPs were identified as instrumental variables. After harmonization, 80 SNPs were available in the depression dataset. The instrumental variables did not exhibit weak instrument bias (age at menarche:  $F = 29.62$ ; BMI:  $F = 20.62$ ). For the sensitivity analyses using recurrent depression as an outcome, a total of 197 SNPs were identified as instrumental variables for age at menarche (UKB sample) and BMI as exposures. 157 SNPs were available for recurrent depression as an outcome, of which 6 SNPs were removed during harmonization. The instrumental variables did not exhibit weak instrument bias for age at menarche or BMI (age at menarche: conditional  $F = 25.94$ ; BMI: conditional  $F = 9.97$ ).

### Note 4. Results for GWAS of Brain Age Gap in Males.

The GWAS of brain age gap in males identified no genome-wide significant SNPs (see Supplementary Figures 2 and 7). As for the female sample, the most significant SNP in the male sample was located on chromosome 17 (*rs199502*;  $p = 7.11 \times 10^{-8}$ ).

### Note 5. Results for Male-Only Depression GWAS Meta-Analysis.

The male-only depression GWAS meta-analysis identified no genome-wide significant SNPs (see Supplementary Figures 3 and 8). The most significant SNP was located on chromosome 11 (*rs145678014*;  $p = 0.81 \times 10^{-8}$ ).

### Note 6. Results for GWAS of Estradiol Levels (Binary Approach).

For the GWAS of estradiol levels using the binary approach in a combined sample of pre- and postmenopausal females, we identified nine independent genomic loci, on

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chromosomes 4, 5, 7, 8, 12, 16, 19, and 20, that were significantly associated with estradiol levels (see Supplementary Figure 1 for Manhattan plot and Supplementary Figure 6 for QQ-plot). The loci included 9 lead SNPs and 21 independent SNPs and mapped onto 73 genes (Supplementary Table 6 and Supplementary Figure 11). A subset of genes expressed lower, on average, across tissue types, compared to the other genes, yet with a cluster (*BRSK1*, *CHGB*, and *UNC5A*) expressing higher across brain tissue (Supplementary Figure 14). The gene-set enrichment analysis identified 7 positional gene sets and 13 associated phenotypes (Supplementary Figure 17).

Previous studies have been conducted on estradiol levels using a binary approach in females in the UKB and have reported partly overlapping significant loci with the present study (on chromosomes 4, 5, 7, 8, 12, 19, and 20)<sup>12,13</sup>. Additionally, the present study identified two significant loci (on chromosome 16 and a further locus on chromosome 12) that were not reported by previous studies using the same approach<sup>12,13</sup>. These loci have been previously associated with age at menopause<sup>14,15</sup>.

### Note 7. Results of Supplemental Analyses Using Factors Related to Exogenous Hormone Use and Health-Related Procedures as Exposure Variables.

No significant associations were found between the exposures HRT use, oral contraceptive use, history of hysterectomy, and history of oophorectomy and the outcomes brain age gap, Alzheimer's disease, and depression (Supplementary Table 5). All results remained robust across the estimation methods (Supplementary Table 7).

### Note 8. Deviations from Preregistration.

The present study was [preregistered](#). However, the scope of the study slightly shifted as we decided to include univariable analyses with the factors related to lifetime estradiol exposure. This decision was made in an attempt to capture the effects of estradiol more comprehensively on brain health and mental health, as the estradiol measurements used from the UKB are measured in an advanced age group at a single timepoint. Furthermore, the sensitivity analyses were adjusted according to the added analyses and available datasets.

After suggestions made by the reviewers, we added sensitivity analyses for estradiol levels by using the male-only samples and the premenopausal-only and postmenopausal-only samples. To this end, we ran a male-only GWAS on brain age gap and the male-only GWAS meta-analysis on depression. Further, we included MRlap as an additional estimation method for analyses with sample overlap.

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### Supplementary Figures

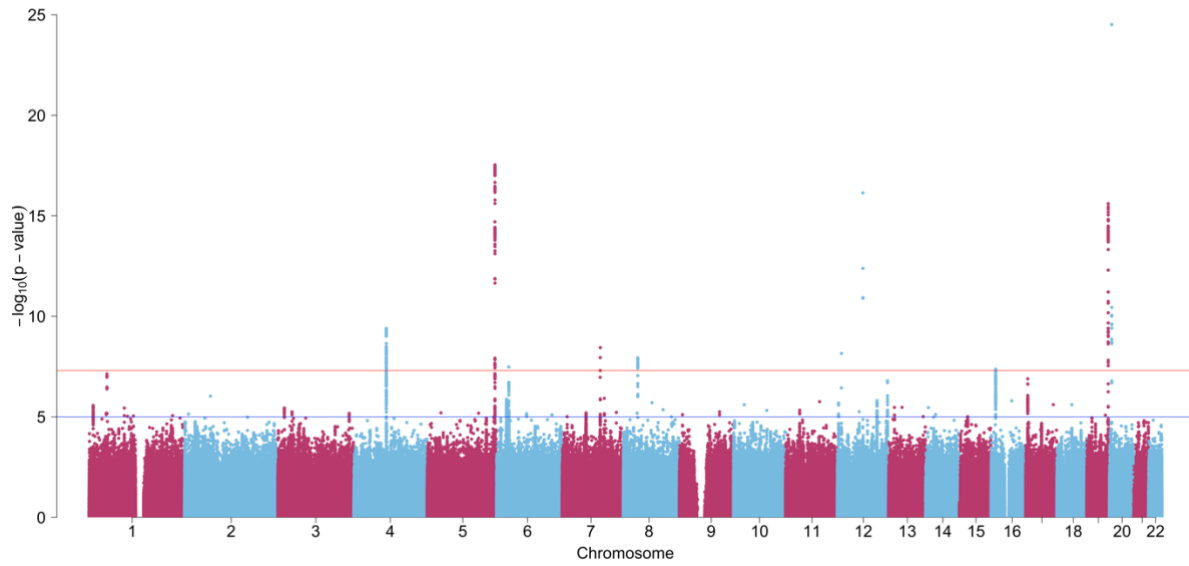


Figure 1. **Manhattan Plot of Estradiol Levels (Binary Approach).** The blue/lower and red/upper lines indicate the suggestive and the genome-wide significance thresholds, respectively. Plotted using the *qqman* package (v0.1.9)<sup>16</sup>.

## Supplementary Information

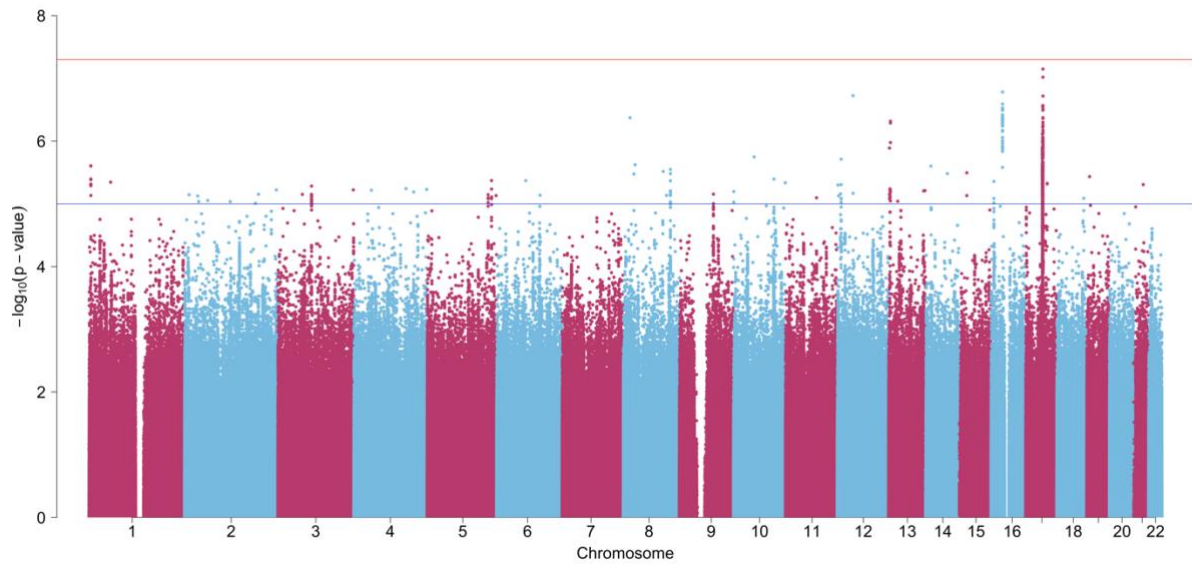


Figure 2. **Manhattan Plot of Brain Age Gap in Males.** The blue/lower and red/upper lines indicate the suggestive and the genome-wide significance thresholds, respectively. Plotted using the *qqman* package (v0.1.9)<sup>16</sup>.

## Supplementary Information

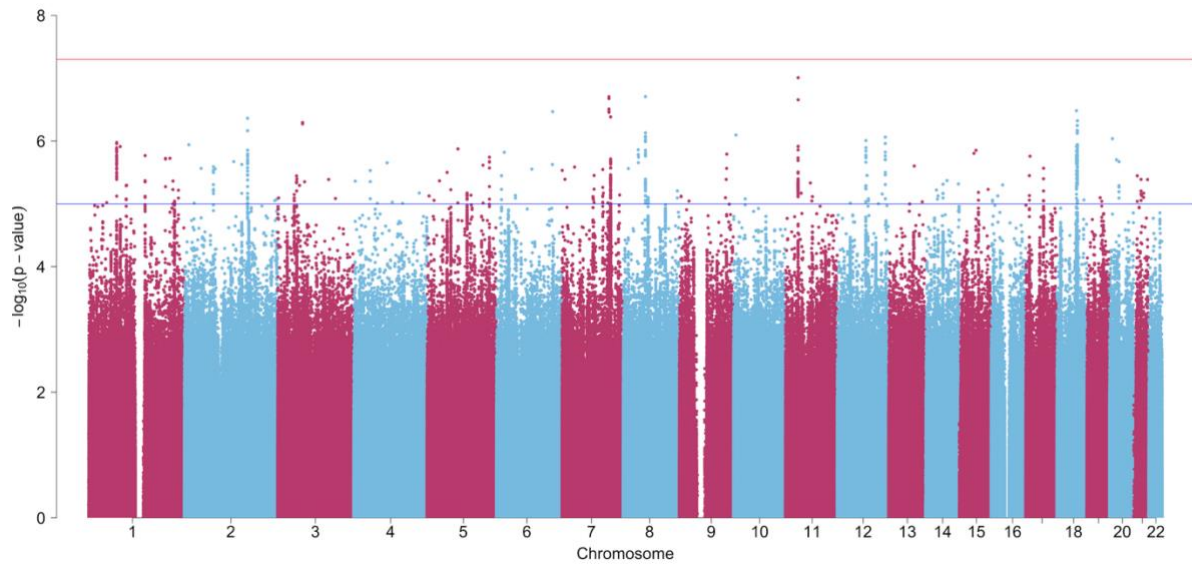


Figure 3. **Manhattan Plot of Male-Only Depression GWAS Meta-Analysis.** The blue/lower and red/upper lines indicate the suggestive and the genome-wide significance thresholds, respectively. Plotted using the *qqman* package (v0.1.9)<sup>16</sup>.



## Supplementary Information

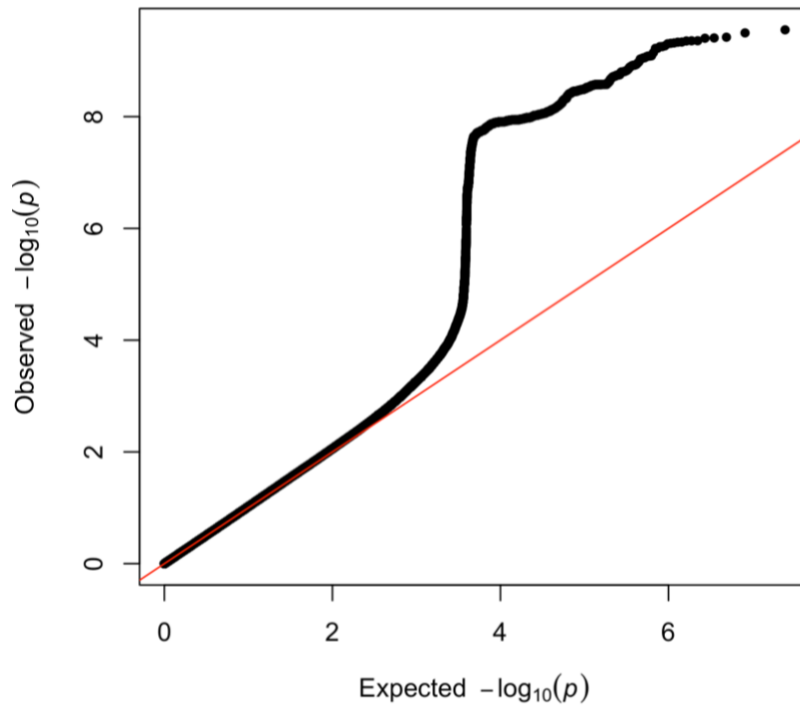


Figure 4. **QQ-Plot for Brain Age Gap in Females.** Plotted using the *qqman* package (v0.1.9)<sup>16</sup>.

## Supplementary Information

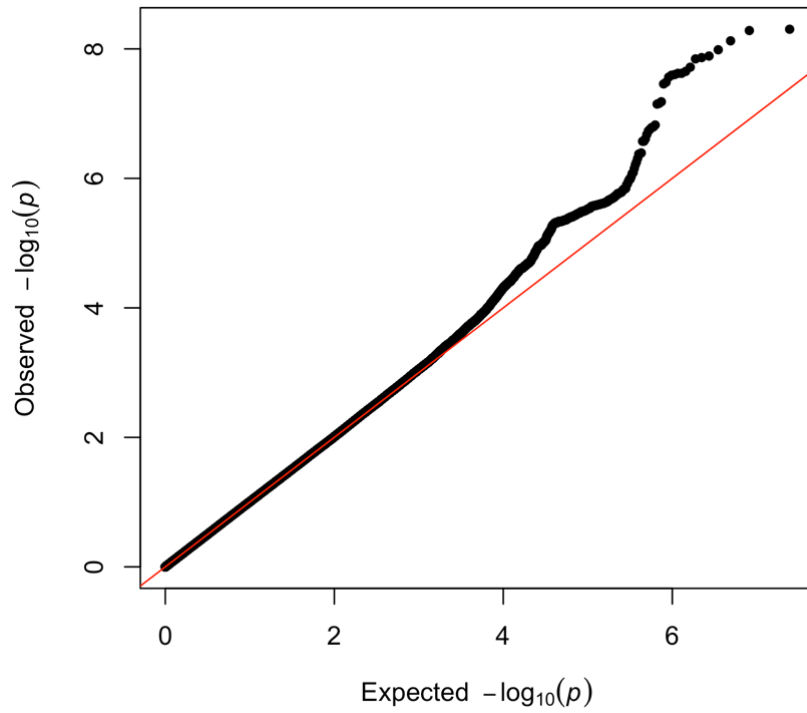


Figure 5. **QQ-Plot for Estradiol Levels (Continuous Approach).** Plotted using the *qqman* package (v0.1.9)<sup>16</sup>.

## Supplementary Information

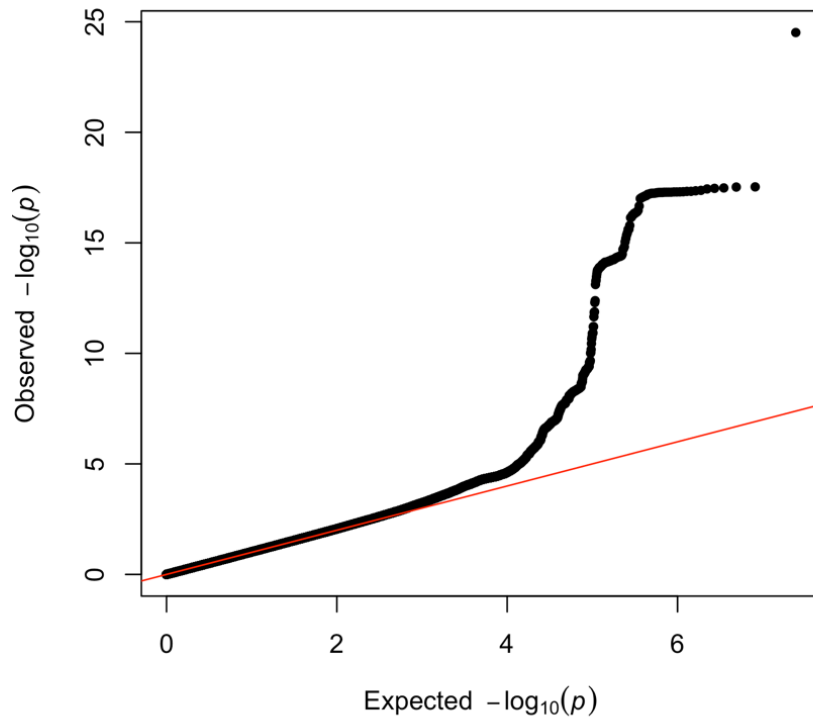


Figure 6. **QQ-Plot for Estradiol Levels (Binary Approach).** Plotted using the *qqman* package (v0.1.9)<sup>16</sup>.

## Supplementary Information

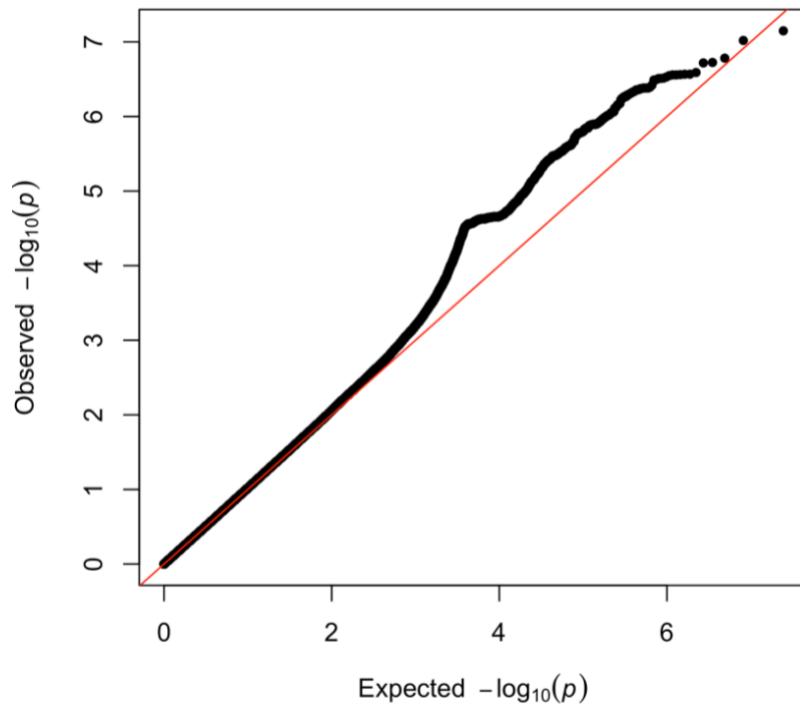


Figure 7. **QQ-Plot for Brain Age Gap in Males.** Plotted using the *qqman* package (v0.1.9)<sup>16</sup>.

## Supplementary Information

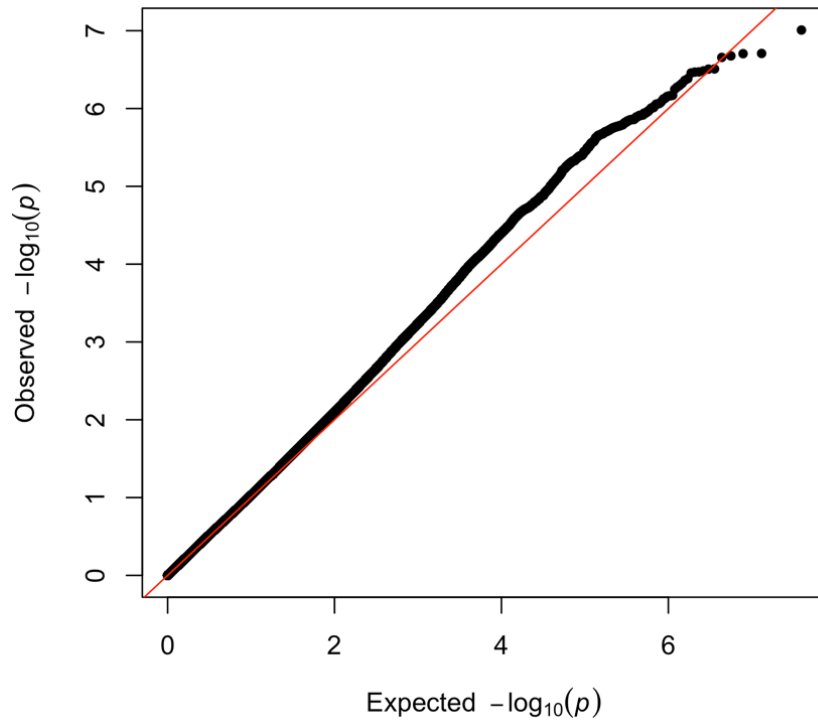


Figure 8. **QQ-Plot for Male-Only Depression GWAS Meta-Analysis.** Plotted using the *qqman* package (v0.1.9)<sup>16</sup>.

## Supplementary Information

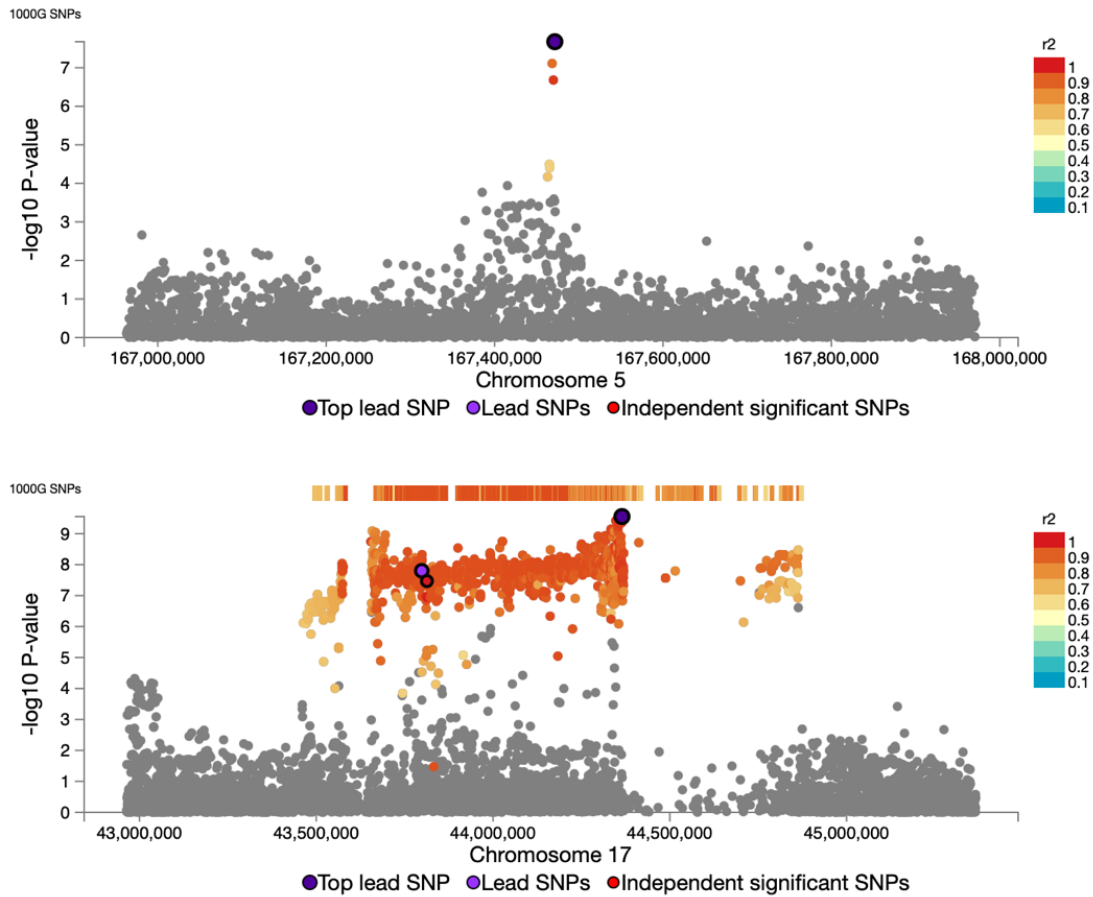


Figure 9. **Regional Plots of Genomic Loci identified in Brain Age Gap in Females.** Plot produced using FUMA, showing top lead SNP, lead SNPs, and independent significant SNPs in each of the identified genomic loci<sup>17</sup>. SNPs are color-coded according to their  $R^2$  values.

## Supplementary Information

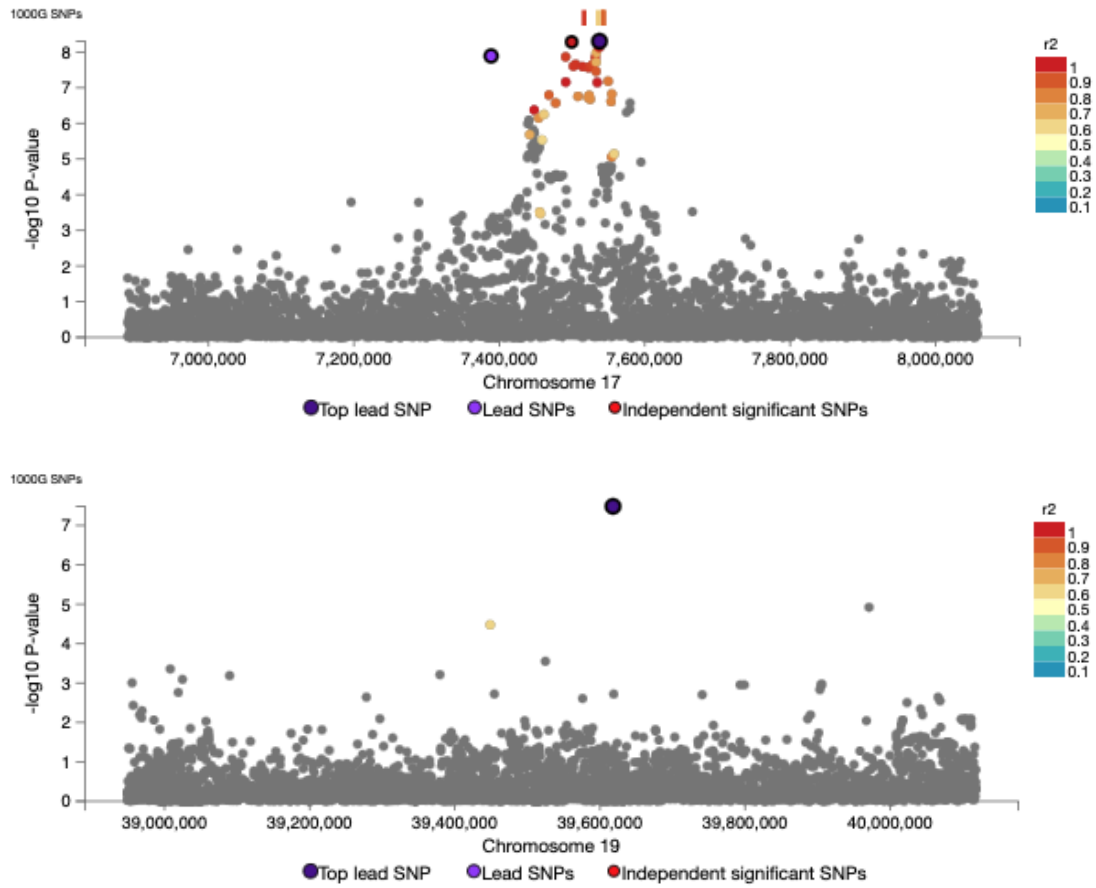


Figure 10. **Regional Plots of Genomic Loci identified in Estradiol Levels (Continuous Approach).** Plot produced using FUMA, showing top lead SNP, lead SNPs, and independent significant SNPs in each of the identified genomic loci<sup>17</sup>. SNPs are color-coded according to their  $R^2$  values.

## Supplementary Information

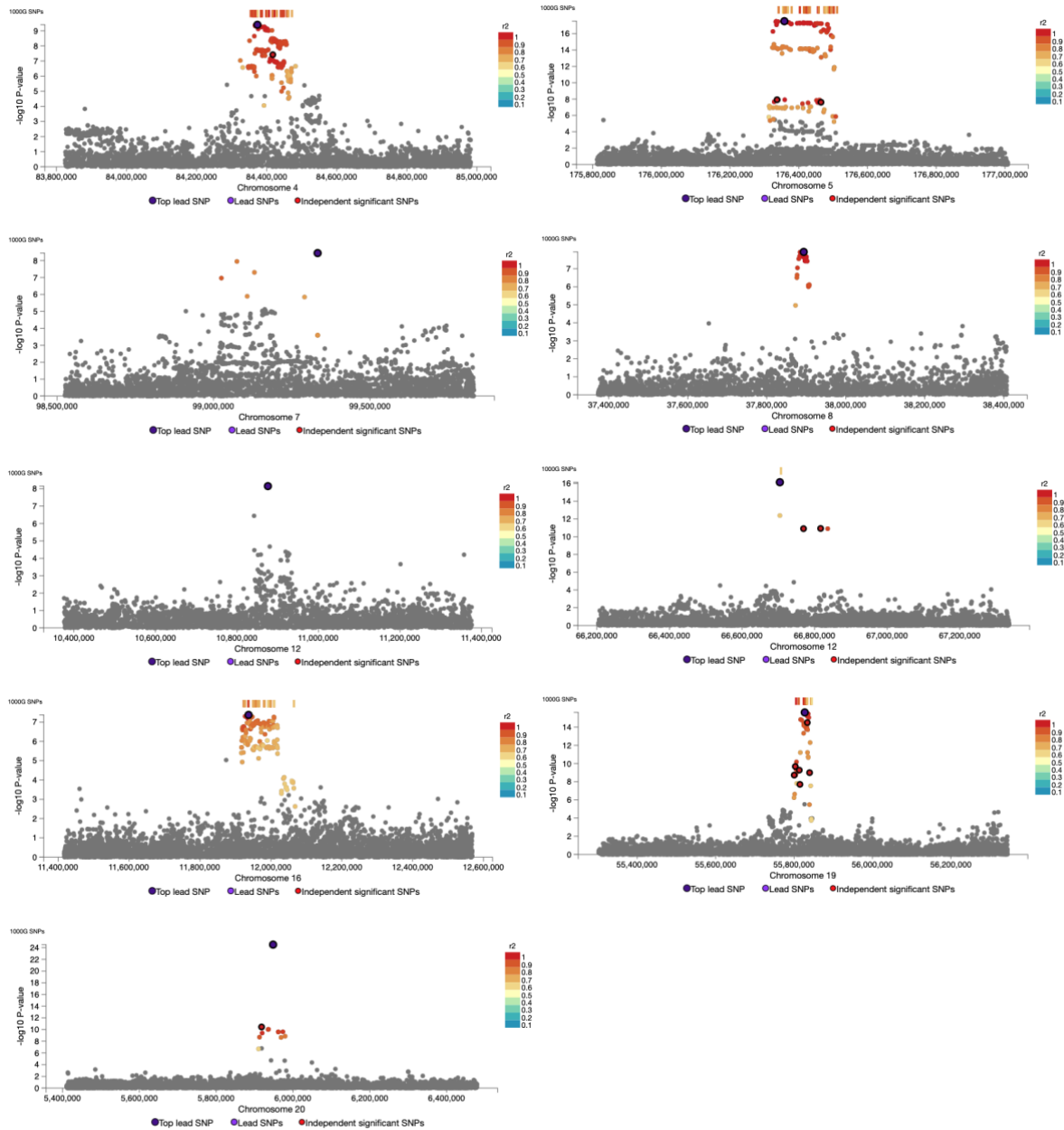


Figure 11. **Regional Plots of Genomic Loci identified in Estradiol Levels (Binary Approach).** Plot produced using FUMA, showing top lead SNP, lead SNPs, and independent significant SNPs in each of the identified genomic loci<sup>17</sup>. SNPs are color-coded according to their  $R^2$  values.



## Supplementary Information

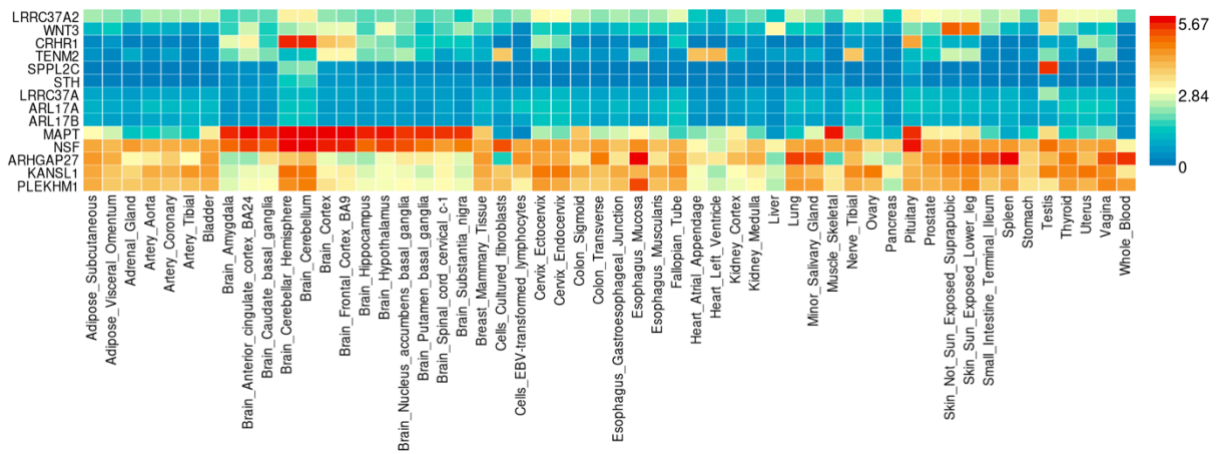


Figure 12. **Gene Expression Heatmap for Brain Age Gap in Females.** Plot produced using FUMA, with the annotated genes ordered by cluster<sup>17</sup>. Colors indicate the expression values as an average per tissue (log2-transformed). GTEx v8 54 tissue types are used<sup>18</sup>.

## Supplementary Information

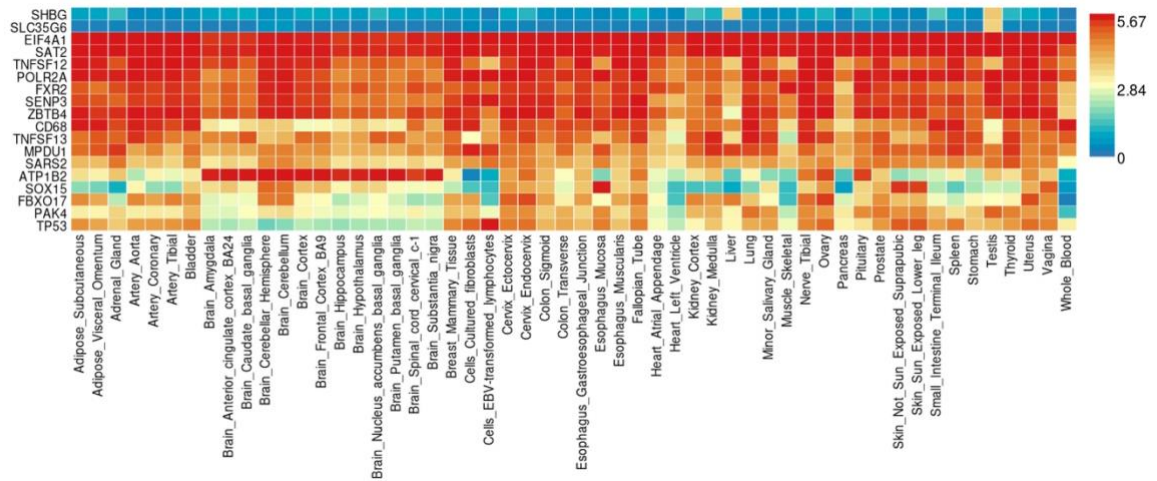


Figure 13. **Gene Expression Heatmap of Estradiol Levels (Continuous Approach).** Plot produced using FUMA, with the annotated genes ordered by cluster<sup>17</sup>. Colors indicate the expression values as an average per tissue (log2-transformed). GTEx v8 54 tissue types are used<sup>18</sup>.

## Supplementary Information

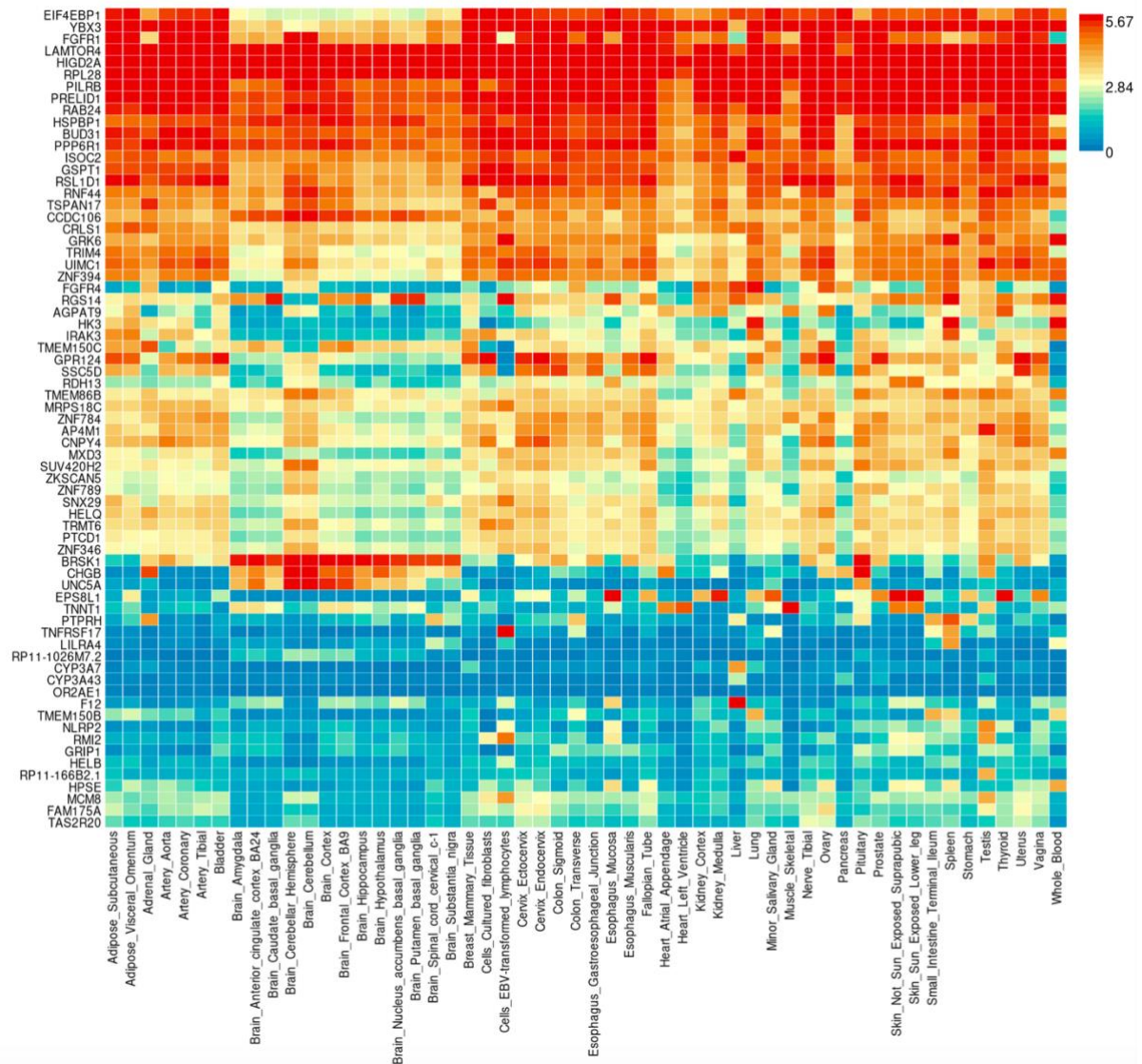
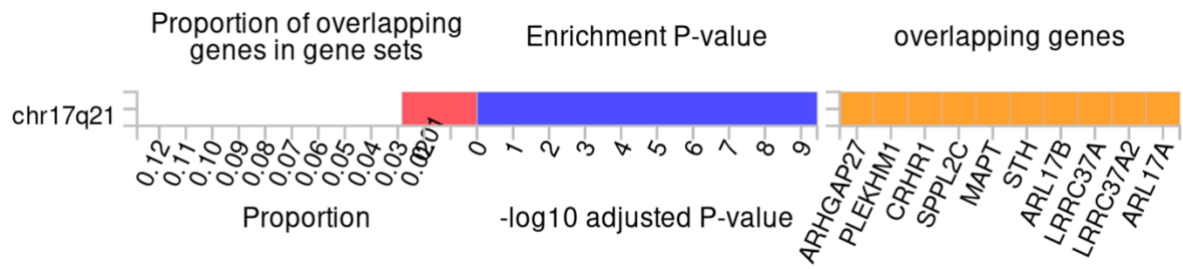


Figure 14. **Gene Expression Heatmap for Estradiol Levels (Binary Approach).** Plot produced using FUMA, with the annotated genes ordered by cluster<sup>17</sup>. Colors indicate the expression values as an average per tissue (log2-transformed). GTEx v8 54 tissue types are used<sup>17</sup>.

## Supplementary Information

### a. Positional Gene Sets



### b. GWAS Catalog Reported Genes

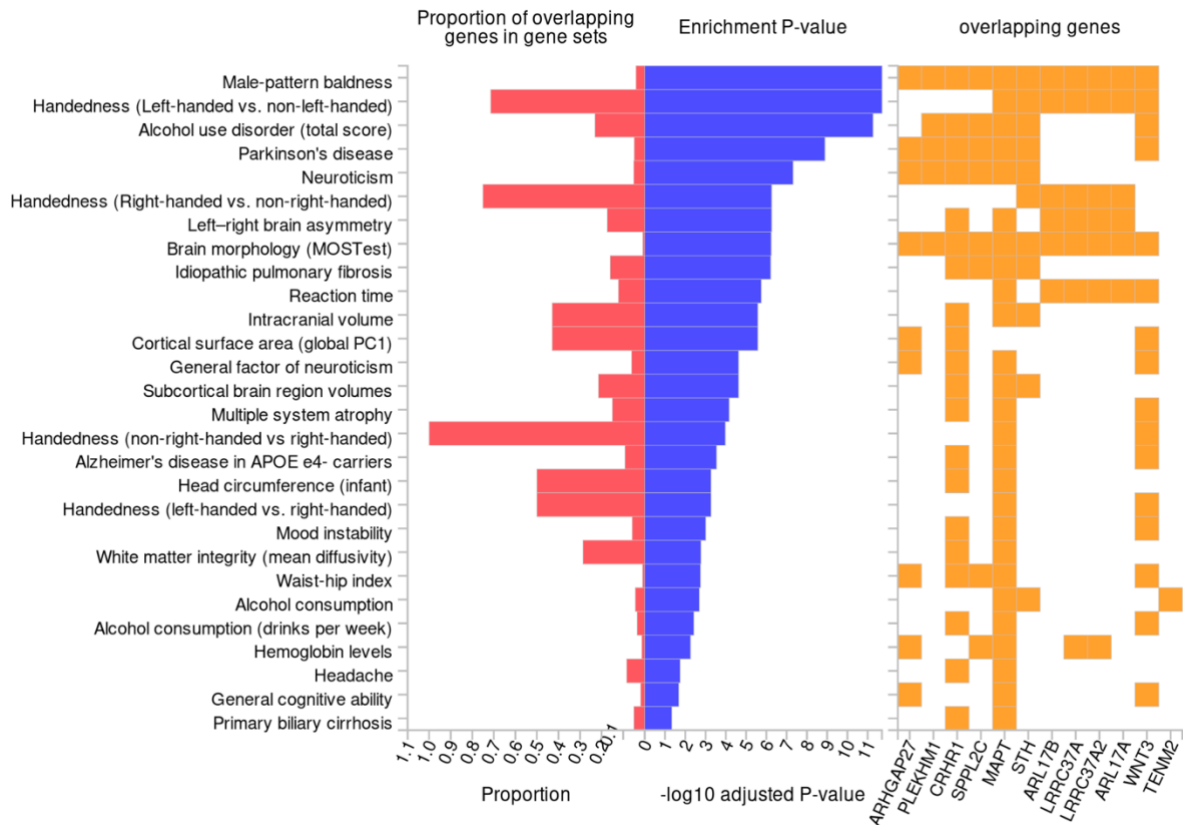
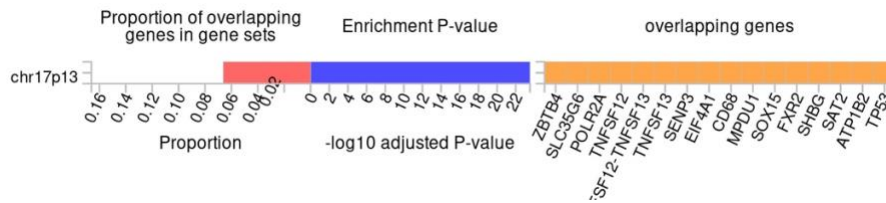


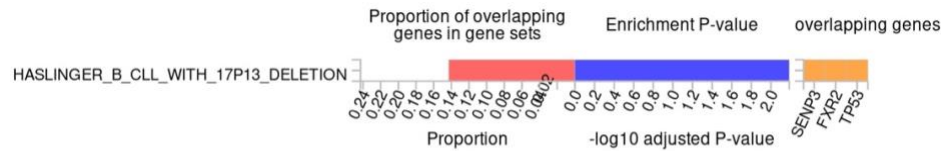
Figure 15. **Gene-Set Enrichment Analysis for Brain Age Gap in Females.** a Gene sets obtained from MsigDB c1. Plots produced using FUMA<sup>17</sup>.

## Supplementary Information

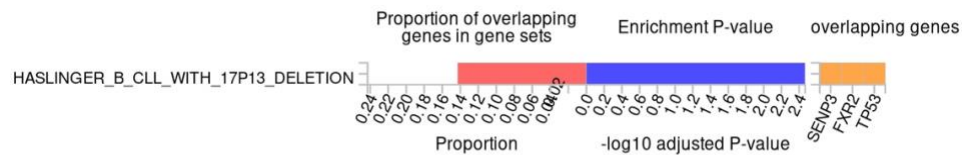
### a. Positional Gene Sets



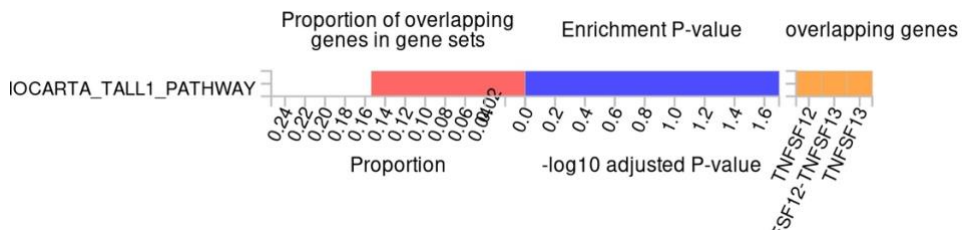
### b. Curated Gene Sets



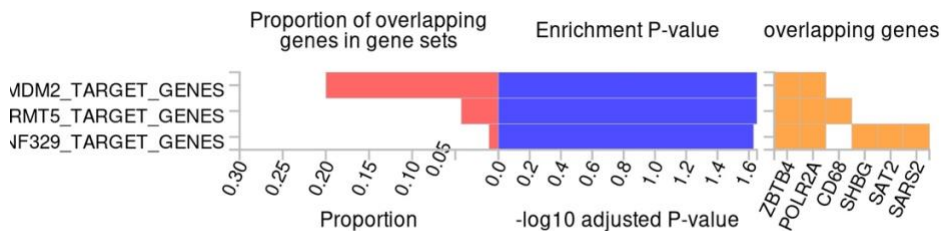
### c. Chemical and Genetic Perturbation Gene Sets



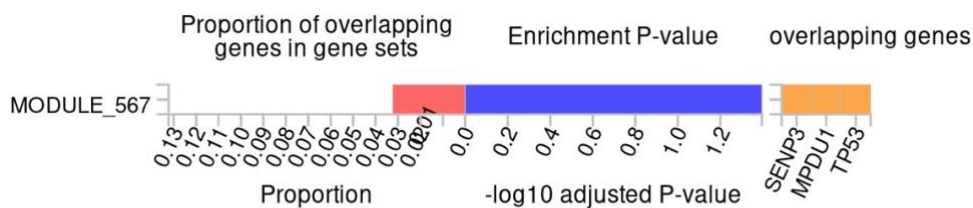
#### d. BioCarta (MsigDB c2)



### e. TF Targets



#### f. Cancer Gene Modules (MsigDB c4)





## Supplementary Information

### g. GWAS Catalog Reported Genes

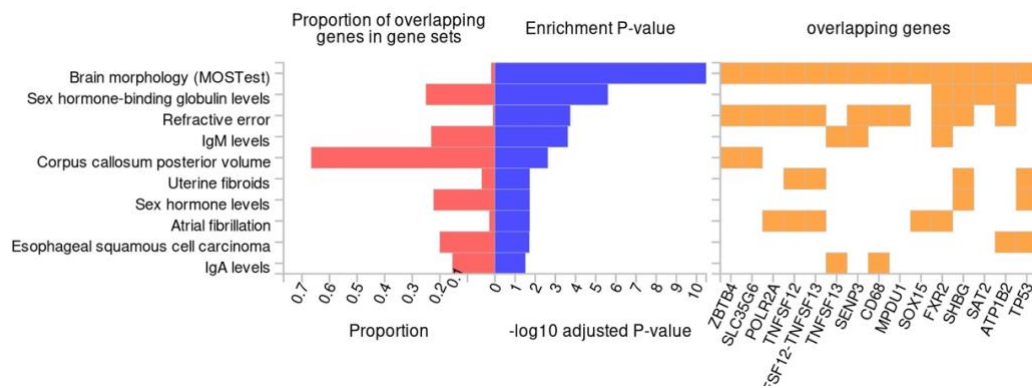
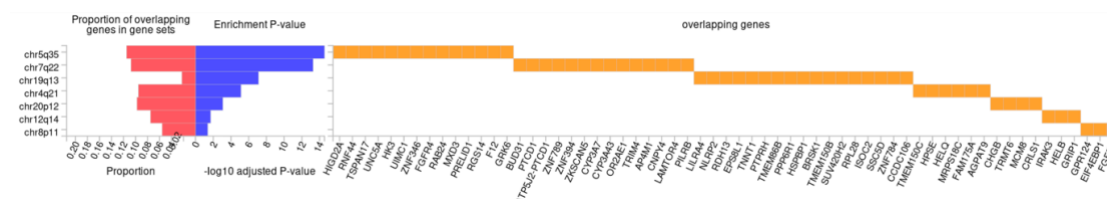


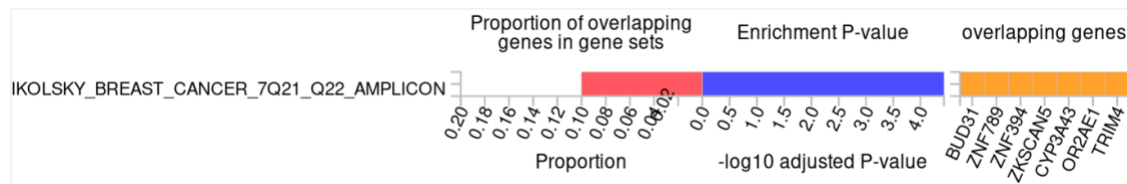
Figure 16. **Gene-Set Enrichment Analysis for Estradiol Levels (Continuous Approach).** **a** Gene sets obtained from MsigDB c1. **c** Gene sets obtained from MsigDB c2. **d** Gene sets obtained from MsigDB c2. **e** Gene sets obtained from MsigDB c3. **f** Gene sets obtained from MsigDB c4. Plots produced using FUMA<sup>17</sup>.

## Supplementary Information

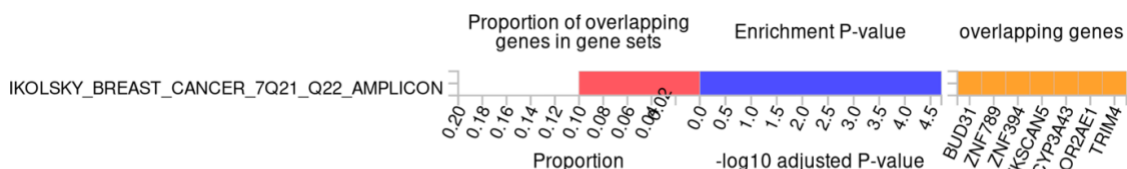
### a. Positional Gene Sets



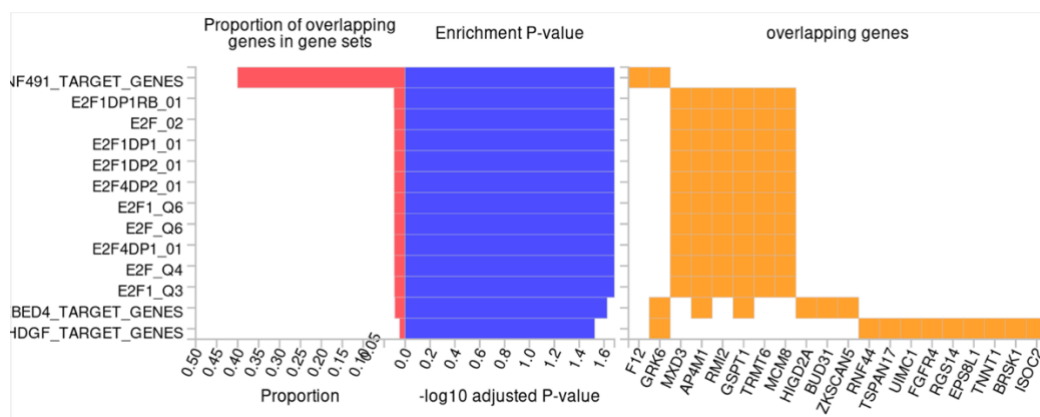
### b. Curated Gene Sets



### c. Chemical and Genetic Perturbation Gene Sets



### d. TF Targets



### e. GWAS Catalog Reported Genes

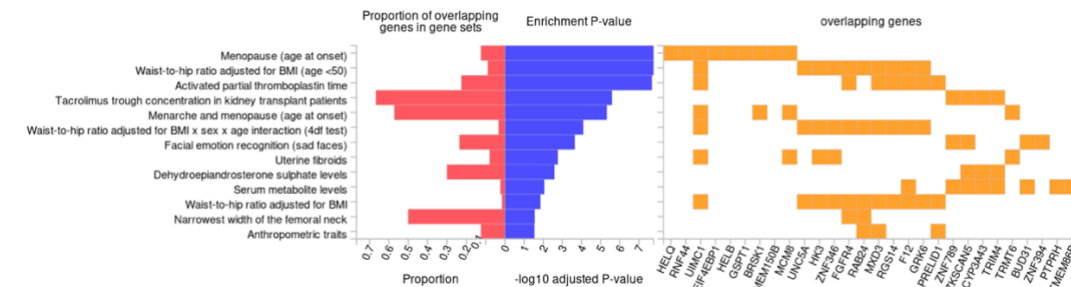


Figure 17. **Gene-Set Enrichment Analysis for Estradiol Levels (Binary Approach).** **a** Gene sets obtained from MsigDB c1. **c** Gene sets obtained from MsigDB c2. **d** Gene sets obtained from MsigDB c3. Plots produced using FUMA<sup>17</sup>.

## Supplementary Information

### Supplementary Tables

Table 1. **Included Datasets and Samples for Sensitivity and Supplementary Analyses.**

Variable	GWAS	Sample Description	Data Source	Definition of Phenotype
Estradiol Levels (binary approach; combined pre- and postmenopausal sample)	Newly conducted	$N = 207,119$ (42,084 above and 165,035 below detection limit)	UKB	Estradiol levels above or below detection limit of 175 pmol/L
Estradiol Levels (binary approach; premenopausal sample)	Haas et al. (2022) <sup>12</sup> – received upon request	$N = 51,081$	UKB	Estradiol levels above or below detection limit
Estradiol Levels (binary approach; postmenopausal sample)	Haas et al. (2022) <sup>12</sup> – received upon request	$N = 84,194$	UKB	Estradiol levels above or below detection limit
Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> – received upon request	$N = 41,937$ (22,214 cases and 19,723 controls)	PGC & iPSYCH	DSM-IV or ICD-10 diagnosis of depression
Recurrent Depression	Blokland et al. (2022) <sup>5</sup> – received upon request	$N = 24,088$ (9,859 cases and 14,229 controls)	PGC & iPSYCH	DSM-IV or ICD-10 diagnosis of recurrent depression
HRT Use	Elsworth et al. (2018) <sup>19</sup> – publicly available	$N = 250,301$ (97,920 users and 152,381 non-users)	UKB	Ever used hormone replacement therapy
Oral Contraceptive Use	Elsworth et al. (2018) <sup>19</sup> – publicly available	$N = 250,440$ (205,516 users and 44,924 non-users)	UKB	Ever used oral contraceptive pill
History of Hysterectomy	Elsworth et al. (2018) <sup>19</sup> – publicly available	$N = 221,697$ (18,171 cases and 203,526 controls)	UKB	Hysterectomy (womb removed)
History of Oophorectomy	Elsworth et al. (2018) <sup>19</sup> – publicly available	$N = 247,538$ (20,120 cases and 227,418 controls)	UKB	Bilateral oophorectomy (both ovaries removed)
BMI	Locke et al. (2015) <sup>20</sup> – publicly available	$N = 171,977$	GIANT Consortium	Body mass index (self-reported or measured weight in kg / height in meters <sup>2</sup> )



## Supplementary Information

Estradiol Levels (male sample)	Neale Lab <sup>21</sup> – publicly available	$N = 13,501$ males	UKB	Estradiol levels above detection limit
Brain Age Gap (male sample)	Newly conducted	$N = 13,423$ males	UKB	Difference between predicted brain age and chronological age
Alzheimer's Disease (male sample)	Wang et al. (2021) <sup>22</sup> – received upon request	$N = 8,682$ males (4,010 cases & 4,672 controls)	ADGC phase 1 & 2	Diagnosis of Alzheimer's disease
Depression (male sample)	Newly conducted (see Supplementary Notes 1 and 2 for details) – GWAS meta-analysis including data from the UKB <sup>2</sup> , MoBa <sup>3</sup> , and summary statistics received from Blokland et al. (2022) <sup>5</sup> upon request	$N = 262,747$ males (22,077 cases & 240,670 controls)	UKB, MoBa, & PGC & iPSYCH	DSM-IV or ICD-10 (F32 or F33) diagnosis of major depressive disorder
Depression (male subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> – received upon request	$N = 28,993$ (10,194 cases and 18,799 controls)	PGC & iPSYCH	DSM-IV or ICD-10 diagnosis of depression

*Note.* All GWAS were conducted in White European female samples, except for estradiol levels (male sample), brain age gap (male sample), Alzheimer's disease (male sample), and depression (male sample), which were conducted in White European male samples. See Table 2 in main manuscript for datasets used in main analyses. HRT: Hormone replacement therapy. UKB: UK Biobank. ADGC: Alzheimer's Disease Genetics Consortium. GIANT: Genetic Investigation of Anthropometric Traits Consortium. MoBa: The Norwegian Mother and Child Cohort Study. PGC: Psychiatric Genomics Consortium.

## Supplementary Information

Table 2. **Maximum Sample Overlap.**

Exposure Variable	Outcome Variable	Maximum Sample Overlap (%)
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample)	Depression	10.53%
Estradiol Levels (continuous approach; premenopausal sample from the UKB)	Brain Age Gap	43.25%
	Depression	10.03%
Estradiol Levels (continuous approach; postmenopausal sample from the UKB)	Brain Age Gap	26.31%
	Depression	1.14%
Estradiol Levels (binary approach; combined pre- and postmenopausal sample)	Depression	62.86%
Estradiol Levels (binary approach; premenopausal sample from the UKB)	Brain Age Gap	27.97%
	Depression	15.50%
Estradiol Levels (binary approach; postmenopausal sample from the UKB)	Brain Age Gap	16.97%
	Depression	25.55%
Reproductive Span	Depression	36.91%
Number of Childbirths	Brain Age Gap	5.70%
	Depression	82.19%
HRT Use	Brain Age Gap	5.71%
	Depression	75.97%
Oral Contraceptive Use	Brain Age Gap	5.70%
	Depression	76.01%
History of Hysterectomy	Brain Age Gap	6.44%
	Depression	67.29%
History of Oophorectomy	Brain Age Gap	5.77%
	Depression	75.13%
Estradiol Levels (male sample)	Brain Age Gap (male sample)	99.42%
	Depression (male sample)	4.80%

*Note.* All GWAS with sample overlap used data from the UK Biobank (UKB). All other analyses did not have sample overlap. HRT: Hormone replacement therapy.

## Supplementary Information

Table 3. **Brain Age Prediction Model Performance Metrics.**

Sex	RMSE		MAE		R <sup>2</sup>		Correlation for predicted and true age		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>r</i>	<i>p</i>	CI
Females	-4.38	0.08	-3.47	0.06	0.63	0.01	.80	.00	.80 - .81
Males	-4.44	0.06	-3.54	0.07	0.66	0.02	.82	.00	.81 - .82

*Note.* Validation metrics for multimodal model including both white matter and grey matter features. T1-weighted features included cortical thickness, volume area, and summary statistics. Diffusion-weighted features included diffusion tensor imaging<sup>23</sup>, spherical mean technique<sup>24,25</sup>, diffusion kurtosis imaging<sup>26</sup>, white matter tract integrity<sup>27</sup>, and white matter features based on Johns Hopkins University atlases for white matter tracts and labels (with 0 thresholding)<sup>28</sup> for region of interest and mean values. Brain age was computed for each individual using the *XGBoost* ([eXtreme Gradient Boosting](#)) regression model, based on a decision-tree ensemble algorithm<sup>29</sup>. Hyperparameters were tuned using a nested cross-validation with 5 inner folds for randomized search and 10 outer folds for validation of the model (see [general model setup](#)). RMSE: root mean square error; MAE: mean absolute error.

## Supplementary Information

Table 4. **Overview of Instrumental Variables and Instrument Strength.**

Exposure(s)	Outcome	Threshold	<i>n</i> SNPs	(conditional) <i>F</i>
Estradiol levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Brain age gap	$p < 5 \times 10^{-6}$	16	23.0
	Alzheimer's disease	$p < 5 \times 10^{-6}$	15	23.0
	Depression	$p < 5 \times 10^{-6}$	16	23.0
	Depression	$p < 5 \times 10^{-6}$	5	22.1
	(subsample excluding UKB)			
Estradiol levels (continuous approach; postmenopausal LIFE samples)	Recurrent depression	$p < 5 \times 10^{-6}$	5	22.1
	Brain age gap	$p < 5 \times 10^{-6}$	10	23.3
	Alzheimer's disease	$p < 5 \times 10^{-6}$	10	23.3
	Depression	$p < 5 \times 10^{-6}$	10	23.3
	Recurrent depression	$p < 5 \times 10^{-6}$	5	22.4
Estradiol levels (continuous approach; premenopausal sample from the UKB)	Brain age gap	$p < 5 \times 10^{-6}$	13	23.6
	Alzheimer's disease	$p < 5 \times 10^{-6}$	13	23.6
	Depression	$p < 5 \times 10^{-6}$	13	23.6
	Depression	$p < 5 \times 10^{-6}$	7	22.3
	(subsample excluding UKB)			
Estradiol levels (continuous approach; postmenopausal sample from the UKB)	Recurrent depression	$p < 5 \times 10^{-6}$	7	22.4
	Brain age gap	$p < 5 \times 10^{-6}$	12	22.6
	Alzheimer's disease	$p < 5 \times 10^{-6}$	12	22.7
	Depression	$p < 5 \times 10^{-6}$	12	23.6
	Depression	$p < 5 \times 10^{-6}$	7	22.4
Reproductive span	(subsample excluding UKB)			
	Recurrent depression	$p < 5 \times 10^{-6}$	6	22.5
	Brain age gap	$p < 5 \times 10^{-8}$	73	79.7
	Alzheimer's disease	$p < 5 \times 10^{-8}$	68	81.1
	Depression	$p < 5 \times 10^{-8}$	73	79.7
Age at menarche (ReproGen sample)*	Depression	$p < 5 \times 10^{-8}$	45	92.0
	(subsample excluding UKB)			
	Recurrent depression	$p < 5 \times 10^{-8}$	43	89.6
	Brain age gap	$p < 5 \times 10^{-8}$	54	83.7
	Depression	$p < 5 \times 10^{-8}$	54	83.7
Age at menarche (UKB sample)	Alzheimer's disease	$p < 5 \times 10^{-8}$	204	66.5
	Recurrent depression	$p < 5 \times 10^{-8}$	136	70.4
Age at natural menopause (ReproGen sample)*	Brain age gap	$p < 5 \times 10^{-8}$	37	78.8
	Alzheimer's disease	$p < 5 \times 10^{-8}$	38	77.6

## Supplementary Information

Age at menopause (UKB sample)	Depression	$p < 5 \times 10^{-8}$	38	77.6
	Alzheimer's disease	$p < 5 \times 10^{-8}$	68	77.2
	Recurrent depression	$p < 5 \times 10^{-8}$	42	82.3
Number of childbirths	Brain age gap	$p < 5 \times 10^{-8}$	8	39.6
	Alzheimer's disease	$p < 5 \times 10^{-8}$	8	39.6
	Depression	$p < 5 \times 10^{-8}$	8	39.6
	Depression	$p < 5 \times 10^{-8}$	7	0.80
	(subsample excluding UKB)			
Estradiol levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Recurrent depression	$p < 5 \times 10^{-8}$	7	0.70
	Brain age gap	$p < 5 \times 10^{-8}$	10	52.1
	Alzheimer's disease	$p < 5 \times 10^{-8}$	10	52.1
	Depression	$p < 5 \times 10^{-8}$	10	52.1
	Depression	$p < 5 \times 10^{-8}$	5	65.0
Estradiol levels (binary approach; premenopausal sample from the UKB)	(subsample excluding UKB)			
	Brain age gap	$p < 5 \times 10^{-8}$	5	44.9
	Alzheimer's disease	$p < 5 \times 10^{-8}$	5	44.9
	Depression	$p < 5 \times 10^{-8}$	5	36.9
	Depression	$p < 5 \times 10^{-6}$	8	32.8
Estradiol levels (binary approach; postmenopausal sample from the UKB)	(subsample excluding UKB)			
	Brain age gap	$p < 5 \times 10^{-8}$	8	48.3
	Alzheimer's disease	$p < 5 \times 10^{-8}$	7	50.2
	Depression	$p < 5 \times 10^{-8}$	8	48.3
	Depression	$p < 5 \times 10^{-8}$	5	51.7
Estradiol levels (male sample)	(subsample excluding UKB)			
	Brain age gap (male sample)	$p < 5 \times 10^{-8}$	44	37.1
	Alzheimer's disease (male sample)	$p < 5 \times 10^{-8}$	42	37.4
	Depression (male sample)	$p < 5 \times 10^{-8}$	45	37.3
	Depression (male subsample excluding UKB)	$p < 5 \times 10^{-8}$	6	37.5
Oral contraceptive use	Brain age gap	$p < 5 \times 10^{-6}$	17	22.6
	Alzheimer's disease	$p < 5 \times 10^{-6}$	19	22.5
	Depression	$p < 5 \times 10^{-6}$	19	22.5

## Supplementary Information

HRT use	Depression (subsample excluding UKB)	$p < 5 \times 10^{-6}$	12	22.4
	Brain age gap	$p < 5 \times 10^{-7}$	14	41.2
	Alzheimer's disease	$p < 5 \times 10^{-7}$	13	41.6
	Depression	$p < 5 \times 10^{-7}$	14	41.2
	Depression (subsample excluding UKB)	$p < 5 \times 10^{-7}$	7	47.6
History of hysterectomy	Brain age gap	$p < 5 \times 10^{-6}$	17	24.4
	Alzheimer's disease	$p < 5 \times 10^{-6}$	17	24.4
	Depression	$p < 5 \times 10^{-6}$	17	24.4
	Depression (subsample excluding UKB)	$p < 5 \times 10^{-6}$	13	24.7
History of oophorectomy	Brain age gap	$p < 5 \times 10^{-8}$	6	44.4
	Alzheimer's disease	$p < 5 \times 10^{-8}$	5	47.0
	Depression	$p < 5 \times 10^{-8}$	6	44.4
	Depression (subsample excluding UKB)	$p < 5 \times 10^{-8}$	5	47.0
<i>Multivariable analysis:</i> Estradiol levels (continuous approach; combined pre- and postmenopausal sample from the UKB) & BMI	Brain age gap	$p < 5 \times 10^{-6}$ (estradiol) & $p < 5 \times 10^{-8}$ (BMI)	38	1.92 (estradiol) 27.97 (BMI)
	Alzheimer's disease	$p < 5 \times 10^{-6}$ (estradiol levels) & $p < 5 \times 10^{-8}$ (BMI)	38	1.92 (estradiol) 27.97 (BMI)
	Depression	$p < 5 \times 10^{-6}$ (estradiol levels) & $p < 5 \times 10^{-8}$ (BMI)	36	1.93 (estradiol) 32.10 (BMI)
	Depression (subsample excluding UKB)	$p < 5 \times 10^{-6}$ (estradiol levels) & $p < 5 \times 10^{-8}$ (BMI)	36	0.99 (estradiol) 13.01 (BMI)
<i>Multivariable analysis:</i>	Brain age gap	$p < 5 \times 10^{-8}$	41	8.87 (estradiol) 56.66 (BMI)
	Alzheimer's disease	$p < 5 \times 10^{-8}$	41	8.87 (estradiol)

## Supplementary Information

Estradiol levels (binary approach; combined pre- and postmenopausal sample from the UKB) & BMI	Depression	$p < 5 \times 10^{-8}$	39	56.66 (BMI) 9.16 (estradiol) 57.88 (BMI)
	Depression (subsample excluding UKB)	$p < 5 \times 10^{-8}$	39	8.49 (estradiol) 58.37 (BMI)
<i>Multivariable analysis:</i> Age at menarche (ReproGen sample) & BMI	Depression	$p < 5 \times 10^{-8}$	80	29.62 (age at menarche) 20.62 (BMI)
<i>Multivariable analysis:</i> Age at menarche (UKB sample) & BMI	Recurrent depression	$p < 5 \times 10^{-8}$	151	25.94 (age at menarche) 10.47 (BMI)

*Note.* First-stage  $F$ -statistics were calculated for all instrumental variables as a measure of instrument strength. For multivariable analyses, conditional  $F$ -statistics are reported. Single-nucleotide polymorphisms (SNPs) selected as instrumental variables were associated with the exposure variables using the respective  $p$ -value threshold as a cut-off (see Supplemental Note 3 for details). The genome-wide significance threshold ( $p < 5 \times 10^{-8}$ ; i.e., accounting for multiple comparisons) was used unless this resulted in few instrumental variables (see Supplementary Note 3). \*To avoid sample overlap, different datasets with smaller sample sizes were used in the analyses with brain age gap and depression as outcomes.  $n$  SNPs: Number of instrumental variables included in each respective analysis. UKB: UK Biobank. BMI: Body mass index. HRT: Hormone replacement therapy.

## Supplementary Information

Table 5. Genomic Loci Identified for Brain Age Gap in Females.

Locus	SNPs	A1	A2	B	SE	<i>p</i>	Identified Genes
CHR5:167462967-167471513	<b>Lead:</b> rs17069705	G	T	0.27	0.05	2.11 x 10 <sup>-8</sup>	TENM2
CHR17:43463493-44865603	<b>Lead:</b> rs55938136  rs2696497 <b>Independent:</b> rs12938476	G  T  C	A  C  T	0.27  0.32  0.23	0.05  0.05  0.04	1.58 x 10 <sup>-8</sup>  2.80 x 10 <sup>-10</sup>  3.39 x 10 <sup>-8</sup>	MAPT, NSF, WNT3, KANSL1, CRHR1, ARHGAP27, LRRC37A, SPPL2C, ARL17A, PLEKHM1, ARL17B, LRRC37A2, STH

*Note.* The genome-wide association study was run using the standard additive model of linear associations. Genomic loci identified using FUMA<sup>17</sup>. Genes are sorted to closest loci. Lead SNPs are also independent SNPs. SNPs identified using the genome-wide significance threshold ( $p < 5 \times 10^{-8}$ ; i.e., accounting for multiple comparisons). A1: effect allele, A2: other allele.



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**Table 6. Genomic Loci Identified for Estradiol Levels (Continuous Approach).**

Locus	SNPs	A1	A2	B	SE	<i>p</i>	Identified Genes
CHR17:7388716-7557834	<b>Lead:</b> rs117573122 rs727428 <b>Independent:</b> rs3933469	C C A	G T G	-0.26 -0.04 0.05	0.05 0.01 0.01	1.29 x 10 <sup>-08</sup> 4.98 x 10 <sup>-09</sup> 5.21 x 10 <sup>-09</sup>	SOX15, SHBG, CD68, ATP1B2, FXR2, MPDU1, SAT2, TP53, TNFSF13, SENP3, EIF4A1, ZBTB4, POLR2A, TNFSF12, TNFSF12- TNFSF13, SLC35G6, AC007421.1 SARS2, PAK4, FBXO17, CTC-360G5.8
CHR19: 39448752-39617966	<b>Lead:</b> rs80265623	G	T	-0.23	0.04	3.28 x 10 <sup>-08</sup>	

*Note.* The genome-wide association study was run using the standard additive model of linear associations. Genomic loci identified using FUMA<sup>17</sup>. Genes are sorted to closest loci. Lead SNPs are also independent SNPs. SNPs identified using the genome-wide significance threshold ( $p < 5 \times 10^{-8}$ ; i.e., accounting for multiple comparisons). A1: effect allele, A2: other allele.

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Table 7. **Genomic Loci Identified for Estradiol Levels (Binary Approach).**

Locus	SNPs	A1	A2	B	SE	<i>p</i>	Identified Genes
CHR4:84324801-84482387	<b>Lead:</b> rs4693089	G	A	1.06	0.01	3.99 x 10 <sup>-10</sup>	AGPAT9, HELQ,
	<b>Independent:</b> rs693162	T	C	1.05	0.01	3.80 x 10 <sup>-08</sup>	MRPS18C, FAM175A, HPSE, TMEM150C
CHR5:176312965-176508364	<b>Lead:</b> rs7718874	G	A	1.09	0.01	2.94 x 10 <sup>-18</sup>	TSPAN17, UIMC1,
	<b>Independent:</b> rs352943	A	C	1.07	0.01	2.45 x 10 <sup>-08</sup>	ZNF346, UNC5A, F12,
	rs6881002	C	T	0.95	0.01	1.21 x 10 <sup>-08</sup>	HIGD2A, RNF44, FGFR4, HK3, RGS14, RAB24, PRELID1, GRK6, MXD3, RP11-1026M7.2
CHR7:99025328-99333000	<b>Lead:</b> rs45446698	T	G	0.87	0.02	3.62 x 10 <sup>-09</sup>	CYP3A43, BUD31, PTCD1, PILRB, TRIM4, CYP3A7, ZNF394, CNPY4, LAMTOR4, ZKSCAN5, ZNF789, AP4M1, OR2AE1, ATP5J2-PTCD1
CHR8:37872776-37907660	<b>Lead:</b> rs28807105	G	A	1.07	0.01	1.16 x 10 <sup>-08</sup>	GPR124, FGFR1, EIF4EBP1
CHR12:10875928-10875928	<b>Lead:</b> rs77100210	C	A	1.13	0.02	7.09 x 10 <sup>-09</sup>	YBX3, TAS2R20

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CHR12:66704225- 66836183	<b>Lead:</b>						IRAK3, HELB, GRIP1
	rs75770066	G	A	1.24	0.03	$7.29 \times 10^{-17}$	
	<b>Independent:</b>						
	rs78598096	C	T	1.18	0.02	$1.24 \times 10^{-11}$	
	rs118039683	A	C	1.20	0.03	$1.18 \times 10^{-11}$	
CHR16:11916632- 12068337	<b>Lead:</b>						TNFRSF17, SNX29, GSPT1, RSL1D1, RMI2, RP11-166B2.1, AC007216.2
	rs7185589	T	G	1.06	0.01	$4.23 \times 10^{-08}$	
	<b>Independent:</b>						
CHR19:55799918- 55844071	<b>Lead:</b>						NLRP2, ISOC2, PTPRH, TNNT1, PPP6R1, RPL28, EPS8L1, SUV420H2, HSPBP1, RDH13, BRSK1, CCDC106, ZNF784, SSC5D, TMEM150B, TMEM86B, LILRA4, AC020922.1, AC010327.2
	rs34962991	A	G	0.92	0.01	$2.48 \times 10^{-16}$	
	<b>Independent:</b>						
	rs897798	G	A	0.93	0.01	$3.23 \times 10^{-15}$	
	rs4806663	T	C	1.06	0.01	$1.01 \times 10^{-09}$	
	rs12611091	C	T	1.06	0.01	$1.88 \times 10^{-09}$	
	rs10403600	T	G	0.94	0.01	$2.13 \times 10^{-10}$	
	rs1172819	A	G	0.94	0.01	$5.38 \times 10^{-10}$	
	rs1551562	G	A	0.94	0.01	$1.97 \times 10^{-08}$	
	<b>Independent:</b>						
CHR20:5910339- 5979615	<b>Lead:</b>						CRLS1, TRMT6, CHGB, MCM8
	rs16991615	A	G	1.21	0.02	$3.07 \times 10^{-25}$	
	<b>Independent:</b>						
	rs236167	T	C	1.08	0.01	$3.60 \times 10^{-11}$	

*Note.* The genome-wide association study was run using logistic associations. Genomic loci identified using FUMA<sup>17</sup>. Genes are sorted to closest loci. Lead SNPs are also independent SNPs. SNPs identified using the genome-wide significance threshold ( $p < 5 \times 10^{-8}$ ; i.e., accounting for multiple comparisons). A1: effect allele, A2: other allele.

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Table 8. **Mendelian Randomization Results Using Factors Related to Exogenous Hormone Use and Health-Related Procedures as Exposure Variables.**

Exposure	Exposure GWAS and Data Source	Outcome	Outcome GWAS and Data Source	<i>n</i> SNPs	Estimate	<i>b</i>	<i>se</i>	<i>p</i>	<i>p</i> <sub>FDR</sub>
Oral Contraceptive Use	Elsworth et al. (2018) <sup>19</sup> ; UKB	Brain Age Gap	Newly run; UKB	17	IVW	0.42	2.06	.84	.98
						0.29*			
					MR-Egger	-3.34	6.89	.64	
					Weighted Median	1.04	2.94	.72	
					Simple Mode	4.64	6.22	.47	
					Weighted Mode	3.86	5.85	.52	
					MRlap	-0.20	0.18	.27	
								(.21)	
		Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	19	IVW	0.51	1.55	.74	.98
						0.35*			
					MR-Egger	7.56	6.36	.25	
					Weighted Median	2.05	1.96	.29	
					Simple Mode	3.09	3.28	.36	
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	19	IVW	-0.05	0.48	.92	.98
						-0.03*			
					MR-Egger	-0.96	1.68	.57	
					Weighted Median	0.23	0.60	.70	
					Simple Mode	0.38	1.02	.71	
					Weighted Mode	0.31	0.97	.75	
					MRlap	0.01	0.11	.92	

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HRT Use	Elsworth et al. (2018) <sup>19</sup> ; UKB	Brain Age Gap	Newly run; UKB	14	IVW	<i>(.81)</i>			
						0.47	1.33	.73	.98
						<i>0.33*</i>			
						MR-Egger	-1.97	2.80	.49
						Weighted Median	0.87	1.68	.60
						Simple Mode	1.72	2.86	.56
		Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	13	IVW	Weighted Mode	1.00	2.30	.67
						MRlap	-0.07	0.16	.68
						<i>(.62)</i>			
						0.50	0.93	.59	.98
						<i>0.35*</i>			
						MR-Egger	-1.21	1.98	.55
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	14	IVW	Weighted Median	1.52	1.26	.23
						Simple Mode	1.12	2.07	.60
						Weighted Mode	1.62	1.96	.42
						0.55	0.28	.05	.76
						<i>0.38*</i>			
						MR-Egger	0.33	0.58	.58
						Weighted Median	0.48	0.38	.21
						Simple Mode	0.61	0.64	.36
History of Hysterectomy	Elsworth et al. (2018) <sup>19</sup> ; UKB	Brain Age Gap	Newly run; UKB	17	IVW	Weighted Mode	0.55	0.53	.32
						MRlap	0.13	0.08	.10
						<i>(.41)</i>			
					IVW	-2.53	2.66	.34	.98
						<i>-1.75*</i>			
					MR-Egger	-7.58	8.40	.38	

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History of Oophorectomy	Elsworth et al. (2018) <sup>19</sup> ; UKB	Brain Age Gap	Newly run; UKB	6	Weighted Median	-3.59	3.56	.31	.99
					Simple Mode	-3.58	6.27	.58	
					Weighted Mode	-4.15	6.87	.55	
					MRlap	-0.07	0.16	.69	
								(.70)	
					IVW	-1.72	1.76	.33	
						-1.19*			
					MR-Egger	-8.56	5.77	.16	
					Weighted Median	-0.27	2.52	.92	
					Simple Mode	2.57	4.48	.57	
					Weighted Mode	2.50	4.02	.54	
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	17	IVW	1.01	0.55	.07	
						0.70*			
					MR-Egger	0.59	1.70	.73	
					Weighted Median	0.86	0.81	.29	
					Simple Mode	0.48	1.37	.73	
					Weighted Mode	0.66	1.34	.63	
					MRlap	0.16	0.09	.07	
								(.17)	
		Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	17	IVW	-1.72	1.76	.33	.98
						-1.19*			
					MR-Egger	-8.56	5.77	.16	
					Weighted Median	-0.27	2.52	.92	
					Simple Mode	2.57	4.48	.57	
					Weighted Mode	2.50	4.02	.54	

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Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	5	IVW	-1.34	2.38	.57	.98
				-0.93*			
				MR-Egger	5.51	8.82	.58
				Weighted Median	-0.03	2.93	.99
				Simple Mode	0.39	3.92	.93
Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	6	IVW	0.43	3.72	.91	
				Weighted Mode	0.43	3.72	.91
				-0.12	0.69	.87	.98
				-0.08*			
				MR-Egger	-0.47	2.59	.86
				Weighted Median	0.23	0.90	.80
				Simple Mode	-0.92	1.27	.50
				Weighted Mode	0.33	1.23	.80
				MRlap	-0.04	0.13	.78

(.62)

*Note.* Analyses were conducted using the inverse-variance weighted (IVW) method (one-sided test). MRlap<sup>30</sup> was only used for analyses with sample overlap. For MRlap, the corrected b, SE, and *p* are reported<sup>30</sup>. *p<sub>diff</sub>* corresponds to the test for the difference between the observed and the corrected effect<sup>30</sup>. \*Conversion to a doubling in genetic liability for binary exposure variables<sup>31</sup>. *p<sub>FDR</sub>*: *p*-values adjusted across the 91 tests using FDR correction<sup>32</sup>. *n* SNPs: Number of instrumental variables included in the respective analysis. GWAS: Genome-wide association study. UKB: UK Biobank. ADGC: Alzheimer's Disease Genetics Consortium. MoBa: The Norwegian Mother and Child Cohort Study. PGC: Psychiatric Genomics Consortium.

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Table 9. Mendelian Randomization Results Using Robust Methods.

Exposure	Exposure GWAS and Data Source	Outcome	Outcome GWAS and Data Source	Estimate	b	se	<i>p</i> ( <i>p<sub>diff</sub></i> )
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)*	Newly run; UKB excluding brain age gap sample	Brain Age Gap	Newly run; UKB	MR-Egger	0.44	0.66	.52
				Weighted Median	0.04	0.39	.92
				Simple Mode	0.16	0.64	.81
				Weighted Mode	0.15	0.65	.83
		Alzheimer’s Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	MR-Egger	1.27	0.48	.02
				Weighted Median	0.50	0.31	.11
				Simple Mode	0.04	0.49	.94
				Weighted Mode	0.57	0.41	.19
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	MR-Egger	-0.14	0.15	.37
				Weighted Median	-0.05	0.09	.55
				Simple Mode	-0.09	0.14	.55
				Weighted Mode	-0.10	0.15	.50
			MRlap	-0.01	113.32	.99	
						(.99)	
Estradiol Levels (continuous approach; postmenopausal LIFE samples)	Pott et al. (2019) <sup>33</sup> ; LIFE-Adult & LIFE-Heart	Brain Age Gap	Newly run; UKB	MR-Egger	0.46	0.43	.32
				Weighted Median	0.11	0.23	.63
				Simple Mode	0.37	0.38	.35
				Weighted Mode	0.32	0.35	.38
		Alzheimer’s Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	MR-Egger	-0.01	0.31	.99
				Weighted Median	-0.03	0.16	.83
				Simple Mode	-0.24	0.25	.36
				Weighted Mode	-0.00	0.23	.99



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Estradiol Levels (continuous approach; premenopausal sample from the UKB)*	Haas et al. (2022) <sup>12</sup> ; UKB	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	MR-Egger	0.08	0.11	.51
				Weighted Median	-0.01	0.05	.92
				Simple Mode	-0.04	0.08	.65
				Weighted Mode	-0.03	0.07	.67
		Brain Age Gap	Newly run; UKB	MR-Egger	-1.20	0.74	.13
				Weighted Median	-0.21	0.43	.62
				Simple Mode	0.11	0.83	.90
				Weighted Mode	0.28	0.75	.72
	Wang et al. (2021) <sup>22</sup> ; ADGC	Alzheimer's Disease		MR-Egger	0.30	0.68	.66
				Weighted Median	0.06	0.34	.85
				Simple Mode	0.74	0.65	.28
				Weighted Mode	-0.07	0.64	.91
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	MR-Egger	0.07	0.18	.70
				Weighted Median	0.08	0.10	.43
				Simple Mode	0.11	0.16	.50
				Weighted Mode	0.13	0.15	.41
Estradiol Levels (continuous approach; postmenopausal sample from the UKB)*	Haas et al. (2022) <sup>12</sup> ; UKB	Brain Age Gap	Newly run; UKB	MRlap	-0.09	1358.71	.99 (.99)
		Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	MR-Egger	0.19	0.29	.52
				Weighted Median	0.22	0.12	.06

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Reproductive Span	Schindler et al. (2022) <sup>34</sup> ; UKB excluding brain age gap sample	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	Simple Mode	0.26	0.21	.24
				Weighted Mode	0.28	0.17	.12
				MR-Egger	-0.01	0.06	.82
				Weighted Median	0.00	0.03	.93
		Brain Age Gap	Newly run; UKB	Simple Mode	0.02	0.06	.76
				Weighted Mode	0.02	0.06	.71
				MR-Egger	0.08	0.27	.77
				Weighted Median	0.13	0.19	.49
	Perry et al. (2014) <sup>35</sup> ; ReproGen	Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	Simple Mode	-0.46	0.41	.27
				Weighted Mode	0.11	0.20	.58
				MR-Egger	0.11	0.19	.54
				Weighted Median	-0.07	0.13	.62
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	Simple Mode	-0.05	0.28	.86
				Weighted Mode	-0.02	0.17	.90
				MR-Egger	-0.07	0.06	.22
				Weighted Median	-0.03	0.04	.44
Age at Menarche	Perry et al. (2014) <sup>35</sup> ; ReproGen	Brain Age Gap	Newly run; UKB	Simple Mode	-0.01	0.09	.90
				Weighted Mode	-0.04	0.05	.35
				MRlap	0.01	0.01	.52
							(.60)
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB,	MR-Egger	-1.06	0.57	.07
				Weighted Median	-0.44	0.21	.04
				Simple Mode	-0.39	0.49	.43
				Weighted Mode	-0.45	0.41	.27
				MR-Egger	0.07	0.15	.64
				Weighted Median	-0.09	0.05	.06

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Age at Menarche	Loh et al. (2018) <sup>36</sup> ; UKB	Alzheimer's Disease	MoBa, PGC & iPSYCH	Simple Mode	-0.08	0.11	.44
			Wang et al. (2021) <sup>22</sup> ; ADGC	Weighted Mode	-0.06	0.08	.47
				MR-Egger	-0.11	0.15	.46
				Weighted Median	-0.10	0.10	.29
Age at Natural Menopause	Day et al. (2015) <sup>37</sup> ; ReproGen	Brain Age Gap	Newly run; UKB	Simple Mode	-0.14	0.22	.54
				Weighted Mode	-0.17	0.13	.20
				MR-Egger	0.09	0.09	.28
				Weighted Median	0.03	0.06	.56
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	Simple Mode	0.00	0.10	.99
				Weighted Mode	0.03	0.06	.66
				MR-Egger	-0.01	0.02	.65
				Weighted Median	-0.01	0.01	.33
Age at Menopause	Loh et al. (2018) <sup>36</sup> ; UKB	Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	Simple Mode	-0.03	0.02	.18
				Weighted Mode	-0.02	0.01	.26
				MR-Egger	0.10	0.05	.06
				Weighted Median	0.00	0.03	.98
Number of Childbirths	Elsworth et al. (2018) <sup>19</sup> ; UKB	Brain Age Gap	Newly run; UKB	Simple Mode	0.01	0.06	.89
				Weighted Mode	0.01	0.05	.91
				MR-Egger	9.85	12.97	.48
				Weighted Median	-0.63	1.03	.54
		Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	Simple Mode	-1.02	1.43	.50
				Weighted Mode	-1.07	1.22	.41
				MRlap	0.43	0.34	.21
							(.21)
		Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	MR-Egger	-3.11	4.27	.49
				Weighted Median	-0.24	0.62	.70

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Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	Simple Mode	-0.77	0.98	.46
		Weighted Mode	-0.39	0.94	.70
		MR-Egger	3.21	2.02	.16
		Weighted Median	0.22	0.25	.36
		Simple Mode	0.13	0.41	.76
		Weighted Mode	0.29	0.36	.45
		MRlap	0.22	0.16	.18
					(.19)

*Note.* Robust methods were used to check consistency of results obtained with the IVW estimate (see main manuscript; one-sided test). MRlap<sup>30</sup> was only used for analyses with sample overlap. For MRlap, the corrected b, SE, and *p* are reported<sup>30</sup>. *p<sub>diff</sub>* corresponds to the test for the difference between the observed and the corrected effect<sup>30</sup>. \*Difficulties occurred when running MRlap due to a low or negative heritability of the exposures. MRlap could not be performed for estradiol levels (continuous, postmenopausal sample) as an exposure due to the negative heritability estimated for the phenotype ( $h^2 = -0.0017$  (SE = 0.1004)). Further, for estradiol levels (continuous, premenopausal sample) and estradiol levels (continuous, combined pre- and postmenopausal sample) low heritability likely compromised the results as some  $h^2$  were negative in the parametric bootstrap, contributing to large standard errors. GWAS: Genome-wide association study. UKB: UK Biobank. ADGC: Alzheimer's Disease Genetics Consortium. MoBa: The Norwegian Mother and Child Cohort Study. PGC: Psychiatric Genomics Consortium. ReproGen: Reproductive Genetics Consortium.

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Table 10. Results of Sensitivity Analyses Using Binary Estradiol Levels and Estradiol Levels in Males.

Exposure	Exposure GWAS and Data Source	Outcome	Outcome GWAS and Data Source	<i>n</i> SNPs	Estimate	<i>b</i>	<i>se</i>	<i>p</i>	<i>p</i> <sub>FDR</sub>
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Brain Age Gap	Newly run; UKB	10	IVW	0.11 <i>0.08*</i>	0.23	.65	.98
					MR-Egger	0.00	0.00	.43	
					Weighted Median	-0.00	0.00	.69	
					Simple Mode	-0.00	0.00	.74	
					Weighted Mode	-0.00	0.00	.85	
		Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	10	MR-Egger	0.00	0.00	.43	
					IVW	0.04 <i>0.03*</i>	0.14	.77	.98
					MR-Egger	0.48	0.38	.26	
					Weighted Median	-0.16	0.22	.46	
					Simple Mode	-0.26	0.31	.43	
					Weighted Mode	-0.26	0.29	.41	
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	10	IVW	0.01 <i>0.01*</i>	0.04	.84	.98
					MR-Egger	-0.10	0.10	.35	
					Weighted Median	-0.04	0.06	.55	
					Simple Mode	-0.08	0.10	.45	
					Weighted Mode	-0.08	0.08	.39	
					MRlap	0.01	0.08	.85	
								(.84)	
Estradiol Levels		Brain Age Gap	Newly run; UKB	5	IVW	0.76	0.44	.09	.82

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(binary approach; premenopausal sample from the UKB)	Haas et al. (2022) <sup>12</sup> ; UKB						0.53*			
						MR-Egger	1.41	1.15	.31	
						Weighted Median	0.54	0.57	.34	
						Simple Mode	0.41	0.87	.66	
						Weighted Mode	0.32	0.72	.67	
						MRlap	0.18	0.10	.08	
										(.10)
		Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	5	IVW		0.13	0.39	.73	.98
							0.09*			
						MR-Egger	1.84	0.90	.13	
						Weighted Median	-0.21	0.47	.65	
						Simple Mode	-0.33	0.77	.69	
						Weighted Mode	-0.40	0.85	.66	
		Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	5	IVW		-0.03	0.12	.81	.98
							-0.02*			
						MR-Egger	-0.32	0.29	.34	
						Weighted Median	-0.12	0.13	.38	
						Simple Mode	-0.16	0.19	.43	
						Weighted Mode	-0.15	0.17	.42	
						MRlap	-0.02	0.08	.82	
										(.90)
Estradiol Levels (binary approach; postmenopausal sample from the UKB)	Haas et al. (2022) <sup>12</sup> ; UKB	Brain Age Gap	Newly run; UKB	8	IVW		0.54	0.45	.22	.98
							0.37*			
						MR-Egger	2.06	0.93	.07	
						Weighted Median	0.22	0.56	.70	

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Estradiol Levels (male sample)**	Neale Lab <sup>21</sup> ; UKB	Brain Age Gap (male sample)	Newly run; UKB	44	Simple Mode	-0.30	0.88	.75	.98
					Weighted Mode	0.08	0.74	.92	
					MRlap	0.13	0.10	.17	
								(.18)	
					IVW	0.29	0.34	.40	
						0.20*			
					MR-Egger	0.81	0.77	.34	
					Weighted Median	0.27	0.44	.54	
					Simple Mode	-0.25	0.74	.75	
					Weighted Mode	0.80	0.54	.18	
					IVW	-0.10	0.10	.29	
						-0.01*			
					MR-Egger	-0.34	0.21	.15	
					Weighted Median	-0.11	0.13	.40	
					Simple Mode	-0.13	0.19	.53	
Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	8	Weighted Mode	-0.12	0.16	.49	.98
					MRlap	0.00	0.07	.98	
								(.91)	
					IVW	0.00	0.00	.80	
					MR-Egger	0.00	0.00	.13	
					Weighted Median	0.00	0.00	.61	
					Simple Mode	0.00	0.00	.67	
					Weighted Mode	0.00	0.00	.59	
					MRlap	0.00	5.43	.99	
								(.99)	
					IVW	0.00	0.00	.80	
					MR-Egger	0.00	0.00	.13	
					Weighted Median	0.00	0.00	.61	
					Simple Mode	0.00	0.00	.67	
					Weighted Mode	0.00	0.00	.59	
					MRlap	0.00	5.43	.99	

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Alzheimer's Disease (male sample)	Wang et al. (2021) <sup>22</sup> ; ADGC	42	IVW	-0.00	0.00	.45	.98
			MR-Egger	-0.00	0.00	.99	
			Weighted Median	-0.00	0.00	.91	
			Simple Mode	-0.00	0.00	.90	
			Weighted Mode	-0.00	0.00	.98	
Depression (male sample)	Run in line with Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	45	IVW	0.00	0.00	.19	.98
			MR-Egger	0.00	0.00	.19	
			Weighted Median	0.00	0.00	.58	
			Simple Mode	0.00	0.00	.66	
			Weighted Mode	0.00	0.00	.73	
			MRlap	0.02	6434.88	.99	
(1)							

*Note.* The inverse-variance weighted (IVW) estimate was used as the main analysis (one-sided test). \*Conversion to a doubling in genetic liability for binary exposure variables<sup>31</sup>. \*\*Difficulties occurred when running MRlap due to a low or negative heritability of the exposures. For estradiol levels (male sample) low heritability likely compromised the results as some  $h^2$  were negative in the parametric bootstrap, contributing to large standard errors.  $p_{FDR}$ :  $p$ -values adjusted across the 91 tests using FDR correction<sup>32</sup>. GWAS: Genome-wide association study. UKB: UK Biobank. ADGC: Alzheimer's Disease Genetics Consortium. MoBa: The Norwegian Mother and Child Cohort Study. PGC: Psychiatric Genomics Consortium. ReproGen: Reproductive Genetics Consortium.  $n$  SNPs: Number of instrumental variables included in the respective analysis.



## Supplementary Information

Table 11. Results of Sensitivity Analyses Using Age at Natural Menopause as an Exposure.

Exposure	Exposure GWAS and Data Source	Outcome	Outcome GWAS and Data Source	Method	<i>b</i>	<i>se</i>	<i>p</i>	<i>p</i> <sub>FDR</sub>
Age at Natural Menopause (ReproGen sample)	Day et al. (2015) <sup>37</sup> ; ReproGen	Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	IVW	-0.01	0.03	.81	.98
				MR-Egger	0.05	0.06	.47	
				Weighted Median	-0.01	0.04	.76	
				Simple Mode	-0.01	0.07	.84	
				Weighted Mode	-0.03	0.06	.60	

*Note.* The inverse-variance weighted (IVW) estimate was used as the main analysis. *p*<sub>FDR</sub>: *p*-values adjusted across the 91 tests using FDR correction<sup>32</sup>. GWAS: Genome-wide association study. ADGC: Alzheimer's Disease Genetics Consortium. PGC: Psychiatric Genomics Consortium. ReproGen: Reproductive Genetics Consortium.

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Table 12. Results of Sensitivity Analyses Using Recurrent Depression and the Depression Subsample Excluding UKB as Outcomes.

Exposure	Exposure GWAS and Data Source	Outcome	Outcome GWAS and Data Source	<i>n</i> SNPs	Estimate	<i>b</i>	<i>se</i>	<i>p</i>	<i>p</i> <sub>FDR</sub>
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	5	IVW	-0.09	0.24	.70	.98
					MR-Egger	-0.20	1.87	.92	
					Weighted Median	-0.14	0.32	.65	
					Simple Mode	-0.56	0.49	.32	
					Weighted Mode	-0.48	0.45	.35	
		Recurrent Depression	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	5	IVW	-0.06	0.45	.90	.98
					MR-Egger	0.02	3.62	.99	
					Weighted Median	-0.15	0.42	.71	
					Simple Mode	-0.71	0.75	.40	
					Weighted Mode	-0.43	0.64	.53	
Estradiol Levels (continuous approach; postmenopausal LIFE samples)	Pott et al. (2019) <sup>33</sup> ; LIFE-Adult & LIFE-Heart	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	7	IVW	0.07	0.09	.44	.98
					MR-Egger	0.14	0.19	.49	
					Weighted Median	0.04	0.11	.74	
					Simple Mode	0.04	0.15	.79	
					Weighted Mode	0.03	0.13	.80	
		Recurrent Depression	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	5	IVW	0.16	0.12	.19	.98
					MR-Egger	0.18	0.26	.54	
					Weighted Median	0.19	0.16	.23	
					Simple Mode	0.22	0.21	.35	
					Weighted Mode	0.09	0.21	.69	
	Haas et al. (2022) <sup>12</sup> ; UKB	Depression (subsample excluding UKB)		7	IVW	-0.01	0.21	.95	.98
					MR-Egger	1.04	0.67	.18	

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Estradiol Levels (continuous approach; premenopausal sample from the UKB)		Recurrent Depression	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	7	Weighted Median	0.23	0.25	.36	
					Simple Mode	0.37	0.36	.34	
					Weighted Mode	0.38	0.32	.28	
					IVW	-0.05	0.25	.83	
					MR-Egger	0.81	0.88	.40	
					Weighted Median	-0.17	0.34	.62	
					Simple Mode	-0.31	0.48	.54	
Estradiol Levels (continuous approach; postmenopausal sample from the UKB)	Haas et al. (2022) <sup>12</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	7	Weighted Mode	-0.28	0.44	.55	
					IVW	-0.04	0.06	.54	
					MR-Egger	-0.26	0.16	.17	
					Weighted Median	-0.02	0.08	.79	
					Simple Mode	-0.00	0.13	.99	
					Weighted Mode	-0.00	0.13	.98	
					IVW	0.00	0.08	.97	
Reproductive Span	Schindler et al. (2022) <sup>34</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	6	MR-Egger	-0.12	0.21	.61	
					Weighted Median	0.02	0.11	.87	
					Simple Mode	0.11	0.17	.56	
					Weighted Mode	0.12	0.16	.50	
					IVW	-0.01	0.07	.87	
					MR-Egger	-0.21	0.14	.14	
					Weighted Median	-0.13	0.09	.16	
Reproductive Span		Recurrent Depression	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	45	Simple Mode	0.10	0.16	.54	
					Weighted Mode	-0.14	0.10	.15	
					IVW	0.01	0.10	.95	
					MR-Egger	-0.25	0.21	.23	
Reproductive Span				43	Weighted Median	-0.05	0.14	.71	

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Age at Menarche	Loh et al. (2018) <sup>36</sup> ; UKB	Recurrent Depression	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	136	Simple Mode	0.39	0.32	.22	
					Weighted Mode	-0.12	0.16	.45	
					IVW	-0.14	0.05	.01	
					MR-Egger	-0.02	0.13	.87	
					Weighted Median	-0.07	0.09	.44	
					Simple Mode	-0.15	0.20	.44	
Age at Menopause	Loh et al. (2018) <sup>36</sup> ; UKB	Recurrent Depression	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	42	Weighted Mode	-0.08	0.12	.48	
					IVW	-0.01	0.02	.72	
					MR-Egger	-0.08	0.05	.10	
					Weighted Median	-0.04	0.03	.25	
					Simple Mode	0.03	0.07	.64	
					Weighted Mode	-0.03	0.04	.57	
Number of Childbirths	Elsworth et al. (2018) <sup>19</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	7	IVW	-1.56	1.12	.16	.98
					MR-Egger	-4.92	2.93	.17	
					Weighted Median	-0.99	2.10	.64	
					Simple Mode	-1.37	1.87	.50	
					Weighted Mode	-0.71	1.88	.72	
		Recurrent Depression	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	7	IVW	0.92	2.00	.65	.98
					MR-Egger	-2.59	5.62	.66	
					Weighted Median	0.26	3.13	.93	
					Simple Mode	-1.49	2.66	.60	
					Weighted Mode	0.23	2.27	.92	
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	5	IVW	-0.02	0.15	.88	.98
						-0.01*			
					MR-Egger	-0.18	0.43	.70	
					Weighted Median	0.15	0.14	.28	

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Estradiol Levels (binary approach; premenopausal sample from the UKB)	Haas et al. (2022) <sup>12</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	8	Simple Mode	0.20	0.19	.37	
					Weighted Mode	0.19	0.18	.33	
					IVW	0.02	0.22	.92	
						<i>0.01*</i>			
					MR-Egger	-0.26	0.61	.69	
					Weighted Median	-0.16	0.27	.56	
					Simple Mode	0.38	0.48	.45	
					Weighted Mode	-0.20	0.33	.57	
Estradiol Levels (binary approach; postmenopausal sample from the UKB)	Haas et al. (2022) <sup>12</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	5	IVW	-0.27	0.26	.30	.98
						<i>-0.19*</i>			
					MR-Egger	-0.19	0.57	.76	
					Weighted Median	-0.32	0.32	.31	
					Simple Mode	-0.48	0.42	.31	
					Weighted Mode	-0.38	0.34	.32	
					IVW	-0.00	0.00	.67	
					MR-Egger	-0.01	0.01	.49	
Estradiol Levels (male sample)	Neale Lab <sup>21</sup> ; UKB	Depression (male subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	6	Weighted Median	-0.00	0.00	.91	
					Simple Mode	-0.00	0.00	.91	
					Weighted Mode	-0.00	0.00	.95	
					IVW	-0.00	0.00	.67	
					MR-Egger	-0.01	0.01	.49	
					Weighted Median	-0.00	0.00	.91	
					Simple Mode	-0.00	0.00	.91	
					Weighted Mode	-0.00	0.00	.95	
Oral Contraceptive Use	Elsworth et al. (2018) <sup>19</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	12	IVW	-0.56	1.35	.68	.98
						<i>-0.39*</i>			
					MR-Egger	-2.64	5.79	.66	
					Weighted Median	0.69	1.55	.65	
					Simple Mode	0.61	2.86	.84	
					Weighted Mode	0.78	2.42	.75	
					IVW	-0.36	0.72	.61	
HRT Use				7	IVW	-0.36	0.72	.61	.98

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	Elsworth et al. (2018) <sup>19</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH			-0.25*			
					MR-Egger	1.72	1.46	.29	
					Weighted Median	0.31	0.94	.74	
					Simple Mode	-0.19	1.42	.90	
					Weighted Mode	0.55	1.04	.61	
History of Hysterectomy	Elsworth et al. (2018) <sup>19</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	13	IVW	0.61	1.54	.69	.98
						0.42*			
					MR-Egger	-0.19	4.86	.97	
					Weighted Median	2.21	1.99	.26	
					Simple Mode	2.78	3.02	.38	
					Weighted Mode	1.87	2.89	.53	
History of Oophorectomy	Elsworth et al. (2018) <sup>19</sup> ; UKB	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	5	IVW	0.56	1.50	.71	.98
						0.39*			
					MR-Egger	-6.32	6.03	.37	
					Weighted Median	1.18	1.91	.54	
					Simple Mode	1.67	2.54	.55	
					Weighted Mode	1.43	2.30	.57	

*Note.* The inverse-variance weighted (IVW) estimate was used as the main analysis (one-sided test). The depression subsample excluding UKB was used as a sensitivity analysis for analyses with sample overlap between the main GWAS used for depression and the respective exposure.

\*Conversion to a doubling in genetic liability for binary exposure variables<sup>31</sup>. GWAS: Genome-wide association study. HRT: Hormone Replacement Therapy. UKB: UK Biobank. PGC: Psychiatric Genomics Consortium.  $p_{FDR}$ :  $p$ -values adjusted across the 91 tests using FDR correction<sup>32</sup>.  $n$  SNPs: Number of instrumental variables included in the respective analysis.

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Table 13. **Multivariable Mendelian Randomization Results.**

Exposures	Exposure GWAS and Data Source	Outcome	Outcome GWAS and Data Source	Estimate	<i>b</i>	<i>se</i>	<i>p</i>	<i>p</i> <sub>FDR</sub>
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Brain Age Gap	Newly run; UKB	IVW	0.41	0.60	.50	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.08	0.20	.69	.98
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Brain Age Gap	Newly run; UKB	MR-Egger	-0.03	0.91	.98	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			MR-Egger	0.19	0.27	.50	
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Alzheimer's disease	Wang et al. (2021) <sup>22</sup> ; ADGC	IVW	0.20	0.52	.70	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.01	0.17	.94	.98
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Alzheimer's disease	Wang et al. (2021) <sup>22</sup> ; ADGC	MR-Egger	-0.23	0.75	.76	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			MR-Egger	0.11	0.21	.42	
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	IVW	-0.02	0.17	.89	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.14	0.05	.01	.30

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Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	MR-Egger	0.06	0.25	.82	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			MR-Egger	0.12	0.07	.06	
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	IVW	-0.10	0.45	.82	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.03	0.10	.77	.98
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	MR-Egger	-0.07	0.72	.93	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			MR-Egger	0.02	0.13	.86	
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Brain Age Gap	Newly run; UKB	IVW	0.04	0.20	.84	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.09	0.19	.64	.98
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Brain Age Gap	Newly run; UKB	MR-Egger	0.10	0.27	.72	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			MR-Egger	0.08	0.21	.72	
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	IVW	0.20	0.18	.26	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.03	0.16	.85	.98



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Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Alzheimer's Disease	Wang et al. (2021) <sup>22</sup> ; ADGC	MR-Egger	0.13	0.22	.55	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			MR-Egger	0.04	0.16	.79	
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	IVW	0.02	0.06	.77	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.15	0.05	.003	.27
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	MR-Egger	-0.02	0.07	.81	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			MR-Egger	0.15	0.05	.003	
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	IVW	-0.05	0.11	.65	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.13	0.09	.15	.98
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Newly run; UKB excluding brain age gap sample	Depression (subsample excluding UKB)	Blokland et al. (2022) <sup>5</sup> ; PGC & iPSYCH	MR-Egger	-0.09	0.13	.47	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			MR-Egger	0.14	0.09	.13	
Age at Menarche (ReproGen sample)	Perry et al. (2014) <sup>35</sup> ; ReproGen	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB, MoBa, PGC & iPSYCH	IVW	-0.06	0.04	.15	.98
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT			IVW	0.12	0.07	.08	.81
Age at Menarche (ReproGen sample)	Perry et al. (2014) <sup>35</sup> ; ReproGen	Depression	Oppenheimer et al. (2025) <sup>1</sup> ; UKB,	MR-Egger	-0.09	0.08	.23	

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BMI	Locke et al. (2015) <sup>20</sup> ; GIANT		MoBa, PGC & iPSYCH	MR-Egger	0.12	0.07	.07	
Age at Menarche	Loh et al. (2018) <sup>36</sup> ; UKB	Recurrent	Blokland et al.	IVW	-0.09	0.06	.10	83
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT	Depression	(2022) <sup>5</sup> ; PGC & iPSYCH	IVW	-0.00	.13	.98	.99
Age at Menarche	Loh et al. (2018) <sup>36</sup> ; UKB	Recurrent	Blokland et al.	MR-Egger	0.07	0.12	.53	
BMI	Locke et al. (2015) <sup>20</sup> ; GIANT	Depression	(2022) <sup>5</sup> ; PGC & iPSYCH	MR-Egger	-0.04	0.14	.78	

*Note.* The inverse-variance weighted (IVW) estimate was used as the main analysis (one-sided test). UKB: UK Biobank. GWAS: Genome-wide association study. UKB: UK Biobank. ADGC: Alzheimer's Disease Genetics Consortium. MoBa: The Norwegian Mother and Child Cohort Study. PGC: Psychiatric Genomics Consortium. ReproGen: Reproductive Genetics Consortium. GIANT: Genetic Investigation of Anthropometric Traits Consortium.  $p_{\text{FDR}}$ :  $p$ -values adjusted across the 91 tests using FDR correction<sup>32</sup>.

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Table 14. **Heterogeneity Test Results.**

Exposure	Outcome	<i>Q</i>	<i>df</i>	<i>p</i>
Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB)	Brain Age Gap	13.99	15	.53
	Alzheimer's disease	15.78	14	.33
	Depression	8.03	15	.92
	Depression (subsample excluding UKB)	3.68	4	.45
	Recurrent Depression	8.32	4	.08
Estradiol Levels (continuous approach; postmenopausal LIFE samples)	Brain Age Gap	6.69	9	.67
	Alzheimer's disease	3.80	9	.92
	Depression	12.12	9	.21
	Recurrent Depression	1.77	4	.78
Estradiol Levels (continuous approach; premenopausal sample from the UKB)	Brain Age Gap	12.89	12	.38
	Alzheimer's disease	13.76	12	.32
	Depression	9.18	12	.69
	Depression (subsample excluding UKB)	7.48	6	.28
	Recurrent Depression	5.74	6	.45
Estradiol Levels (continuous approach; postmenopausal sample from the UKB)	Brain Age Gap	10.32	11	.50
	Alzheimer's disease	22.16	11	.02
	Depression	11.53	11	.40
	Depression (subsample excluding UKB)	5.38	6	.50
	Recurrent Depression	10.32	11	.50
Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB)	Brain Age Gap	13.60	9	.14
	Alzheimer's disease	5.50	9	.79
	Depression	7.62	9	.57
	Depression (subsample excluding UKB)	7.83	4	.10
Estradiol Levels (binary approach; premenopausal sample from the UKB)	Brain Age Gap	4.02	4	.40
	Alzheimer's disease	5.05	4	.28
	Depression	6.38	7	.50
	Depression (subsample excluding UKB)	8.82	7	.27
Estradiol Levels (binary approach; postmenopausal sample from the UKB)	Brain Age Gap	7.64	7	.37
	Alzheimer's disease	3.79	6	.71

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	Depression	7.17	7	.41
	Depression (subsample excluding UKB)	1.32	4	.86
Estradiol Levels (male sample)	Brain Age Gap (male sample)	35.55	43	.78
	Alzheimer's disease (male sample)	47.84	41	.21
	Depression (male sample)	74.24	44	2.93e <sup>-3</sup>
	Depression (male subsample excluding UKB)	3.80	5	.58
Reproductive Span	Brain Age Gap	93.72	72	.04
	Alzheimer's disease	59.22	67	.74
	Depression	81.91	72	.20
	Depression (subsample excluding UKB)	59.38	44	.06
	Recurrent Depression	69.83	42	.004
Age at Menarche (ReproGen sample)	Brain Age Gap	68.54	53	.07
	Depression	107.26	53	1.52e <sup>-5</sup>
Age at Menarche (UKB sample)	Alzheimer's disease	215.90	203	.25
	Recurrent Depression	148.57	135	.20
Age at Natural Menopause (ReproGen sample)	Brain Age Gap	37.91	36	.38
	Depression	41.42	37	.28
	Alzheimer's disease	41.31	37	.29
Age at Menopause (UKB sample)	Alzheimer's disease	78.70	67	.16
	Recurrent Depression	46.37	41	.26
Number of Childbirths	Brain Age Gap	32.56	7	3.19e <sup>-5</sup>
	Alzheimer's disease	5.90	7	.55
	Depression	17.06	7	.02
	Depression (subsample excluding UKB)	3.07	5	.69
	Recurrent Depression	14.71	6	.02
Oral Contraceptive Use	Brain Age Gap	18.10	16	.32
	Alzheimer's disease	22.83	18	.20
	Depression	23.08	18	.19

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	Depression (subsample excluding UKB)	19.31	11	.06
HRT Use	Brain Age Gap	15.57	13	.27
	Alzheimer's disease	8.18	12	.77
	Depression	11.05	13	.61
	Depression (subsample excluding UKB)	5.65	6	.46
History of Hysterectomy	Brain Age Gap	19.52	16	.24
	Alzheimer's disease	13.61	16	.63
	Depression	13.60	16	.63
	Depression (subsample excluding UKB)	14.81	12	.25
History of Oophorectomy	Brain Age Gap	5.82	5	.32
	Alzheimer's disease	2.23	4	.68
	Depression	2.57	5	.77
	Depression (subsample excluding UKB)	4.38	4	.36
<i>Multivariable analyses: Estradiol Levels (continuous approach; combined pre- and postmenopausal sample from the UKB) and BMI</i>	Brain age gap	31.64	36	.68
	Alzheimer's disease	47.25	36	.10
	Depression	45.29	34	.09
	Depression (subsample excluding UKB)	44.29	34	.11
<i>Multivariable analyses: Estradiol Levels (binary approach; combined pre- and postmenopausal sample from the UKB) and BMI</i>	Brain age gap	31.37	39	.80
	Alzheimer's disease	48.71	39	.14
	Depression	47.43	37	.12
	Depression (subsample excluding UKB)	39.41	37	.36
<i>Multivariable analyses: Age at Menarche (ReproGen sample) and BMI</i>	Depression	133.67	74	< .001
<i>Multivariable analyses: Age at Menarche (UKB sample) and BMI</i>	Recurrent Depression	164.79	149	.18

*Note.* Heterogeneity was assessed using Cochran's  $Q$  for the inverse-variance weighted (IVW) estimate (two-sided test). HRT: Hormone Replacement Therapy. BMI: body mass index. UKB: UK Biobank. ReproGen: Reproductive Genetics Consortium.

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Table 15. Reported Traits in the GWAS Catalog for SNPs found in GWAS of Continuous Estradiol Levels.

Independent Significant SNP	SNP	Mapped Gene	Trait	First Author	Date	Journal
rs117573122	rs117573122	POLR2A	Testosterone levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs117573122	rs117573122	POLR2A	Sex hormone-binding globulin levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs3933469	rs34445439	Y_RNA - TNFSF12	Cryptic phenotype that captures alpha-1-antitrypsin deficiency severity	Blair DR	27/06/2022	Nat Commun
rs3933469	rs12940684	TNFSF12, TNFSF12-TNFSF13	SHBG plasma levels	Caron B	09/03/2022	Genome Med
rs3933469	rs12940684	TNFSF12, TNFSF12-TNFSF13	Metabolic biomarkers (multivariate analysis)	Martin S	12/05/2021	Diabetes
rs3933469	rs12940684	TNFSF12, TNFSF12-TNFSF13	Body fat percentage	Martin S	12/05/2021	Diabetes
rs3933469	rs12940684	TNFSF12, TNFSF12-TNFSF13	Aspartate aminotransferase levels	Martin S	12/05/2021	Diabetes
rs3933469	rs12940684	TNFSF12, TNFSF12-TNFSF13	Sex hormone-binding globulin levels	Martin S	12/05/2021	Diabetes
rs3933469	rs4511593	TNFSF12, TNFSF12-TNFSF13	Birth weight	Warrington NM	01/05/2019	Nat Genet
rs3933469	rs4511593	TNFSF12, TNFSF12-TNFSF13	Systolic blood pressure	Plotnikov D	01/06/2022	Invest Ophthalmol Vis Sci
rs3933469	rs116600817	TNFSF12-TNFSF13, TNFSF12	Cardioembolic stroke (MTAG)	Carcel-Marquez J	08/07/2022	Front Cardiovasc Med
rs3933469	rs78744936	TNFSF12-TNFSF13	Systolic blood pressure	Kichaev G	27/12/2018	Am J Hum Genet
rs3933469	rs4227	MPDU1	Testosterone levels	Pott J	06/06/2019	J Clin Endocrinol Metab
rs3933469	rs4227	MPDU1	IgA nephropathy	Li M	01/06/2015	Nat Commun
rs3933469	rs4227	MPDU1	IgA nephropathy	Yu XQ	25/12/2011	Nat Genet
rs3933469	rs4227	MPDU1	IgA nephropathy	Li M	10/09/2020	J Am Soc Nephrol
rs3933469	rs4227	MPDU1	Testosterone levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs3933469	rs4227	MPDU1	Sex hormone-binding globulin levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs3933469	rs4227	MPDU1	Insulin-like growth factor 1 levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs3933469	rs4227	MPDU1	Glycated hemoglobin levels	Sinnott-Armstrong N	18/01/2021	Nat Genet

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rs3933469	rs4227	MPDU1	Serum alkaline phosphatase levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs117573122	rs545206972	MPDU1	Sex hormone-binding globulin levels adjusted for BMI	Ruth KS	10/02/2020	Nat Med
rs117573122	rs545206972	MPDU1	Sex hormone-binding globulin levels	Ruth KS	10/02/2020	Nat Med
rs117573122	rs545206972	MPDU1	Bioavailable testosterone levels	Ruth KS	10/02/2020	Nat Med
rs3933469	rs12150660	SHBG	Sex hormone-binding globulin levels	Coviello AD	19/07/2012	PLoS Genet
rs3933469	rs12150660	SHBG	Testosterone levels	Ohlsson C	06/10/2011	PLoS Genet
rs3933469	rs12150660	SHBG	Sex hormone-binding globulin levels	Harrison S	28/07/2021	Sci Adv
rs727428	rs858519	SHBG	Blood protein levels	Emilsson V	02/08/2018	Science
rs727428	rs858519	SHBG	Type 2 diabetes	Vujkovic M	15/06/2020	Nat Genet
rs727428	rs858519	SHBG	Sex hormone-binding globulin levels adjusted for BMI	Ruth KS	10/02/2020	Nat Med
rs727428	rs858519	SHBG	Sex hormone-binding globulin levels	Ruth KS	10/02/2020	Nat Med
rs727428	rs858519	SHBG	Sex hormone-binding globulin levels	Harrison S	28/07/2021	Sci Adv
rs727428	rs858519	SHBG	Serum levels of protein SHBG	Gudjonsson A	25/01/2022	Nat Commun
rs727428	rs858519	SHBG	Waist-hip ratio	Kichaev G	27/12/2018	Am J Hum Genet
rs3933469	rs62059839	SHBG	Total testosterone levels	Ruth KS	10/02/2020	Nat Med
rs3933469	rs62059839	SHBG	Total testosterone levels	Harrison S	28/07/2021	Sci Adv
rs3933469	rs62059839	SHBG	Testosterone levels	Haas CB	22/02/2022	Endocrinology
rs3933469	rs62059839	SHBG	Testosterone levels in postmenopausal women	Haas CB	22/02/2022	Endocrinology
rs3933469	rs62059839	SHBG	Estradiol levels	Schmitz D	13/07/2021	J Clin Endocrinol Metab
rs3933469	rs62059839	SHBG	Testosterone levels in premenopausal women	Haas CB	22/02/2022	Endocrinology
rs727428	rs858518	SHBG	Red cell distribution width	Astle WJ	17/11/2016	Cell
rs3933469	rs1799941	SHBG	Sex hormone-binding globulin levels	Ruth KS	10/02/2020	Nat Med
rs3933469	rs1799941	SHBG	Sex hormone-binding globulin levels adjusted for BMI	Ruth KS	10/02/2020	Nat Med
rs3933469	rs1799941	SHBG	Total testosterone levels	Ruth KS	10/02/2020	Nat Med
rs3933469	rs1799941	SHBG	Bioavailable testosterone levels	Ruth KS	10/02/2020	Nat Med
rs3933469	rs1799941	SHBG	Total testosterone levels	Harrison S	28/07/2021	Sci Adv

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rs3933469	rs1799941	SHBG	Serum levels of protein SHBG	Gudjonsson A	25/01/2022	Nat Commun
rs117573122	rs6258	SHBG	Sex hormone-binding globulin levels	Coviello AD	19/07/2012	PLoS Genet
rs117573122	rs6258	SHBG	Testosterone levels	Ohlsson C	06/10/2011	PLoS Genet
rs117573122	rs6258	SHBG	Heel bone mineral density	Morris JA	31/12/2018	Nat Genet
rs117573122	rs6258	SHBG	Heel bone mineral density	Kichaev G	27/12/2018	Am J Hum Genet
rs117573122	rs6258	SHBG	Sex hormone-binding globulin levels	Ruth KS	10/02/2020	Nat Med
rs117573122	rs6258	SHBG	Sex hormone-binding globulin levels adjusted for BMI	Ruth KS	10/02/2020	Nat Med
rs117573122	rs6258	SHBG	Total testosterone levels	Ruth KS	10/02/2020	Nat Med
rs117573122	rs6258	SHBG	Bioavailable testosterone levels	Ruth KS	10/02/2020	Nat Med
rs117573122	rs6258	SHBG	Heel bone mineral density	Kim SK	26/07/2018	PLoS One
rs117573122	rs6258	SHBG	Sex hormone-binding globulin levels	Barton AR	05/07/2021	Nat Genet
rs117573122	rs6258	SHBG	Heel bone mineral density T score	Barton AR	05/07/2021	Nat Genet
rs727428	rs858516	SHBG - ATP1B2	Testosterone levels	Pott J	06/06/2019	J Clin Endocrinol Metab
rs727428	rs858516	SHBG - ATP1B2	Waist-hip ratio	Pulit SL	14/09/2018	Hum Mol Genet
rs727428	rs858516	SHBG - ATP1B2	Bioavailable testosterone levels	Harrison S	28/07/2021	Sci Adv
rs727428	rs858516	SHBG - ATP1B2	Sex hormone-binding globulin levels	Harrison S	28/07/2021	Sci Adv
rs727428	rs858516	SHBG - ATP1B2	Glycated hemoglobin levels	Chen J	31/05/2021	Nat Genet
rs727428	rs727428	SHBG - ATP1B2	Androgen levels	Jin G	30/08/2012	Hum Mol Genet
rs727428	rs727428	SHBG - ATP1B2	Blood protein levels	Sun W	17/08/2016	PLoS Genet
rs727428	rs727428	SHBG - ATP1B2	Waist-to-hip ratio adjusted for BMI	Zhu Z	24/10/2019	J Allergy Clin Immunol
rs727428	rs727428	SHBG - ATP1B2	Subcortical volume (MOSTest)	van der Meer D	14/07/2020	Nat Commun
rs727428	rs727428	SHBG - ATP1B2	Waist-to-hip ratio adjusted for BMI	Pulit SL	14/09/2018	Hum Mol Genet
rs727428	rs727428	SHBG - ATP1B2	Waist-to-hip ratio adjusted for BMI	Lotta LA	01/12/2018	JAMA
rs727428	rs727428	SHBG - ATP1B2	Waist-hip ratio	Lotta LA	01/12/2018	JAMA
rs727428	rs727428	SHBG - ATP1B2	Waist-hip ratio	Pulit SL	14/09/2018	Hum Mol Genet
rs727428	rs727428	SHBG - ATP1B2	Sex hormone-binding globulin levels	Prescott J	04/06/2012	PLoS One
rs727428	rs727428	SHBG - ATP1B2	Estradiol levels	Ruth KS	10/02/2020	Nat Med



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rs727428	rs727428	SHBG - ATP1B2	Bioavailable testosterone levels	Ruth KS	10/02/2020	Nat Med
rs727428	rs727428	SHBG - ATP1B2	Triglycerides	Klarin D	01/10/2018	Nat Genet
rs727428	rs727428	SHBG - ATP1B2	Bioavailable testosterone levels	Harrison S	28/07/2021	Sci Adv
rs727428	rs727428	SHBG - ATP1B2	Free testosterone levels	Harrison S	28/07/2021	Sci Adv
rs727428	rs727428	SHBG - ATP1B2	Sex hormone-binding globulin levels	Harrison S	28/07/2021	Sci Adv
rs727428	rs727428	SHBG - ATP1B2	Waist-to-hip ratio adjusted for BMI	Christakoudi S	21/05/2021	Sci Rep
rs727428	rs727428	SHBG - ATP1B2	Estradiol levels	Haas CB	22/02/2022	Endocrinology
rs727428	rs727428	SHBG - ATP1B2	Estradiol levels in premenopausal women	Haas CB	22/02/2022	Endocrinology
rs727428	rs727428	SHBG - ATP1B2	Sex hormone-binding globulin levels	Thareja G	28/09/2022	Hum Mol Genet
rs727428	rs727428	SHBG - ATP1B2	A body shape index	Christakoudi S	21/05/2021	Sci Rep
rs727428	rs727428	SHBG - ATP1B2	Sex hormone-binding globulin levels	Katz DH	24/11/2021	Circulation
rs727428	rs727428	SHBG - ATP1B2	Waist-hip index	Christakoudi S	21/05/2021	Sci Rep
rs727428	rs727428	SHBG - ATP1B2	Hemoglobin A1c levels	Sakaue S	30/09/2021	Nat Genet
rs727428	rs2955617	SHBG - ATP1B2	Body fat percentage and HDL-C (pairwise)	Huang LO	22/02/2021	Nat Metab
rs727428	rs2955617	SHBG - ATP1B2	Waist circumference adjusted for body mass index	Christakoudi S	21/05/2021	Sci Rep
rs727428	rs1641523	SHBG - ATP1B2	Type 2 diabetes (adjusted for BMI)	Mahajan A	08/10/2018	Nat Genet
rs727428	rs1641523	SHBG - ATP1B2	Serum levels of protein ATP1B2	Gudjonsson A	25/01/2022	Nat Commun
rs727428	rs1624085	ATP1B2	Waist circumference adjusted for body mass index	Christakoudi S	21/05/2021	Sci Rep
rs727428	rs1642762	ATP1B2	Blood protein levels	Sun BB	06/06/2018	Nature
rs727428	rs1642764	ATP1B2	Esophageal squamous cell carcinoma	Wu C	17/08/2014	Nat Genet
rs727428	rs1642764	ATP1B2	Waist circumference adjusted for body mass index	Zhu Z	24/10/2019	J Allergy Clin Immunol
rs727428	rs1642764	ATP1B2	Platelet count	Chen MH	01/09/2020	Cell
rs727428	rs1642764	ATP1B2	Platelet count	Vuckovic D	01/09/2020	Cell

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*Note.* List of single-nucleotide polymorphisms (SNPs) and reported traits from studies included in the GWAS Catalog<sup>38</sup> based on independent significant SNPs identified in the GWAS summary statistics of continuous estradiol levels (see Supplementary Table 6). Table created using FUMA<sup>17</sup>. SNP: All SNPs from the GWAS Catalog<sup>38</sup> in linkage disequilibrium of the identified independent significant SNPs.

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Table 16. Reported Traits in the GWAS Catalog for SNPs found in GWAS of Binary Estradiol Levels.

Independent Significant SNP	SNP	Mapped Gene	Trait	First Author	Date	Journal
rs4693089	rs4235062	HELQ	Aerodigestive squamous cell cancer (pleiotropy)	Lesseur C	05/03/2021	PLoS Genet
rs693162	rs7665103	HELQ	Menopause (age at onset)	Horikoshi M	17/05/2018	Nat Commun
rs4693089	rs4693089	HELQ	Menopause (age at onset)	Day FR	01/11/2015	Nat Genet
rs4693089	rs4693089	HELQ	Menarche (age at onset)	Horikoshi M	17/05/2018	Nat Commun
rs4693089	rs4693089	HELQ	Menopause (age at onset)	Stolk L	22/01/2012	Nat Genet
rs4693089	rs1494961	HELQ	Oral cavity and pharyngeal cancer	McKay JD	17/03/2011	PLoS Genet
rs4693089	rs1565909	ABRAXAS1	Age at menopause	Kichaev G	27/12/2018	Am J Hum Genet
rs4693089	rs6834006	ABRAXAS1	AFP levels	Lee CJ	03/11/2022	Commun Biol
rs4693089	rs1963045	GPAT3	Breast cancer	Michailidou K	23/10/2017	Nature
rs7718874	rs6861925	HK3	Uterine fibroids	Rafnar T	07/09/2018	Nat Commun
rs7718874	rs6861925	HK3	Educational attainment (years of education)	Lee JJ	23/07/2018	Nat Genet
rs7718874	rs6861925	HK3	Educational attainment (MTAG)	Lee JJ	23/07/2018	Nat Genet
rs7718874	rs365132	UIMC1	Menopause (age at onset)	Day FR	01/11/2015	Nat Genet
rs7718874	rs365132	UIMC1	Menarche (age at onset)	Horikoshi M	17/05/2018	Nat Commun
rs7718874	rs365132	UIMC1	Menarche and menopause (age at onset)	He C	17/05/2009	Nat Genet
rs7718874	rs365132	UIMC1	Menopause (age at onset)	Stolk L	22/01/2012	Nat Genet
rs352943	rs394335	UIMC1	Waist circumference adjusted for body mass index	Zhu Z	24/10/2019	J Allergy Clin Immunol
rs7718874	rs353474	UIMC1	Educational attainment (years of education)	Lee JJ	23/07/2018	Nat Genet
rs7718874	rs353490	UIMC1	Highest math class taken (MTAG)	Lee JJ	23/07/2018	Nat Genet
rs352943	rs7726380	UIMC1	Waist circumference adjusted for body mass index	Christakoudi S	21/05/2021	Sci Rep
rs7718874	rs58279426	UIMC1	Age at menopause	Kichaev G	27/12/2018	Am J Hum Genet
rs7718874	rs58400555	ZNF346	Uterine fibroids	Rafnar T	07/09/2018	Nat Commun
rs7718874	rs34933909	ZNF346	Menopause (age at onset)	Horikoshi M	17/05/2018	Nat Commun
rs7718874	rs34933909	ZNF346	Uterine fibroids	Sakaue S	30/09/2021	Nat Genet
rs7718874	rs2454949	ZNF346	Detectable estradiol levels	Haas CB	22/02/2022	Endocrinology
rs7718874	rs2454949	ZNF346	Detectable estradiol levels in postmenopausal women	Haas CB	22/02/2022	Endocrinology

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rs7718874	rs2454949	ZNF346	Detectable estradiol levels in premenopausal women	Haas CB	22/02/2022	Endocrinology
rs352943	rs166138	ZNF346	Height	Tachmazidou I	01/06/2017	Am J Hum Genet
rs7718874	rs251844	ZNF346	Insomnia	Watanabe K	14/07/2022	Nat Genet
rs7718874	rs251848	ZNF346	Educational attainment	Okbay A	31/03/2022	Nat Genet
rs7718874	rs183686	ZNF346	Noncognitive aspects of educational attainment	Demange PA	07/01/2021	Nat Genet
rs45446698	rs148982377	ZNF789, ZNF394	Sex hormone levels	Ruth KS	27/05/2015	Eur J Hum Genet
rs45446698	rs148982377	ZNF789, ZNF394	Free testosterone levels	Harrison S	28/07/2021	Sci Adv
rs45446698	rs148982377	ZNF789, ZNF394	Bioavailable testosterone levels	Harrison S	28/07/2021	Sci Adv
rs45446698	rs34670419	ZKSCAN5	Urinary metabolite levels in chronic kidney disease	Schlosser P	20/01/2020	Nat Genet
rs45446698	rs34670419	ZKSCAN5	Lumbar spine bone mineral density	Pei YF	27/02/2018	Bone
rs45446698	rs34670419	ZKSCAN5	Femoral neck bone mineral density	Pei YF	27/02/2018	Bone
rs45446698	rs34670419	ZKSCAN5	Total body bone mineral density	Medina-Gomez C	04/01/2018	Am J Hum Genet
rs45446698	rs34670419	ZKSCAN5	Total body bone mineral density (age over 60)	Medina-Gomez C	04/01/2018	Am J Hum Genet
rs45446698	rs34670419	ZKSCAN5	Sex hormone levels	Ruth KS	27/05/2015	Eur J Hum Genet
rs45446698	rs34670419	ZKSCAN5	Endometrial cancer	O'Mara TA	09/08/2018	Nat Commun
rs45446698	rs34670419	ZKSCAN5	Hormone measurements	Wood AR	16/05/2013	PLoS One
rs45446698	rs34670419	ZKSCAN5	Serum uric acid levels	Sakaue S	30/09/2021	Nat Genet
rs45446698	rs118168183	CYP3A51P, CYP3A7-CYP3A51P	5alpha-androstan-3alpha,17alpha-diol monosulfate levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Urinary metabolite modules (eigenmetabolites) in chronic kidney disease	Schlosser P	20/01/2020	Nat Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Urinary metabolite levels in chronic kidney disease	Schlosser P	20/01/2020	Nat Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Heel bone mineral density	Morris JA	31/12/2018	Nat Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Heel bone mineral density	Kichaev G	27/12/2018	Am J Hum Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Serum metabolite levels	Feofanova EV	01/10/2020	Am J Hum Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Height	Kichaev G	27/12/2018	Am J Hum Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Offspring birth weight	Warrington NM	01/05/2019	Nat Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Bioavailable testosterone levels	Ruth KS	10/02/2020	Nat Med

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rs45446698	rs45446698	CYP3A7 - CYP3A4	Blood protein levels	Sun BB	06/06/2018	Nature
rs45446698	rs45446698	CYP3A7 - CYP3A4	Total testosterone levels	Ruth KS	10/02/2020	Nat Med
rs45446698	rs45446698	CYP3A7 - CYP3A4	Heel bone mineral density	Kim SK	26/07/2018	PLoS One
rs45446698	rs45446698	CYP3A7 - CYP3A4	Estrone-3-glucuronide levels	Johnson N	26/01/2021	Br J Cancer
rs45446698	rs45446698	CYP3A7 - CYP3A4	Estradiol levels	Ruth KS	10/02/2020	Nat Med
rs45446698	rs45446698	CYP3A7 - CYP3A4	Testosterone levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Urate levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	Free testosterone levels	Harrison S	28/07/2021	Sci Adv
rs45446698	rs45446698	CYP3A7 - CYP3A4	Bioavailable testosterone levels	Harrison S	28/07/2021	Sci Adv
rs45446698	rs45446698	CYP3A7 - CYP3A4	Total testosterone levels	Harrison S	28/07/2021	Sci Adv
rs45446698	rs45446698	CYP3A7 - CYP3A4	Testosterone levels	Haas CB	22/02/2022	Endocrinology
rs45446698	rs45446698	CYP3A7 - CYP3A4	Testosterone levels in postmenopausal women	Haas CB	22/02/2022	Endocrinology
rs45446698	rs45446698	CYP3A7 - CYP3A4	Estradiol levels	Schmitz D	13/07/2021	J Clin Endocrinol Metab
rs45446698	rs45446698	CYP3A7 - CYP3A4	Testosterone levels in premenopausal women	Haas CB	22/02/2022	Endocrinology
rs45446698	rs45446698	CYP3A7 - CYP3A4	16 $\alpha$ -hydroxy DHEA 3-sulfate levels in elite athletes	Al-Khelaifi F	27/12/2019	Sci Rep
rs45446698	rs45446698	CYP3A7 - CYP3A4	Androstenediol (3 $\alpha$ , 17 $\alpha$ ) monosulfate (3) levels in elite athletes	Al-Khelaifi F	27/12/2019	Sci Rep
rs45446698	rs45446698	CYP3A7 - CYP3A4	C-reactive protein levels	Sinnott-Armstrong N	18/01/2021	Nat Genet
rs45446698	rs45446698	CYP3A7 - CYP3A4	5 $\alpha$ -androstane-3 $\alpha$ ,17 $\beta$ -diol monosulfate (1) levels in elite athletes	Al-Khelaifi F	27/12/2019	Sci Rep
rs45446698	rs45446698	CYP3A7 - CYP3A4	5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol disulfate levels in elite athletes	Al-Khelaifi F	27/12/2019	Sci Rep
rs45446698	rs45446698	CYP3A7 - CYP3A4	Andro steroid monosulfate C19H28O6S (1) levels in elite athletes	Al-Khelaifi F	27/12/2019	Sci Rep
rs45446698	rs45446698	CYP3A7 - CYP3A4	Androsterone sulfate levels in elite athletes	Al-Khelaifi F	27/12/2019	Sci Rep
rs45446698	rs45446698	CYP3A7 - CYP3A4	Epiandrosterone sulfate levels in elite athletes	Al-Khelaifi F	27/12/2019	Sci Rep
rs45446698	rs45446698	CYP3A7 - CYP3A4	X-21470 levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	X-24574 levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	X-24947 levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Metabolonic lactone sulfate levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Tauro-beta-muricholate levels in elite athletes	Al-Khelaifi F	27/12/2019	Sci Rep

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rs45446698	rs45446698	CYP3A7 - CYP3A4	Androsterone sulfate levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	X-21410 levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Epiandrosterone sulfate levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Androstenediol (3beta,17beta) disulfate (1) levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	5alpha-androstan-3alpha,17beta-diol monosulfate (1) levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	5alpha-androstan-3beta,17alpha-diol disulfate levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	5alpha-androstan-3beta,17beta-diol monosulfate (2) levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Androstenediol (3alpha, 17alpha) monosulfate (3) levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Androstenediol (3beta,17beta) monosulfate (2) levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Andro steroid monosulfate C19H28O6S (1) levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	16a-hydroxy DHEA 3-sulfate levels	Yin X	28/03/2022	Nat Commun
rs45446698	rs45446698	CYP3A7 - CYP3A4	Height	Sakaue S	30/09/2021	Nat Genet
rs45446698	rs45467892	CYP3A7 - CYP3A4 RPL12P48 -	Serum metabolite levels	Feofanova EV	01/10/2020	Am J Hum Genet
rs28807105	rs28797500	EIF4EBP1	Age at menopause	Kichaev G	27/12/2018	Am J Hum Genet
rs28807105	rs28807105	EIF4EBP1	Menopause (age at onset)	Horikoshi M	17/05/2018	Nat Commun
rs28807105	rs28807105	EIF4EBP1	Detectable estradiol levels	Haas CB	22/02/2022	Endocrinology
rs28807105	rs28807105	EIF4EBP1	Detectable estradiol levels in postmenopausal women	Haas CB	22/02/2022	Endocrinology
rs28807105	rs28807105	EIF4EBP1	Detectable estradiol levels in premenopausal women	Haas CB	22/02/2022	Endocrinology
rs77100210	rs77100210	YBX3 - LINC02366	Age at menopause	Kichaev G	27/12/2018	Am J Hum Genet
rs75770066	rs75770066	HELB	Menopause (age at onset)	Day FR	01/11/2015	Nat Genet
rs75770066	rs75770066	HELB	Age at menopause	Kichaev G	27/12/2018	Am J Hum Genet
rs75770066	rs75770066	HELB	Detectable estradiol levels	Haas CB	22/02/2022	Endocrinology
rs75770066	rs75770066	HELB	Detectable estradiol levels in postmenopausal women	Haas CB	22/02/2022	Endocrinology
rs75770066	rs75770066	HELB	Detectable estradiol levels in premenopausal women	Haas CB	22/02/2022	Endocrinology

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rs78598096	rs78598096	GRIP1	Heel bone mineral density	Kichaev G	27/12/2018	Am J Hum Genet
rs7185589	rs7189510	BCAR4	Red blood cell count	Chen MH	01/09/2020	Cell
rs7185589	rs4561483	BCAR4	Testicular germ cell tumor	Wang Z	12/06/2017	Nat Genet
rs7185589	rs4561483	BCAR4	Testicular germ cell tumor	Litchfield K	12/06/2017	Nat Genet
rs7185589	rs4561483	BCAR4	Testicular germ cell tumor	Litchfield K	27/10/2015	Nat Commun
rs7185589	rs2018199	RSL1D1	Adolescent idiopathic scoliosis	Liu J	17/07/2018	Hum Genet
rs7185589	rs1029285	GSPT1, RSL1D1-DT	Age at menopause	Kichaev G	27/12/2018	Am J Hum Genet
rs7185589	rs33638	GSPT1	Red blood cell count	Vuckovic D	01/09/2020	Cell
rs7185589	rs10852344	GSPT1 - NPIP2	Menopause (age at onset)	Day FR	01/11/2015	Nat Genet
rs7185589	rs10852344	GSPT1 - NPIP2	Menopause (age at onset)	Perry JR	09/01/2013	Hum Mol Genet
rs7185589	rs10852344	GSPT1 - NPIP2	Menopause (age at onset)	Stolk L	22/01/2012	Nat Genet
rs7185589	rs256400	GSPT1 - NPIP2	Blood protein levels	Emilsson V	02/08/2018	Science
rs7185589	rs3850997	NPIP2	Gastric cancer	Du M	20/05/2020	Sci Adv
rs7185589	rs1126889	TNFRSF17, NPIP2	Systolic blood pressure	Kichaev G	27/12/2018	Am J Hum Genet
rs34962991	rs1172821	BRSK1	Breast cancer	Michailidou K	23/10/2017	Nature
rs34962991	rs1172822	BRSK1	Menarche and menopause (age at onset)	He C	17/05/2009	Nat Genet
rs34962991	rs1172822	BRSK1	Menopause (age at onset)	Stolk L	15/05/2009	Nat Genet
rs897798	rs7246479	TMEM150B	Aspartate aminotransferase levels	Chen VL	05/02/2021	Nat Commun
rs34962991	rs34962991	TMEM150B	Age at menopause	Kichaev G	27/12/2018	Am J Hum Genet
rs34962991	rs11668344	TMEM150B	Menopause (age at onset)	Day FR	01/11/2015	Nat Genet
rs34962991	rs11668344	TMEM150B	Menarche (age at onset)	Horikoshi M	17/05/2018	Nat Commun
rs34962991	rs11668344	TMEM150B	Menopause (age at onset)	Perry JR	09/01/2013	Hum Mol Genet
rs34962991	rs11668344	TMEM150B	Menopause (age at onset)	Stolk L	22/01/2012	Nat Genet
rs236167	rs236114	MCM8	Menopause (age at onset)	Stolk L	15/05/2009	Nat Genet
rs16991615	rs16991615	MCM8	Uterine fibroids	Gallagher CS	24/10/2019	Nat Commun
rs16991615	rs16991615	MCM8	Heavy menstrual bleeding	Gallagher CS	24/10/2019	Nat Commun
rs16991615	rs16991615	MCM8	Breast cancer	Michailidou K	23/10/2017	Nature
rs16991615	rs16991615	MCM8	Menopause (age at onset)	Day FR	01/11/2015	Nat Genet
rs16991615	rs16991615	MCM8	Menarche and menopause (age at onset)	He C	17/05/2009	Nat Genet
rs16991615	rs16991615	MCM8	Menopause (age at onset)	Perry JR	09/01/2013	Hum Mol Genet
rs16991615	rs16991615	MCM8	Menopause (age at onset)	Stolk L	22/01/2012	Nat Genet

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rs16991615	rs16991615	MCM8	Uterine fibroids	Rafnar T	07/09/2018	Nat Commun
rs16991615	rs16991615	MCM8	Anti-Mullerian hormone levels in pre-menopausal women of late reproductive age	Ruth KS	14/01/2019	Hum Mol Genet
rs16991615	rs16991615	MCM8	Age at menopause	Kichaev G	27/12/2018	Am J Hum Genet
rs16991615	rs16991615	MCM8	Detectable estradiol levels	Haas CB	22/02/2022	Endocrinology
rs16991615	rs16991615	MCM8	Detectable estradiol levels in postmenopausal women	Haas CB	22/02/2022	Endocrinology
rs16991615	rs16991615	MCM8	Estradiol levels	Schmitz D	13/07/2021	J Clin Endocrinol Metab
rs16991615	rs16991615	MCM8	Detectable estradiol levels in premenopausal women	Haas CB	22/02/2022	Endocrinology
rs16991615	rs16991615	MCM8	Uterine leiomyoma or ER negative breast cancer (pleiotropy)	Wu X	01/07/2022	Am J Hum Genet
rs16991615	rs16991615	MCM8	Uterine leiomyoma or ER positive breast cancer (pleiotropy)	Wu X	01/07/2022	Am J Hum Genet
rs16991615	rs16991615	MCM8	Anti-Mullerian hormone levels	Verdiesen RMG	11/03/2022	Hum Reprod
rs16991615	rs16991615	MCM8	Uterine fibroids	Sakaue S	30/09/2021	Nat Genet

*Note.* List of single-nucleotide polymorphisms (SNPs) and reported traits from studies included in the GWAS Catalog<sup>38</sup> based on independent significant SNPs identified in the GWAS summary statistics of binary estradiol levels (see Supplementary Table 7). Table created using FUMA<sup>17</sup>.

SNP: All SNPs from the GWAS Catalog<sup>38</sup> in linkage disequilibrium of the identified independent significant SNPs.



## Supplementary Information

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