

**Associations between reproductive history, hormone use, *APOE*  $\epsilon$ 4 genotype and cognition in middle- to older-aged women from the UK Biobank.**

Linn R. S. Lindseth <sup>1</sup>, Ann-Marie G. de Lange <sup>2,3,4</sup>, Dennis van der Meer <sup>1,5</sup>, Ingrid Agartz <sup>1,6,7</sup>, Lars T. Westlye <sup>3,8</sup>, Christian K. Tamnes <sup>6,8,9</sup> and Claudia Barth <sup>1,6\*</sup>

<sup>1</sup> NORMENT, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

<sup>2</sup> LREN, Department of Clinical Neurosciences, Centre for Research in Neurosciences, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland

<sup>3</sup> Department of Psychology, University of Oslo, Oslo, Norway

<sup>4</sup> Department of Psychiatry, University of Oxford, Oxford, United Kingdom

<sup>5</sup> School of Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands

<sup>6</sup> Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway

<sup>7</sup> Department of Clinical Neuroscience, Centre for Psychiatry Research, Stockholm Health Care Services, Karolinska Institute, Stockholm County Council, Stockholm, Sweden

<sup>8</sup> NORMENT, Division of Mental Health and Addiction, Oslo University Hospital, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

<sup>9</sup> Department of Psychology, PROMENTA Research Center, University of Oslo, Oslo, Norway

**\*Corresponding author:** Claudia Barth, PhD, E-Mail: [claudia.barth@medisin.uio.no](mailto:claudia.barth@medisin.uio.no)

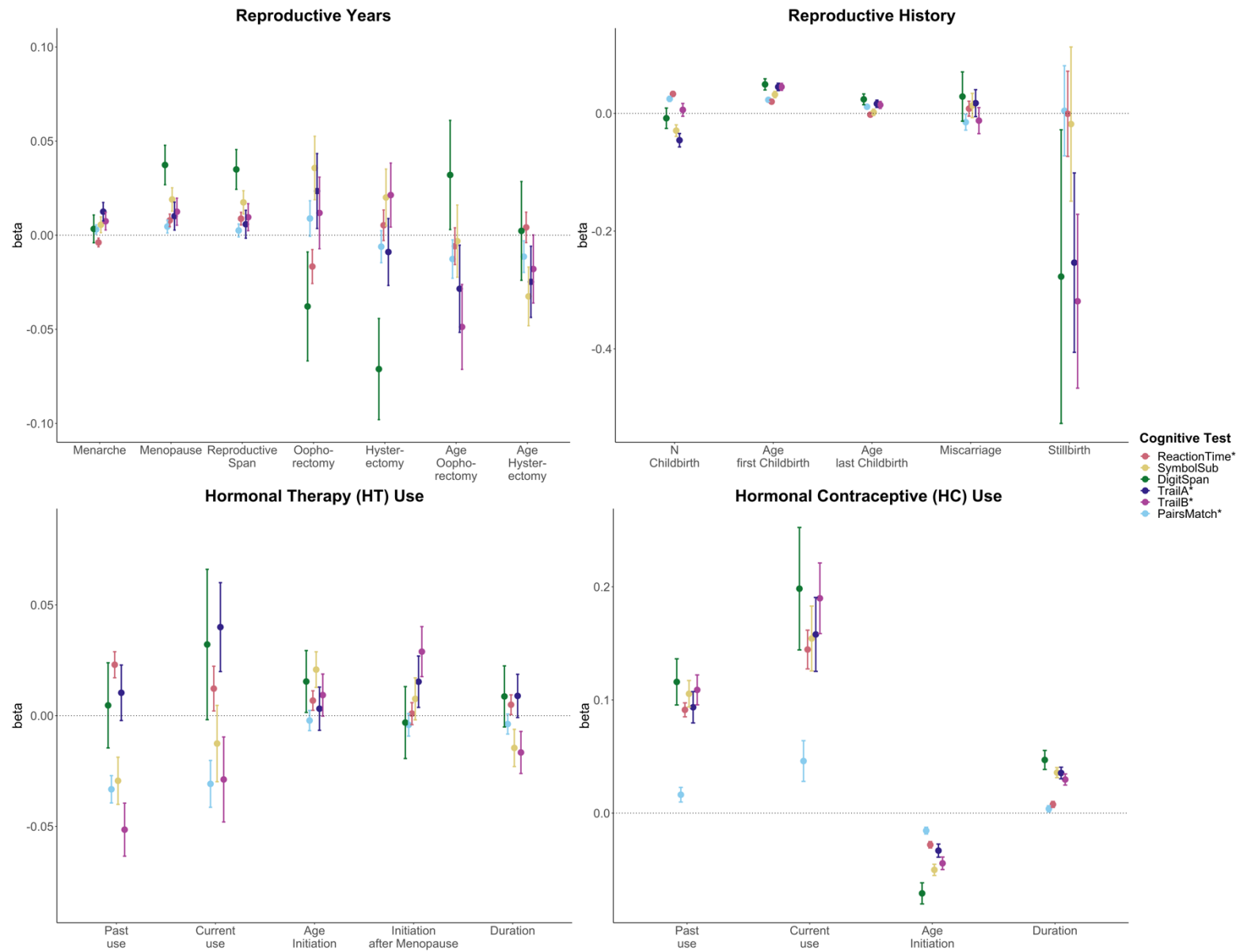
### ***Note 1: Participants with diagnosis known to influence cognition***

Participants with diagnosed brain disorders known to influence cognition were excluded from the main sample (n = 39,011). Brain disorders were based on International Classification of Diseases (ICD)-10 diagnoses (chapter V and VI, field F; mental and behavioral disorders), including F00-F03 for Alzheimer's disease and dementia, and F06.7 ('Mild cognitive disorder'), field G ('Diseases of the nervous system'), including inflammatory and neurodegenerative diseases (except G55-59; 'Nerve, nerve root and plexus disorders') and field I ('Diseases of the circulatory system'), including I64 for stroke. An overview of the diagnoses is provided in the UK Biobank online resources (<https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=41270>), and the diagnostic criteria are listed in the ICD10 diagnostic manual (<https://www.who.int/classifications/icd/icdonlineversions>).

### ***Note 2: Townsend deprivation index and lifestyle score***

The Townsend deprivation index was derived from national census data about car ownership, household overcrowding, owner occupation, and unemployment aggregated for postcodes of residence in the UK<sup>1</sup>. Higher scores reflect higher levels of socioeconomic deprivation. The lifestyle score was calculated based on sleep duration, time spent watching television, current and past smoking status, alcohol consumption frequency, physical activity level, intake of fruits and vegetables, and intake of oily fish, beef, lamb/mutton, pork and processed meat<sup>1</sup>. Each unhealthy lifestyle factor was scored with one point (e.g., smoking), and each participant's points were summed to generate an unweighted score (from 0-9): the higher the lifestyle score, the healthier the participant's lifestyle.

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### **Figure S1| Associations between female-specific factors and cognitive performance.**

Point plot of beta-values with standard error from separate multiple regression analysis with cognitive task as dependent variable and female-specific variables as independent variable. All models are adjusted for age, education, body mass index, Townsend deprivation score, lifestyle score. In addition, the analyses for reproductive span and age at menopause were corrected for use of HT, use of HC, history of hysterectomy and bilateral oophorectomy, and number of live births. The HT models were additionally adjusted for history of hysterectomy and bilateral oophorectomy, and the hysterectomy/oophorectomy model was co-varied for use of HT. All variables were standardized prior to performing the multiple linear regression analysis (subtracting the mean and dividing by the standard deviation). For visualization purposes, cognitive tests marked with \* are inverted (multiplied by -1) so that positive beta-values always indicate associations between higher values on the female-specific variables and better performance on cognitive tests.

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**Table S1| Sample demographics stratified by hormone therapy (HT) user groups.**

|                                          | Never-User    | Current-User | Past-User     | p-value | test     |
|------------------------------------------|---------------|--------------|---------------|---------|----------|
| <b>Total N</b>                           | 138,963       | 12,663       | 60,083        |         |          |
| <b>Age (years)*</b>                      | 53.5 ± 8.0    | 56.7 ± 6.3   | 61.2 ± 5.1    | <0.001  | KW       |
| <b>Age range (years)</b>                 | 39 – 70       | 40 – 70      | 40 – 70       |         |          |
| <b>Education, N (%)</b>                  |               |              |               | <0.001  | $\chi^2$ |
| College/University degree                | 51,475 (37.3) | 4,343 (34.7) | 16,020 (26.9) |         |          |
| O levels/GCSEs or equivalent             | 32,214 (23.3) | 3,017 (24.1) | 14,620 (24.5) |         |          |
| None of the above                        | 15,542 (11.3) | 1,580 (12.6) | 12,965 (21.7) |         |          |
| A levels/AS levels or equivalent         | 18,609 (13.5) | 1,561 (12.5) | 6,233 (10.5)  |         |          |
| Other professional qualifications        | 6,766 (4.9)   | 814 (6.5)    | 4,562 (7.7)   |         |          |
| CSEs or equivalent                       | 8,120 (5.9)   | 673 (5.4)    | 2,320 (3.9)   |         |          |
| NVQ/HND/HNC or equivalent                | 5,337 (3.9)   | 537 (4.3)    | 2,912 (4.9)   |         |          |
| <b>Townsend Deprivation Score*</b>       | -1.5 ± 3.0    | -1.6 ± 2.9   | -1.7 ± 2.9    | <0.001  | KW       |
| <b>Lifestyle score*</b>                  | 2.9 ± 1.6     | 3.0 ± 1.6    | 2.9 ± 1.6     | <0.001  | KW       |
| <b>BMI (kg/m<sup>2</sup>)</b>            | 26.7 ± 5.1    | 26.3 ± 4.5   | 27.1 ± 4.7    | <0.001  | KW       |
| <b>Bilateral Oophorectomy, Yes N (%)</b> | 3,151 (2.3)   | 3,135 (24.8) | 9,458 (15.7)  | <0.001  | $\chi^2$ |
| <b>Hysterectomy, Yes N (%)</b>           | 4,241 (3.2)   | 1,325 (14.9) | 7,540 (15.2)  | <0.001  | $\chi^2$ |
| <b>Age first used HT** (years)</b>       |               | 47.1 ± 5.9   | 47.8 ± 5.1    | <0.001  | KW       |
| <b>Age last used HT** (years)</b>        |               | 56.6 ± 6.3   | 54.1 ± 5.7    | <0.001  | KW       |
| <b>Duration HT use** (years)</b>         |               | 9.4 ± 6.8    | 6.3 ± 5.2     | <0.001  | KW       |

\* Continuous data in mean ± standard deviation and categorical data as number (%).

\*\* Complete data for 12,270 current-users and 58,467 past-users.

Abbreviations: N = Number; O = Ordinary Level Qualification; GCSE = General Certificate of Secondary Education; A = Advanced Level Qualification; AS = Advanced Subsidiary Level Qualification; CSE = Certificate of Secondary Education; NVQ = National Vocational Qualification; HND = Higher National Diploma; HNC = Higher National Certificate; KW = Kruskal-Wallis.

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**Table S2| Sample demographics stratified by hormonal contraceptive (HC) user groups.**

|                                    | Never-User    | Current-User | Past-User     | p-value | test     |
|------------------------------------|---------------|--------------|---------------|---------|----------|
| <b>Total N</b>                     | 39,908        | 4,322        | 160,392       |         |          |
| <b>Age (years)*</b>                | 60.0 ± 7.8    | 45.6 ± 4.0   | 55.3 ± 7.7    | <0.001  | KW       |
| <b>Age range (years)</b>           | 39 – 70       | 40 – 70      | 40 – 70       |         |          |
| <b>Education, N (%)</b>            |               |              |               | <0.001  | $\chi^2$ |
| College/University degree          | 11,215 (28.3) | 1,742 (40.7) | 56,262 (35.3) |         |          |
| O levels/GCSEs or equivalent       | 8,695 (22.0)  | 1,100 (25.7) | 38,212 (24.0) |         |          |
| None of the above                  | 9,794 (24.7)  | 116 (2.7)    | 19,761 (12.4) |         |          |
| A levels/AS levels or equivalent   | 3,863 (9.8)   | 747 (17.4)   | 20,675 (13.0) |         |          |
| Other professional qualifications  | 2,851 (7.2)   | 109 (2.5)    | 8,882 (5.6)   |         |          |
| CSEs or equivalent                 | 1,440 (3.6)   | 333 (7.8)    | 8,844 (5.6)   |         |          |
| NVQ/HND/HNC or equivalent          | 1,737 (4.4)   | 136 (3.2)    | 6,680 (4.2)   |         |          |
| <b>Townsend Deprivation Score*</b> | -1.3 ± 3.0    | -1.3 ± 3.0   | -1.6 ± 2.9    | <0.001  | KW       |
| <b>Lifestyle score*</b>            | 2.8 ± 1.6     | 3.1 ± 1.6    | 2.9 ± 1.6     | <0.001  | KW       |
| <b>BMI (kg/m<sup>2</sup>)</b>      | 27.2 ± 5.2    | 25.8 ± 4.7   | 26.8 ± 4.9    | <0.001  | KW       |
| <b>Age first used HC**</b>         |               | 20.3 ± 5.6   | 21.5 ± 4.6    | <0.001  | KW       |
| <b>Age last used HC** (years)</b>  |               | 45.6 ± 4.0   | 31.9 ± 7.5    | <0.001  | KW       |
| <b>Duration HC use**</b>           |               | 25.2 ± 6.6   | 10.4 ± 7.7    | <0.001  | KW       |

\* Continuous data in mean ± standard deviation and categorical data as number (%).

<sup>x</sup> Complete data for 4,219 current-users and 158,920 past-users.

Abbreviations: N = Number; O = Ordinary Level Qualification; GCSE = General Certificate of Secondary Education; A = Advanced Level Qualification; AS = Advanced Subsidiary Level Qualification; CSE = Certificate of Secondary Education; NVQ = National Vocational Qualification; HND = Higher National Diploma; HNC = Higher National Certificate; KW = Kruskal-Wallis.

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**Table S3| Sample demographics stratified by history of oophorectomy and/or hysterectomy.**

|                                                           | <b>Women<br/>without Surgery</b><br>166,278 | <b>Women<br/>with Hysterectomy</b><br>6,691 | <b>Women<br/>with Bilateral Oophorectomy</b><br>6,445 | p-value | test     |
|-----------------------------------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------------|---------|----------|
| <b>Total N</b>                                            |                                             |                                             |                                                       |         |          |
| <b>Age (years)*</b>                                       | 55.4 ± 8.1                                  | 61.8 ± 5.5                                  | 61.1 ± 5.8                                            | <0.001  | KW       |
| <b>Range (years)</b>                                      | 39-70                                       | 40-70                                       | 40-70                                                 |         |          |
| <b>Education, N (%)</b>                                   |                                             |                                             |                                                       | <0.001  | $\chi^2$ |
| College/University degree                                 | 59,082 (35.8)                               | 1,382 (20.8)                                | 1,652 (25.9)                                          |         |          |
| O levels/GCSEs or equivalent                              | 38,481 (23.3)                               | 1,636 (24.6)                                | 1,431 (22.4)                                          |         |          |
| None of the above                                         | 22,176 (13.4)                               | 1,800 (27.1)                                | 1,568 (24.5)                                          |         |          |
| A levels/AS levels or equivalent                          | 20,980 (12.7)                               | 623 (9.4)                                   | 615 (9.6)                                             |         |          |
| Other professional qualifications                         | 9,165 (5.5)                                 | 498 (7.5)                                   | 497 (7.8)                                             |         |          |
| CSEs or equivalent                                        | 8,691 (5.3)                                 | 289 (4.3)                                   | 268 (4.2)                                             |         |          |
| NVQ/HND/HNC or equivalent                                 | 6,574 (4.0)                                 | 416 (6.3)                                   | 356 (5.6)                                             |         |          |
| <b>Townsend Deprivation Score*</b>                        | -1.5 ± 2.9                                  | -1.6 ± 2.9                                  | -1.5 ± 3.0                                            | 0.003   | KW       |
| <b>Lifestyle score*</b>                                   | 2.9 ± 1.6                                   | 2.8 ± 1.5                                   | 2.9 ± 1.6                                             | 0.001   | KW       |
| <b>BMI (kg/m<sup>2</sup>)</b>                             | 26.6 ± 4.9                                  | 27.5 ± 4.7                                  | 27.7 ± 5.2                                            | <0.001  | KW       |
| <b>Menopause, yes N(%)</b>                                | 112,191 (67.5)                              | 6,523 (97.5)                                | 6,381 (99.0)                                          | <0.001  | $\chi^2$ |
| <b>Age at menopause* (years)</b>                          | 50.4 ± 4.4                                  | 43.5 ± 6.9                                  | 47.4 ± 6.3                                            | <0.001  | KW       |
| <b>Range (years)</b>                                      | 18-68                                       | 18-65                                       | 18-66                                                 |         |          |
| <b>Age at hysterectomy* (years)</b>                       |                                             | 44.8 ± 8.9                                  | 49.8 ± 8.0                                            |         |          |
| <b>Range (years)</b>                                      |                                             | 10-69                                       | 17-69                                                 |         |          |
| <b>Age at bilateral oophorectomy* (years)</b>             |                                             |                                             | 50.2 ± 8.1                                            |         |          |
| <b>Range (years)</b>                                      |                                             |                                             | 11-69                                                 |         |          |
| <b>Age at surgery relative to age at menopause, N (%)</b> |                                             |                                             |                                                       |         |          |
| Same Age                                                  |                                             | 4,312 (66.2)                                | 3,151 (49.5)                                          |         |          |
| After Age at Menopause                                    |                                             | 1,634 (25.1)                                | 2,847 (44.7)                                          |         |          |
| Before Age at Menopause                                   |                                             | 567 (8.7)                                   | 366 (5.8)                                             |         |          |

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\* Continuous data in mean  $\pm$  standard deviation and categorical data as number (%).

Abbreviations: N = Number; O = Ordinary Level Qualification; GCSE = General Certificate of Secondary Education; A = Advanced Level Qualification; AS = Advanced Subsidiary Level Qualification; CSE = Certificate of Secondary Education; NVQ = National Vocational Qualification; HND = Higher National Diploma; HNC = Higher National Certificate; KW = Kruskal-Wallis.



**Table S4| Definitions of female-specific variables in the UK Biobank**

| Female specific variable                   | UKB Data-field | ACE touchscreen question                                                       | Coding                                                                                                                       |
|--------------------------------------------|----------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| Age at Menarche                            | 2714           | “How old were you when your periods started?”                                  | Age in years<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                                            |
| Menopause                                  | 2724           | “Have you had your menopause (periods stopped)?”                               | 1 (“Yes”)<br>0 (“No”)<br>2 («Not sure – had a hysterectomy»)<br>3 (“Not sure – other reason”)<br>-3 («Prefer not to answer») |
| Age at Menopause                           | 3581           | “How old were you when your periods stopped?”                                  | Age in years<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                                            |
| Oophorectomy                               | 2834           | “Have you had BOTH ovaries removed?”                                           | 1 (“Yes”)<br>0 (“No”)<br>-5 («Not sure»)<br>-3 («Prefer not to answer»)                                                      |
| Age at Oophorectomy                        | 3882           | “How old were you when you had BOTH ovaries removed?”                          | Age in years<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                                            |
| Hysterectomy                               | 3591           | “Have you had a hysterectomy (womb removed)?”                                  | 1 (“Yes”)<br>0 (“No”)<br>-5 («Not sure»)<br>-3 («Prefer not to answer»)                                                      |
| Age at Hysterectomy                        | 2824           | “How old were you when you had your hysterectomy?”                             | Age in years<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                                            |
| N Childbirth                               | 2734           | “How many children have you given birth to? (please include live births only)” | Number of children<br>-3 («Prefer not to answer»)                                                                            |
| Age last Birth                             | 2764           | “How old were you when you had your LAST child?”                               | Age in years<br>-4 («Do not remember»)<br>-3 («Prefer not to answer»)                                                        |
| Age first Birth                            | 2754           | “How old were you when you had your FIRST child?”                              | Age in years<br>-4 («Do not remember»)<br>-3 («Prefer not to answer»)                                                        |
| Had Stillbirth, Miscarriage or Termination | 2774           | “Have you ever had any stillbirths, spontaneous miscarriages or terminations?” | 1 (“Yes”)<br>0 (“No”)<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                                   |
| N Stillbirths                              | 3829           | “How many stillbirths? (enter 0 if none)”                                      | Number of stillbirths<br>-1 («Do not know»)                                                                                  |

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|                   |      |                                                                         |                                                                                                            |
|-------------------|------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| N Miscarriages    | 3839 | “How many spontaneous miscarriages? (enter 0 if none)”                  | -3 («Prefer not to answer»)<br>Number of miscarriages<br>-1 («Do not know»)<br>-3 («Prefer not to answer») |
| N Terminations    | 3849 | “How many terminations? (enter 0 if none)”                              | Number of miscarriages<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                |
| HT use            | 2814 | “Have you ever used hormone replacement therapy (HRT)?”                 | 1 (“Yes”)<br>0 (“No”)<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                 |
| Age last HT use   | 3546 | “How old were you when you last used HRT?”                              | Age in years<br>-1 («Do not know»)<br>-11 (“Still taking HRT”)<br>-3 («Prefer not to answer»)              |
| Age HT initiation | 3536 | “How old were you when you first used HRT?”                             | Age in years<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                          |
| HC use            | 2784 | “Have you ever taken the contraceptive pill? (include the ‘mini-pill’)  | 1 (“Yes”)<br>0 (“No”)<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                 |
| Age last HC use   | 2804 | “How old were you when you last used the contraceptive pill?”           | Age in years<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)<br>-11 (“Still taking the pill”)         |
| Age HC initiation | 2794 | “About how old were you when you first went on the contraceptive pill?” | Age in years<br>-1 («Do not know»)<br>-3 («Prefer not to answer»)                                          |

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Abbreviation: N = Number, HT = Hormone Therapy, HC = Hormonal Contraceptive.

**Table S5| Sample demographics stratified by APOE ε4 status.**

|                                    | Non-Carrier       | Carrier           | p-value | test           |
|------------------------------------|-------------------|-------------------|---------|----------------|
| <b>Total N</b>                     | <b>153,395</b>    | <b>55,423</b>     |         |                |
| <b>Age (years)*</b>                | 57.0 [50.0, 63.0] | 57.0 [50.0, 63.0] | <0.001  | KW             |
| <b>Education, N (%)</b>            |                   |                   | 0.039   | χ <sup>2</sup> |
| College/University degree          | 51,463 (33.6)     | 18,497 (33.4)     |         |                |
| O levels/GCSEs or equivalent       | 36,225 (23.6)     | 13,369 (24.1)     |         |                |
| None of the above                  | 23,253 (15.2)     | 8,168 (14.7)      |         |                |
| A levels/AS levels or equivalent   | 18,949 (12.4)     | 6,921 (12.5)      |         |                |
| Other professional qualifications  | 8,951 (5.8)       | 3,143 (5.7)       |         |                |
| CSEs or equivalent                 | 7,991 (5.2)       | 2,897 (5.2)       |         |                |
| NVQ/HND/HNC or equivalent          | 6,423 (4.2)       | 2,382 (4.3)       |         |                |
| <b>Townsend Deprivation Score*</b> | -2.3 [-3.7, 0.1]  | -2.3 [-3.7, 0.1]  | 0.003   | KW             |
| <b>Lifestyle score*</b>            | 3.0 [2.0, 4.0]    | 3.0 [2.0, 4.0]    | <0.001  | KW             |
| <b>BMI (kg/m<sup>2</sup>)</b>      | 25.9 [23.3, 29.4] | 25.8 [23.3, 29.3] | <0.001  | KW             |
| <b>APOE ε4 alleles, N (%)</b>      |                   |                   |         |                |
| 1 x ε4 allele                      |                   | 50458 (91.0)      |         |                |
| 2 x ε4 allele                      |                   | 4965 (9.0)        |         |                |

\*Continuous data in median [Interquartile range] and categorical data as number (%).

Abbreviations: N = Number; O = Ordinary Level Qualification; GCSE = General Certificate of Secondary Education; A = Advanced Level Qualification; AS = Advanced Subsidiary Level Qualification; CSE = Certificate of Secondary Education; NVQ = National Vocational Qualification; HND = Higher National Diploma; HNC = Higher National Certificate; KW = Kruskal-Wallis.

**Table S6| ICD-10 codes for autoimmune diseases, metabolic disorders and cancer.**

| Category            | Disorder                                                | ICD10 Code   |
|---------------------|---------------------------------------------------------|--------------|
| Autoimmune disease* | Pernicious anemia                                       | D51          |
| Autoimmune disease  | Autoimmune hemolytic anemia                             | D59.0, D59.1 |
| Autoimmune disease  | Paroxysmal nocturnal haemoglobinuria                    | D59.5        |
| Autoimmune disease  | Acquired pure red cell aplasia                          | D60          |
| Autoimmune disease  | Aplastic anaemia, unspecified                           | D61.9        |
| Autoimmune disease  | Haemorrhagic disorder due to circulating anticoagulants | D68.3        |
| Autoimmune disease  | Other Thrombophilia (e.g. Antiphospholipid syndrome)    | D68.6        |
| Autoimmune disease  | Immune thrombocytopenic purpura                         | D69.2        |
| Autoimmune disease  | Idiopathic thrombocytopenic purpura                     | D69.3        |
| Autoimmune disease  | Other primary thrombocytopenia (e.g. Evans syndrome)    | D69.4        |
| Autoimmune disease  | Sarcoidosis                                             | D86.9        |
| Autoimmune disease  | Autoimmune disease, not elsewhere classified            | D89.89       |
| Autoimmune disease  | Grave's disease                                         | E05.0        |
| Autoimmune disease  | Hashimoto's thyroiditis                                 | E06.3        |
| Autoimmune disease  | Type I diabetes                                         | E10          |
| Autoimmune disease  | Addison disease                                         | E27.2        |
| Autoimmune disease  | Autoimmune polyglandular failure                        | E31.0        |
| Autoimmune disease  | Other encephalitis, myelitis and encephalomyelitis      | G04.8        |
| Autoimmune disease  | Multiple sclerosis                                      | G35          |
| Autoimmune disease  | Neuromyelitis optica                                    | G36.0        |
| Autoimmune disease  | Acute and subacute hemorrhagic leukoencephalitis        | G36.1        |
| Autoimmune disease  | Concentric sclerosis                                    | G37.5        |
| Autoimmune disease  | Neuralgic amyotrophy                                    | G54.5        |
| Autoimmune disease  | Guillain–Barre's syndrome                               | G61.0        |
| Autoimmune disease  | Chronic inflammatory demyelinating polyneuritis         | G61.81       |
| Autoimmune disease  | Myasthenia gravis                                       | G70.0        |
| Autoimmune disease  | Inflammatory myopathy, not elsewhere classified         | G72.4        |
| Autoimmune disease  | Acute rheumatic fever                                   | I00-I02      |
| Autoimmune disease  | Myocarditis, unspecified                                | I51.4        |
| Autoimmune disease  | Raynaud's syndrome                                      | I73.0        |
| Autoimmune disease  | Chronic atrophic gastritis                              | K29.4        |
| Autoimmune disease  | Inflammatory bowel disease                              | K50-K52      |
| Autoimmune disease  | Primary biliary cirrhosis                               | K74.3        |
| Autoimmune disease  | Autoimmune hepatitis                                    | K75.4        |
| Autoimmune disease  | Autoimmune pancreatitis                                 | K86.1        |
| Autoimmune disease  | Celiac disease                                          | K90.0        |
| Autoimmune disease  | Pemphigus                                               | L10          |
| Autoimmune disease  | Bullous pemphigoid                                      | L12.0        |
| Autoimmune disease  | Cicatricial pemphigoid                                  | L12.1        |
| Autoimmune disease  | Dermatitis herpetiformis                                | L13.0        |
| Autoimmune disease  | Other specified bullous disorders                       | L13.8        |

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|                     |                                             |              |
|---------------------|---------------------------------------------|--------------|
| Autoimmune disease  | Autoimmune progesterone dermatitis          | L30.8        |
| Autoimmune disease  | Psoriasis                                   | L40          |
| Autoimmune disease  | Alopecia areata                             | L63          |
| Autoimmune disease  | Vitiligo                                    | L80          |
| Autoimmune disease  | Discoid lupus erythematosus                 | L93.0        |
| Autoimmune disease  | Scleroderma                                 | L94.0, L94.1 |
| Autoimmune disease  | Vasculitis limited to the skin, unspecified | L95.9        |
| Autoimmune disease  | Reactive arthritis                          | M02.9        |
| Autoimmune disease  | Rheumatoid arthritis                        | M06.9        |
| Autoimmune disease  | Juvenile rheumatoid arthritis               | M08.0        |
| Autoimmune disease  | Palindromic rheumatism                      | M12.3        |
| Autoimmune disease  | Systemic connective tissue disorders        | M30-M36      |
| Autoimmune disease  | Ankylosing spondylitis                      | M45.9        |
| Autoimmune disease  | Relapsing polychondritis                    | M94.1        |
| Autoimmune disease  | Salpingitis and oophoritis, unspecified     | N70.9        |
| Cancer              | Malignant neoplasms                         | C00-C97      |
| Metabolic disorders | Metabolic disorders                         | E70-E90      |

\* Autoimmune diseases are selected based on Autoimmune disease list of the Global Autoimmune Institute (<https://www.autoimmuneinstitute.org/resources/autoimmune-disease-list/>)

**Table S7** *Associations between female-specific factors and late life cognition.*

| Model               | Test         | beta   | S.E.  | t      | p               | pFDR         | d      |
|---------------------|--------------|--------|-------|--------|-----------------|--------------|--------|
| Reproductive Span   | PairsMatch   | 0.003  | 0.003 | 0.731  | 0.465           | 0.586        | 0.005  |
|                     | ReactionTime | 0.009  | 0.003 | 2.619  | <b>0.009</b>    | <b>0.025</b> | 0.017  |
|                     | SymbolSub    | 0.017  | 0.006 | 2.817  | <b>0.005</b>    | <b>0.016</b> | 0.035  |
|                     | DigitSpan    | 0.035  | 0.011 | 3.309  | <b>0.001</b>    | <b>0.003</b> | 0.066  |
|                     | TrailA       | 0.006  | 0.007 | 0.784  | 0.433           | 0.566        | 0.010  |
|                     | TrailB       | 0.010  | 0.007 | 1.333  | 0.182           | 0.319        | 0.018  |
| Age at Menarche     | PairsMatch   | 0.003  | 0.002 | 1.271  | 0.204           | 0.336        | 0.006  |
|                     | ReactionTime | -0.004 | 0.002 | -1.675 | 0.094           | 0.191        | -0.008 |
|                     | SymbolSub    | 0.006  | 0.004 | 1.322  | 0.186           | 0.319        | 0.012  |
|                     | DigitSpan    | 0.003  | 0.007 | 0.456  | 0.649           | 0.702        | 0.007  |
|                     | TrailA       | 0.013  | 0.005 | 2.560  | <b>0.010</b>    | <b>0.028</b> | 0.025  |
|                     | TrailB       | 0.007  | 0.005 | 1.591  | 0.112           | 0.220        | 0.016  |
| Age at Menopause    | PairsMatch   | 0.005  | 0.003 | 1.339  | 0.181           | 0.319        | 0.009  |
|                     | ReactionTime | 0.008  | 0.003 | 2.346  | <b>0.019</b>    | <b>0.046</b> | 0.015  |
|                     | SymbolSub    | 0.019  | 0.006 | 3.062  | <b>0.002</b>    | <b>0.008</b> | 0.037  |
|                     | DigitSpan    | 0.037  | 0.010 | 3.564  | <b>3.67e-04</b> | <b>0.001</b> | 0.071  |
|                     | TrailA       | 0.010  | 0.007 | 1.365  | 0.172           | 0.319        | 0.018  |
|                     | TrailB       | 0.012  | 0.007 | 1.737  | 0.082           | 0.172        | 0.023  |
| Oophorectomy        | PairsMatch   | 0.009  | 0.009 | 0.941  | 0.347           | 0.487        | 0.009  |
|                     | ReactionTime | -0.017 | 0.009 | -1.846 | 0.065           | 0.141        | -0.017 |
|                     | SymbolSub    | 0.036  | 0.017 | 2.120  | <b>0.034</b>    | 0.079        | 0.040  |
|                     | DigitSpan    | -0.038 | 0.029 | -1.308 | 0.191           | 0.319        | -0.037 |
|                     | TrailA       | 0.023  | 0.020 | 1.178  | 0.239           | 0.371        | 0.024  |
|                     | TrailB       | 0.012  | 0.019 | 0.622  | 0.534           | 0.618        | 0.013  |
| Age at Oophorectomy | PairsMatch   | -0.013 | 0.010 | -1.241 | 0.215           | 0.346        | -0.022 |
|                     | ReactionTime | -0.006 | 0.010 | -0.597 | 0.550           | 0.632        | -0.011 |
|                     | SymbolSub    | -0.003 | 0.019 | -0.164 | 0.870           | 0.897        | -0.006 |
|                     | DigitSpan    | 0.032  | 0.029 | 1.104  | 0.270           | 0.397        | 0.061  |
|                     | TrailA       | -0.028 | 0.023 | -1.228 | 0.220           | 0.349        | -0.049 |
|                     | TrailB       | -0.049 | 0.023 | -2.161 | <b>0.031</b>    | 0.073        | -0.086 |
| Hysterectomy        | PairsMatch   | -0.006 | 0.009 | -0.716 | 0.474           | 0.590        | -0.006 |
|                     | ReactionTime | 0.005  | 0.008 | 0.650  | 0.515           | 0.613        | 0.006  |
|                     | SymbolSub    | 0.020  | 0.015 | 1.329  | 0.184           | 0.319        | 0.023  |
|                     | DigitSpan    | -0.071 | 0.027 | -2.648 | <b>0.008</b>    | <b>0.025</b> | -0.072 |
|                     | TrailA       | -0.009 | 0.018 | -0.502 | 0.616           | 0.683        | -0.009 |
|                     | TrailB       | 0.021  | 0.017 | 1.254  | 0.210           | 0.342        | 0.023  |
| Age at Hysterectomy | PairsMatch   | -0.011 | 0.008 | -1.354 | 0.176           | 0.319        | -0.022 |
|                     | ReactionTime | 0.004  | 0.008 | 0.513  | 0.608           | 0.680        | 0.008  |
|                     | SymbolSub    | -0.033 | 0.016 | -2.085 | <b>0.037</b>    | 0.084        | -0.068 |
|                     | DigitSpan    | 0.002  | 0.026 | 0.087  | 0.931           | 0.945        | 0.005  |
|                     | TrailA       | -0.025 | 0.019 | -1.311 | 0.190           | 0.319        | -0.046 |

# SUPPLEMENTARY MATERIAL

|                           |              |        |       |        |                 |                 |        |
|---------------------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| N Childbirth              | TrailB       | -0.018 | 0.018 | -0.993 | 0.321           | 0.465           | -0.035 |
|                           | PairsMatch   | 0.025  | 0.004 | 5.628  | <b>1.82e-08</b> | <b>1.05e-07</b> | 0.027  |
|                           | ReactionTime | 0.033  | 0.004 | 7.785  | <b>6.99e-15</b> | <b>1.03e-13</b> | 0.037  |
|                           | SymbolSub    | -0.029 | 0.010 | -2.978 | <b>0.003</b>    | <b>0.010</b>    | -0.027 |
|                           | DigitSpan    | -0.008 | 0.017 | -0.474 | 0.636           | 0.693           | -0.007 |
|                           | TrailA       | -0.046 | 0.011 | -4.002 | <b>6.29e-05</b> | <b>2.68e-04</b> | -0.039 |
| N Childbirth <sup>2</sup> | TrailB       | 0.006  | 0.011 | 0.555  | 0.579           | 0.655           | 0.005  |
|                           | PairsMatch   | -0.011 | 0.004 | -2.533 | <b>0.011</b>    | <b>0.029</b>    | -0.012 |
|                           | ReactionTime | -0.033 | 0.004 | -7.631 | <b>2.34e-14</b> | <b>3.09e-13</b> | -0.036 |
|                           | SymbolSub    | -0.011 | 0.012 | -0.888 | 0.374           | 0.515           | -0.008 |
|                           | DigitSpan    | -0.013 | 0.019 | -0.694 | 0.488           | 0.601           | -0.010 |
|                           | TrailA       | -0.010 | 0.014 | -0.665 | 0.506           | 0.613           | -0.006 |
| Age last Birth            | TrailB       | -0.028 | 0.014 | -2.059 | <b>0.039</b>    | 0.088           | -0.020 |
|                           | PairsMatch   | 0.011  | 0.003 | 3.780  | <b>1.57e-04</b> | <b>0.001</b>    | 0.022  |
|                           | ReactionTime | -0.002 | 0.003 | -0.741 | 0.459           | 0.586           | -0.004 |
|                           | SymbolSub    | 0.002  | 0.005 | 0.350  | 0.726           | 0.779           | 0.004  |
|                           | DigitSpan    | 0.024  | 0.009 | 2.618  | <b>0.009</b>    | <b>0.025</b>    | 0.047  |
|                           | TrailA       | 0.016  | 0.006 | 2.642  | <b>0.008</b>    | <b>0.025</b>    | 0.032  |
| Age first Birth           | TrailB       | 0.014  | 0.006 | 2.431  | <b>0.015</b>    | <b>0.037</b>    | 0.030  |
|                           | PairsMatch   | 0.023  | 0.003 | 7.443  | <b>9.90e-14</b> | <b>1.01e-12</b> | 0.043  |
|                           | ReactionTime | 0.020  | 0.003 | 6.727  | <b>1.74e-11</b> | <b>1.35e-10</b> | 0.039  |
|                           | SymbolSub    | 0.032  | 0.005 | 6.001  | <b>1.98e-09</b> | <b>1.31e-08</b> | 0.068  |
|                           | DigitSpan    | 0.049  | 0.009 | 5.209  | <b>1.93e-07</b> | <b>9.44e-07</b> | 0.094  |
|                           | TrailA       | 0.045  | 0.006 | 7.202  | <b>6.11e-13</b> | <b>5.76e-12</b> | 0.088  |
| Miscarriage & Termination | TrailB       | 0.045  | 0.006 | 7.593  | <b>3.24e-14</b> | <b>3.56e-13</b> | 0.093  |
|                           | PairsMatch   | -0.015 | 0.013 | -1.102 | 0.271           | 0.397           | -0.015 |
|                           | ReactionTime | 0.008  | 0.013 | 0.631  | 0.528           | 0.617           | 0.009  |
|                           | SymbolSub    | 0.013  | 0.021 | 0.654  | 0.513           | 0.613           | 0.015  |
|                           | DigitSpan    | 0.029  | 0.042 | 0.684  | 0.494           | 0.603           | 0.030  |
|                           | TrailA       | 0.017  | 0.023 | 0.761  | 0.447           | 0.578           | 0.019  |
| Stillbirth                | TrailB       | -0.012 | 0.022 | -0.553 | 0.580           | 0.655           | -0.014 |
|                           | PairsMatch   | 0.004  | 0.077 | 0.058  | 0.954           | 0.961           | 0.005  |
|                           | ReactionTime | -0.001 | 0.072 | -0.009 | 0.993           | 0.993           | -0.001 |
|                           | SymbolSub    | -0.018 | 0.131 | -0.138 | 0.890           | 0.911           | -0.021 |
|                           | DigitSpan    | -0.277 | 0.249 | -1.111 | 0.266           | 0.397           | -0.288 |
|                           | TrailA       | -0.254 | 0.152 | -1.663 | 0.096           | 0.193           | -0.274 |
| Current HT use            | TrailB       | -0.319 | 0.148 | -2.161 | <b>0.031</b>    | 0.073           | -0.356 |
|                           | PairsMatch   | -0.031 | 0.011 | -2.911 | <b>0.004</b>    | <b>0.012</b>    | -0.026 |
|                           | ReactionTime | 0.012  | 0.010 | 1.212  | 0.225           | 0.354           | 0.011  |
|                           | SymbolSub    | -0.013 | 0.017 | -0.729 | 0.466           | 0.586           | -0.012 |
|                           | DigitSpan    | 0.032  | 0.034 | 0.947  | 0.344           | 0.487           | 0.016  |
|                           | TrailA       | 0.040  | 0.020 | 1.993  | <b>0.046</b>    | 0.102           | 0.022  |
|                           | TrailB       | -0.029 | 0.019 | -1.501 | 0.133           | 0.255           | -0.017 |

# SUPPLEMENTARY MATERIAL

|                       |              |        |       |         |                 |                 |        |
|-----------------------|--------------|--------|-------|---------|-----------------|-----------------|--------|
| Past HT use           | PairsMatch   | -0.033 | 0.006 | -5.394  | <b>6.89e-08</b> | <b>3.64e-07</b> | -0.048 |
|                       | ReactionTime | 0.023  | 0.006 | 3.911   | <b>9.19e-05</b> | <b>3.79e-04</b> | 0.036  |
|                       | SymbolSub    | -0.029 | 0.011 | -2.763  | <b>0.006</b>    | <b>0.018</b>    | -0.046 |
|                       | DigitSpan    | 0.005  | 0.019 | 0.242   | 0.809           | 0.854           | 0.004  |
|                       | TrailA       | 0.010  | 0.013 | 0.826   | 0.409           | 0.550           | 0.009  |
|                       | TrailB       | -0.051 | 0.012 | -4.299  | <b>1.72e-05</b> | <b>7.56e-05</b> | -0.048 |
| Age HT initiation     | PairsMatch   | -0.002 | 0.005 | -0.478  | 0.633           | 0.693           | -0.004 |
|                       | ReactionTime | 0.007  | 0.004 | 1.546   | 0.122           | 0.237           | 0.013  |
|                       | SymbolSub    | 0.021  | 0.008 | 2.588   | <b>0.010</b>    | <b>0.027</b>    | 0.042  |
|                       | DigitSpan    | 0.015  | 0.014 | 1.105   | 0.269           | 0.397           | 0.029  |
|                       | TrailA       | 0.003  | 0.010 | 0.323   | 0.747           | 0.795           | 0.006  |
|                       | TrailB       | 0.009  | 0.009 | 0.982   | 0.326           | 0.468           | 0.017  |
| Age HT rel. Menopause | PairsMatch   | -0.004 | 0.005 | -0.815  | 0.415           | 0.554           | -0.008 |
|                       | ReactionTime | 0.001  | 0.005 | 0.188   | 0.851           | 0.885           | 0.002  |
|                       | SymbolSub    | 0.008  | 0.009 | 0.802   | 0.422           | 0.558           | 0.016  |
|                       | DigitSpan    | -0.003 | 0.016 | -0.191  | 0.848           | 0.885           | -0.006 |
|                       | TrailA       | 0.015  | 0.012 | 1.323   | 0.186           | 0.319           | 0.028  |
|                       | TrailB       | 0.029  | 0.011 | 2.562   | <b>0.010</b>    | <b>0.028</b>    | 0.054  |
| Duration HT use       | PairsMatch   | -0.004 | 0.005 | -0.836  | 0.403           | 0.548           | -0.007 |
|                       | ReactionTime | 0.005  | 0.004 | 1.112   | 0.266           | 0.397           | 0.009  |
|                       | SymbolSub    | -0.015 | 0.008 | -1.732  | 0.083           | 0.172           | -0.028 |
|                       | DigitSpan    | 0.009  | 0.014 | 0.631   | 0.528           | 0.617           | 0.017  |
|                       | TrailA       | 0.009  | 0.010 | 0.915   | 0.360           | 0.501           | 0.016  |
|                       | TrailB       | -0.017 | 0.009 | -1.751  | 0.080           | 0.170           | -0.031 |
| Current HC use        | PairsMatch   | 0.046  | 0.018 | 2.558   | <b>0.011</b>    | <b>0.028</b>    | 0.021  |
|                       | ReactionTime | 0.145  | 0.017 | 8.440   | <b>3.19e-17</b> | <b>8.41e-16</b> | 0.059  |
|                       | SymbolSub    | 0.154  | 0.029 | 5.387   | <b>7.19e-08</b> | <b>3.65e-07</b> | 0.069  |
|                       | DigitSpan    | 0.198  | 0.054 | 3.666   | <b>2.47e-04</b> | <b>0.001</b>    | 0.072  |
|                       | TrailA       | 0.158  | 0.033 | 4.836   | <b>1.33e-06</b> | <b>6.07e-06</b> | 0.068  |
|                       | TrailB       | 0.190  | 0.031 | 6.085   | <b>1.18e-09</b> | <b>8.64e-09</b> | 0.087  |
| Past HC use           | PairsMatch   | 0.016  | 0.006 | 2.521   | <b>0.012</b>    | <b>0.030</b>    | 0.020  |
|                       | ReactionTime | 0.091  | 0.006 | 14.795  | <b>1.70e-49</b> | <b>2.25e-47</b> | 0.113  |
|                       | SymbolSub    | 0.105  | 0.012 | 9.023   | <b>1.89e-19</b> | <b>6.25e-18</b> | 0.116  |
|                       | DigitSpan    | 0.116  | 0.020 | 5.688   | <b>1.30e-08</b> | <b>7.83e-08</b> | 0.113  |
|                       | TrailA       | 0.094  | 0.014 | 6.763   | <b>1.37e-11</b> | <b>1.13e-10</b> | 0.089  |
|                       | TrailB       | 0.109  | 0.013 | 8.239   | <b>1.79e-16</b> | <b>3.93e-15</b> | 0.117  |
| Age HC initiation     | PairsMatch   | -0.015 | 0.003 | -5.195  | <b>2.05e-07</b> | <b>9.65e-07</b> | -0.028 |
|                       | ReactionTime | -0.028 | 0.003 | -9.927  | <b>3.22e-23</b> | <b>1.42e-21</b> | -0.053 |
|                       | SymbolSub    | -0.050 | 0.005 | -10.117 | <b>4.94e-24</b> | <b>3.26e-22</b> | -0.100 |
|                       | DigitSpan    | -0.071 | 0.009 | -7.603  | <b>3.08e-14</b> | <b>3.56e-13</b> | -0.126 |
|                       | TrailA       | -0.033 | 0.006 | -5.699  | <b>1.21e-08</b> | <b>7.63e-08</b> | -0.060 |
|                       | TrailB       | -0.044 | 0.006 | -8.014  | <b>1.15e-15</b> | <b>1.89e-14</b> | -0.085 |
| Duration HC use       | PairsMatch   | 0.004  | 0.003 | 1.385   | 0.166           | 0.313           | 0.008  |



# SUPPLEMENTARY MATERIAL

|              |       |       |       |                 |                 |       |
|--------------|-------|-------|-------|-----------------|-----------------|-------|
| ReactionTime | 0.008 | 0.003 | 2.934 | <b>0.003</b>    | <b>0.011</b>    | 0.016 |
| SymbolSub    | 0.036 | 0.004 | 8.057 | <b>8.06e-16</b> | <b>1.52e-14</b> | 0.082 |
| DigitSpan    | 0.047 | 0.008 | 5.596 | <b>2.23e-08</b> | <b>1.23e-07</b> | 0.095 |
| TrailA       | 0.035 | 0.005 | 6.908 | <b>4.99e-12</b> | <b>4.39e-11</b> | 0.075 |
| TrailB       | 0.030 | 0.005 | 6.045 | <b>1.51e-09</b> | <b>1.05e-08</b> | 0.066 |

Abbreviation: PairMatch = Pair Matching Test, ReactionTime = Reaction Time Test, SymbolSub = Symbol Substitution Test, DigitSpan = Digit Span Test, Trail A & B = Trail Making Test A & B, N = Number, HT = Hormone Therapy, HC = Hormonal Contraceptive, S.E. = Standard Error, FDR = False Discovery Rate. Significant results are highlighted in bold.

**Table S8| Non-linear effects of number of childbirths on cognitive functioning.**

| N Childbirth  | Reaction Time |       |        |                   | Pair Matching |       |        |                 |
|---------------|---------------|-------|--------|-------------------|---------------|-------|--------|-----------------|
|               | beta          | S.E.  | t      | p                 | beta          | S.E.  | t      | p               |
| 0 (intercept) | -0.036        | 0.005 | -7.032 | <b>2.05e-12</b>   | -0.032        | 0.005 | -5.848 | <b>4.99e-09</b> |
| 1             | 0.035         | 0.008 | 4.362  | <b>1.29e-05</b>   | 0.021         | 0.008 | 2.498  | <b>0.0125</b>   |
| 2             | 0.059         | 0.006 | 9.444  | <b>&lt; 2e-16</b> | 0.031         | 0.007 | 4.767  | <b>1.87e-06</b> |
| 3             | 0.042         | 0.008 | 5.580  | <b>2.40e-08</b>   | 0.051         | 0.008 | 6.524  | <b>6.87e-11</b> |
| 4             | -0.002        | 0.012 | -0.143 | 0.886             | 0.054         | 0.013 | 4.317  | <b>1.58e-05</b> |
| 5             | -0.066        | 0.024 | -2.719 | <b>0.007</b>      | 0.025         | 0.026 | 0.963  | 0.336           |
| 6             | -0.107        | 0.046 | -2.341 | <b>0.019</b>      | 0.022         | 0.047 | 0.467  | 0.640           |
| 7+            | -0.107        | 0.063 | 1.715  | 0.086             | 0.061         | 0.065 | 0.950  | 0.342           |

Abbreviation: N = Number, S.E. = Standard Error

**Table S9| Associations between female-specific factors and late life cognition after removal of extreme values.**

| Model               | Test         | beta   | S.E.  | t      | p               | pFDR            | d      |
|---------------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| Reproductive Span   | PairsMatch   | 0.004  | 0.003 | 1.150  | 0.250           | 0.393           | 0.007  |
|                     | ReactionTime | 0.008  | 0.003 | 2.455  | <b>0.014</b>    | <b>0.038</b>    | 0.016  |
|                     | SymbolSub    | 0.015  | 0.006 | 2.436  | <b>0.015</b>    | <b>0.039</b>    | 0.030  |
|                     | DigitSpan    | 0.037  | 0.010 | 3.538  | <b>4.05e-04</b> | <b>0.002</b>    | 0.072  |
|                     | TrailA       | 0.008  | 0.007 | 1.077  | 0.281           | 0.413           | 0.014  |
|                     | TrailB       | 0.010  | 0.007 | 1.416  | 0.157           | 0.291           | 0.019  |
| Age at Menarche     | PairsMatch   | 0.003  | 0.002 | 1.364  | 0.173           | 0.312           | 0.007  |
|                     | ReactionTime | -0.001 | 0.002 | -0.496 | 0.620           | 0.682           | -0.002 |
|                     | SymbolSub    | 0.007  | 0.004 | 1.598  | 0.110           | 0.220           | 0.015  |
|                     | DigitSpan    | 0.008  | 0.007 | 1.032  | 0.302           | 0.424           | 0.016  |
|                     | TrailA       | 0.013  | 0.005 | 2.614  | <b>0.009</b>    | <b>0.028</b>    | 0.026  |
|                     | TrailB       | 0.008  | 0.005 | 1.710  | 0.087           | 0.186           | 0.017  |
| Age at Menopause    | PairsMatch   | 0.005  | 0.003 | 1.570  | 0.117           | 0.230           | 0.010  |
|                     | ReactionTime | 0.008  | 0.003 | 2.549  | <b>0.011</b>    | <b>0.032</b>    | 0.016  |
|                     | SymbolSub    | 0.017  | 0.006 | 2.763  | <b>0.006</b>    | <b>0.019</b>    | 0.034  |
|                     | DigitSpan    | 0.041  | 0.010 | 3.955  | <b>7.70e-05</b> | <b>3.18e-04</b> | 0.079  |
|                     | TrailA       | 0.012  | 0.007 | 1.722  | 0.085           | 0.184           | 0.023  |
|                     | TrailB       | 0.012  | 0.007 | 1.701  | 0.089           | 0.186           | 0.023  |
| Oophorectomy        | PairsMatch   | 0.009  | 0.009 | 0.941  | 0.347           | 0.477           | 0.009  |
|                     | ReactionTime | -0.017 | 0.009 | -1.846 | 0.065           | 0.148           | -0.017 |
|                     | SymbolSub    | 0.036  | 0.017 | 2.120  | <b>0.034</b>    | 0.085           | 0.040  |
|                     | DigitSpan    | -0.038 | 0.029 | -1.308 | 0.191           | 0.327           | -0.037 |
|                     | TrailA       | 0.023  | 0.020 | 1.178  | 0.239           | 0.379           | 0.024  |
|                     | TrailB       | 0.012  | 0.019 | 0.622  | 0.534           | 0.623           | 0.013  |
| Age at Oophorectomy | PairsMatch   | -0.011 | 0.010 | -1.106 | 0.269           | 0.406           | -0.020 |
|                     | ReactionTime | -0.008 | 0.010 | -0.765 | 0.444           | 0.574           | -0.014 |
|                     | SymbolSub    | 0.000  | 0.019 | 0.025  | 0.980           | 0.987           | 0.001  |
|                     | DigitSpan    | 0.031  | 0.029 | 1.061  | 0.289           | 0.414           | 0.059  |
|                     | TrailA       | -0.018 | 0.023 | -0.771 | 0.441           | 0.574           | -0.031 |
|                     | TrailB       | -0.040 | 0.023 | -1.772 | 0.076           | 0.168           | -0.070 |
| Hysterectomy        | PairsMatch   | -0.006 | 0.009 | -0.716 | 0.474           | 0.582           | -0.006 |
|                     | ReactionTime | 0.005  | 0.008 | 0.650  | 0.515           | 0.613           | 0.006  |
|                     | SymbolSub    | 0.020  | 0.015 | 1.329  | 0.184           | 0.327           | 0.023  |
|                     | DigitSpan    | -0.071 | 0.027 | -2.648 | <b>0.008</b>    | <b>0.026</b>    | -0.072 |
|                     | TrailA       | -0.009 | 0.018 | -0.502 | 0.616           | 0.682           | -0.009 |
|                     | TrailB       | 0.021  | 0.017 | 1.254  | 0.210           | 0.355           | 0.023  |
| Age at Hysterectomy | PairsMatch   | -0.010 | 0.008 | -1.234 | 0.217           | 0.363           | -0.020 |
|                     | ReactionTime | 0.003  | 0.008 | 0.336  | 0.737           | 0.791           | 0.005  |
|                     | SymbolSub    | -0.029 | 0.015 | -1.893 | 0.058           | 0.135           | -0.062 |

# SUPPLEMENTARY MATERIAL

|                           |              |        |       |         |                 |                 |        |
|---------------------------|--------------|--------|-------|---------|-----------------|-----------------|--------|
| N Childbirth              | DigitSpan    | 0.012  | 0.027 | 0.459   | 0.647           | 0.700           | 0.024  |
|                           | TrailA       | -0.025 | 0.019 | -1.323  | 0.186           | 0.327           | -0.047 |
|                           | TrailB       | -0.020 | 0.018 | -1.090  | 0.276           | 0.409           | -0.038 |
|                           | PairsMatch   | 0.026  | 0.006 | 4.423   | <b>9.74e-06</b> | <b>4.43e-05</b> | 0.021  |
|                           | ReactionTime | 0.064  | 0.006 | 11.277  | <b>1.75e-29</b> | <b>1.15e-27</b> | 0.054  |
|                           | SymbolSub    | -0.023 | 0.010 | -2.243  | <b>0.025</b>    | 0.064           | -0.020 |
|                           | DigitSpan    | -0.013 | 0.018 | -0.713  | 0.476           | 0.582           | -0.011 |
| N Childbirth <sup>2</sup> | TrailA       | -0.040 | 0.012 | -3.397  | <b>0.001</b>    | <b>0.003</b>    | -0.033 |
|                           | TrailB       | 0.007  | 0.011 | 0.615   | 0.538           | 0.623           | 0.006  |
|                           | PairsMatch   | -0.012 | 0.006 | -1.955  | 0.051           | 0.119           | -0.009 |
|                           | ReactionTime | -0.063 | 0.006 | -11.023 | <b>3.04e-28</b> | <b>1.34e-26</b> | -0.053 |
|                           | SymbolSub    | -0.017 | 0.011 | -1.502  | 0.133           | 0.252           | -0.014 |
|                           | DigitSpan    | -0.005 | 0.018 | -0.252  | 0.801           | 0.852           | -0.004 |
|                           | TrailA       | -0.014 | 0.013 | -1.070  | 0.285           | 0.413           | -0.010 |
| Age last Birth            | TrailB       | -0.025 | 0.012 | -1.990  | <b>0.047</b>    | 0.112           | -0.019 |
|                           | PairsMatch   | 0.012  | 0.003 | 4.156   | <b>3.24e-05</b> | <b>1.38e-04</b> | 0.024  |
|                           | ReactionTime | -0.003 | 0.003 | -0.872  | 0.383           | 0.521           | -0.005 |
|                           | SymbolSub    | 0.002  | 0.005 | 0.458   | 0.647           | 0.700           | 0.005  |
|                           | DigitSpan    | 0.022  | 0.009 | 2.451   | <b>0.014</b>    | <b>0.038</b>    | 0.044  |
|                           | TrailA       | 0.016  | 0.006 | 2.606   | <b>0.009</b>    | <b>0.028</b>    | 0.032  |
|                           | TrailB       | 0.016  | 0.006 | 2.753   | <b>0.006</b>    | <b>0.019</b>    | 0.034  |
| Age first Birth           | PairsMatch   | 0.022  | 0.003 | 7.191   | <b>6.48e-13</b> | <b>6.58e-12</b> | 0.042  |
|                           | ReactionTime | 0.018  | 0.003 | 6.070   | <b>1.28e-09</b> | <b>9.41e-09</b> | 0.036  |
|                           | SymbolSub    | 0.032  | 0.005 | 5.982   | <b>2.23e-09</b> | <b>1.47e-08</b> | 0.068  |
|                           | DigitSpan    | 0.049  | 0.010 | 5.204   | <b>1.99e-07</b> | <b>1.05e-06</b> | 0.094  |
|                           | TrailA       | 0.043  | 0.006 | 6.914   | <b>4.83e-12</b> | <b>4.56e-11</b> | 0.085  |
|                           | TrailB       | 0.046  | 0.006 | 7.744   | <b>9.96e-15</b> | <b>1.31e-13</b> | 0.095  |
| Miscarriage & Termination | PairsMatch   | -0.015 | 0.013 | -1.102  | 0.271           | 0.406           | -0.015 |
|                           | ReactionTime | 0.008  | 0.013 | 0.631   | 0.528           | 0.623           | 0.009  |
|                           | SymbolSub    | 0.013  | 0.021 | 0.654   | 0.513           | 0.613           | 0.015  |
|                           | DigitSpan    | 0.029  | 0.042 | 0.684   | 0.494           | 0.598           | 0.030  |
|                           | TrailA       | 0.017  | 0.023 | 0.761   | 0.447           | 0.574           | 0.019  |
|                           | TrailB       | -0.012 | 0.022 | -0.553  | 0.580           | 0.650           | -0.014 |
| Stillbirth                | PairsMatch   | 0.004  | 0.077 | 0.058   | 0.954           | 0.968           | 0.005  |
|                           | ReactionTime | -0.001 | 0.072 | -0.009  | 0.993           | 0.993           | -0.001 |
|                           | SymbolSub    | -0.018 | 0.131 | -0.138  | 0.890           | 0.918           | -0.021 |
|                           | DigitSpan    | -0.277 | 0.249 | -1.111  | 0.266           | 0.406           | -0.288 |
|                           | TrailA       | -0.254 | 0.152 | -1.663  | 0.096           | 0.199           | -0.274 |
|                           | TrailB       | -0.319 | 0.148 | -2.161  | <b>0.031</b>    | 0.078           | -0.356 |
| Current HT use            | PairsMatch   | -0.031 | 0.011 | -2.911  | <b>0.004</b>    | <b>0.013</b>    | -0.026 |
|                           | ReactionTime | 0.012  | 0.010 | 1.212   | 0.225           | 0.368           | 0.011  |
|                           | SymbolSub    | -0.013 | 0.017 | -0.729  | 0.466           | 0.580           | -0.012 |
|                           | DigitSpan    | 0.032  | 0.034 | 0.947   | 0.344           | 0.477           | 0.016  |

# SUPPLEMENTARY MATERIAL

|                       |              |        |       |        |                 |                 |        |
|-----------------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| Past HT use           | TrailA       | 0.040  | 0.020 | 1.993  | <b>0.046</b>    | 0.112           | 0.022  |
|                       | TrailB       | -0.029 | 0.019 | -1.501 | 0.133           | 0.252           | -0.017 |
|                       | PairsMatch   | -0.033 | 0.006 | -5.394 | <b>6.89e-08</b> | <b>3.95e-07</b> | -0.048 |
|                       | ReactionTime | 0.023  | 0.006 | 3.911  | <b>9.19e-05</b> | <b>3.68e-04</b> | 0.036  |
|                       | SymbolSub    | -0.029 | 0.011 | -2.763 | <b>0.006</b>    | <b>0.019</b>    | -0.046 |
| Age HT initiation     | DigitSpan    | 0.005  | 0.019 | 0.242  | 0.809           | 0.854           | 0.004  |
|                       | TrailA       | 0.010  | 0.013 | 0.826  | 0.409           | 0.550           | 0.009  |
|                       | TrailB       | -0.051 | 0.012 | -4.299 | <b>1.72e-05</b> | <b>7.56e-05</b> | -0.048 |
|                       | PairsMatch   | 0.000  | 0.005 | -0.088 | 0.930           | 0.951           | -0.001 |
|                       | ReactionTime | 0.006  | 0.004 | 1.312  | 0.190           | 0.327           | 0.011  |
| Age HT rel. Menopause | SymbolSub    | 0.012  | 0.008 | 1.500  | 0.134           | 0.252           | 0.025  |
|                       | DigitSpan    | 0.010  | 0.014 | 0.745  | 0.456           | 0.574           | 0.020  |
|                       | TrailA       | 0.005  | 0.010 | 0.552  | 0.581           | 0.650           | 0.010  |
|                       | TrailB       | 0.007  | 0.009 | 0.756  | 0.450           | 0.574           | 0.013  |
|                       | PairsMatch   | -0.003 | 0.005 | -0.586 | 0.558           | 0.635           | -0.006 |
| Duration HT use       | ReactionTime | -0.001 | 0.005 | -0.225 | 0.822           | 0.861           | -0.002 |
|                       | SymbolSub    | 0.007  | 0.009 | 0.791  | 0.429           | 0.572           | 0.016  |
|                       | DigitSpan    | -0.003 | 0.016 | -0.197 | 0.844           | 0.877           | -0.006 |
|                       | TrailA       | 0.012  | 0.011 | 1.041  | 0.298           | 0.423           | 0.022  |
|                       | TrailB       | 0.027  | 0.011 | 2.501  | <b>0.012</b>    | <b>0.035</b>    | 0.053  |
| Current HC use        | PairsMatch   | -0.005 | 0.005 | -1.190 | 0.234           | 0.377           | -0.010 |
|                       | ReactionTime | 0.005  | 0.005 | 1.109  | 0.267           | 0.406           | 0.009  |
|                       | SymbolSub    | -0.012 | 0.009 | -1.404 | 0.160           | 0.294           | -0.023 |
|                       | DigitSpan    | 0.010  | 0.014 | 0.744  | 0.457           | 0.574           | 0.020  |
|                       | TrailA       | 0.006  | 0.010 | 0.595  | 0.552           | 0.633           | 0.011  |
| Past HC use           | TrailB       | -0.016 | 0.010 | -1.644 | 0.100           | 0.203           | -0.030 |
|                       | PairsMatch   | 0.046  | 0.018 | 2.558  | <b>0.011</b>    | <b>0.032</b>    | 0.021  |
|                       | ReactionTime | 0.145  | 0.017 | 8.440  | <b>3.19e-17</b> | <b>6.01e-16</b> | 0.059  |
|                       | SymbolSub    | 0.154  | 0.029 | 5.387  | <b>7.19e-08</b> | <b>3.95e-07</b> | 0.069  |
|                       | DigitSpan    | 0.198  | 0.054 | 3.666  | <b>2.47e-04</b> | <b>0.001</b>    | 0.072  |
| Age HC initiation     | TrailA       | 0.158  | 0.033 | 4.836  | <b>1.33e-06</b> | <b>6.28e-06</b> | 0.068  |
|                       | TrailB       | 0.190  | 0.031 | 6.085  | <b>1.18e-09</b> | <b>9.15e-09</b> | 0.087  |
|                       | PairsMatch   | 0.016  | 0.006 | 2.521  | <b>0.012</b>    | <b>0.034</b>    | 0.020  |
|                       | ReactionTime | 0.091  | 0.006 | 14.795 | <b>1.70e-49</b> | <b>2.25e-47</b> | 0.113  |
|                       | SymbolSub    | 0.105  | 0.012 | 9.023  | <b>1.89e-19</b> | <b>4.17e-18</b> | 0.116  |
| Age HC initiation     | DigitSpan    | 0.116  | 0.020 | 5.688  | <b>1.30e-08</b> | <b>7.83e-08</b> | 0.113  |
|                       | TrailA       | 0.094  | 0.014 | 6.763  | <b>1.37e-11</b> | <b>1.21e-10</b> | 0.089  |
|                       | TrailB       | 0.109  | 0.013 | 8.239  | <b>1.79e-16</b> | <b>2.95e-15</b> | 0.117  |
|                       | PairsMatch   | -0.018 | 0.003 | -5.970 | <b>2.37e-09</b> | <b>1.49e-08</b> | -0.032 |
|                       | ReactionTime | -0.027 | 0.003 | -9.142 | <b>6.21e-20</b> | <b>1.64e-18</b> | -0.049 |
| Age HC initiation     | SymbolSub    | -0.050 | 0.005 | -9.676 | <b>4.04e-22</b> | <b>1.33e-20</b> | -0.096 |
|                       | DigitSpan    | -0.073 | 0.010 | -7.395 | <b>1.49e-13</b> | <b>1.79e-12</b> | -0.123 |
|                       | TrailA       | -0.030 | 0.006 | -4.961 | <b>7.04e-07</b> | <b>3.44e-06</b> | -0.053 |

## SUPPLEMENTARY MATERIAL

|                 |              |        |       |        |                 |                 |        |
|-----------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| Duration HC use | TrailB       | -0.042 | 0.006 | -7.335 | <b>2.26e-13</b> | <b>2.49e-12</b> | -0.078 |
|                 | PairsMatch   | 0.003  | 0.003 | 1.211  | 0.226           | 0.368           | 0.007  |
|                 | ReactionTime | 0.005  | 0.003 | 1.786  | 0.074           | 0.166           | 0.010  |
|                 | SymbolSub    | 0.036  | 0.005 | 7.866  | <b>3.76e-15</b> | <b>5.51e-14</b> | 0.081  |
|                 | DigitSpan    | 0.044  | 0.009 | 5.168  | <b>2.40e-07</b> | <b>1.22e-06</b> | 0.089  |
|                 | TrailA       | 0.034  | 0.005 | 6.601  | <b>4.14e-11</b> | <b>3.42e-10</b> | 0.072  |
|                 | TrailB       | 0.030  | 0.005 | 6.057  | <b>1.40e-09</b> | <b>9.72e-09</b> | 0.066  |

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Abbreviation: PairMatch = Pair Matching Test. ReactionTime = Reaction Time Test. SymbolSub = Symbol Substitution Test. DigitSpan = Digit Span Test. Trail A & B = Trail Making Test A & B. N = Number. HT = Hormone Therapy. HC = Hormonal Contraceptive. S.E. = Standard Error. FDR = False Discovery Rate. Significant results are highlighted in bold.

**Table S10| Associations between female-specific factors and late life cognition, including participants with ICD-10 diagnoses known to impact the brain and cognition.**

| Model               | Test         | beta   | S.E.  | t      | p               | pFDR            | d      |
|---------------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| Reproductive Span   | PairsMatch   | 0.001  | 0.003 | 0.370  | 0.712           | 0.794           | 0.002  |
|                     | ReactionTime | 0.014  | 0.003 | 4.368  | <b>1.25e-05</b> | <b>5.01e-05</b> | 0.026  |
|                     | SymbolSub    | 0.021  | 0.006 | 3.545  | <b>3.94e-04</b> | <b>0.001</b>    | 0.042  |
|                     | DigitSpan    | 0.044  | 0.010 | 4.524  | <b>6.13e-06</b> | <b>2.53e-05</b> | 0.084  |
|                     | TrailA       | 0.011  | 0.007 | 1.552  | 0.121           | 0.213           | 0.020  |
|                     | TrailB       | 0.017  | 0.007 | 2.432  | <b>0.015</b>    | <b>0.036</b>    | 0.031  |
| Age at Menarche     | PairsMatch   | 0.003  | 0.002 | 1.279  | 0.201           | 0.320           | 0.006  |
|                     | ReactionTime | -0.005 | 0.002 | -2.120 | <b>0.034</b>    | 0.072           | -0.010 |
|                     | SymbolSub    | 0.005  | 0.004 | 1.236  | 0.216           | 0.332           | 0.011  |
|                     | DigitSpan    | 0.005  | 0.007 | 0.730  | 0.465           | 0.574           | 0.010  |
|                     | TrailA       | 0.013  | 0.005 | 2.761  | <b>0.006</b>    | <b>0.014</b>    | 0.026  |
|                     | TrailB       | 0.009  | 0.004 | 2.114  | <b>0.035</b>    | 0.072           | 0.020  |
| Age at Menopause    | PairsMatch   | 0.003  | 0.003 | 0.928  | 0.353           | 0.471           | 0.005  |
|                     | ReactionTime | 0.013  | 0.003 | 4.132  | <b>3.59e-05</b> | <b>1.40e-04</b> | 0.025  |
|                     | SymbolSub    | 0.023  | 0.006 | 3.778  | <b>1.59e-04</b> | <b>0.001</b>    | 0.044  |
|                     | DigitSpan    | 0.048  | 0.010 | 4.938  | <b>8.00e-07</b> | <b>3.52e-06</b> | 0.091  |
|                     | TrailA       | 0.016  | 0.007 | 2.263  | <b>0.024</b>    | 0.054           | 0.028  |
|                     | TrailB       | 0.022  | 0.007 | 3.148  | <b>0.002</b>    | <b>0.005</b>    | 0.040  |
| Oophorectomy        | PairsMatch   | 0.007  | 0.009 | 0.836  | 0.403           | 0.514           | 0.007  |
|                     | ReactionTime | -0.018 | 0.008 | -2.183 | <b>0.029</b>    | 0.065           | -0.018 |
|                     | SymbolSub    | 0.029  | 0.016 | 1.864  | 0.062           | 0.118           | 0.032  |
|                     | DigitSpan    | -0.052 | 0.026 | -2.000 | <b>0.046</b>    | 0.090           | -0.051 |
|                     | TrailA       | 0.027  | 0.018 | 1.469  | 0.142           | 0.237           | 0.028  |
|                     | TrailB       | 0.014  | 0.018 | 0.769  | 0.442           | 0.550           | 0.014  |
| Age at Oophorectomy | PairsMatch   | -0.014 | 0.009 | -1.525 | 0.127           | 0.221           | -0.025 |
|                     | ReactionTime | 0.005  | 0.009 | 0.537  | 0.591           | 0.697           | 0.009  |
|                     | SymbolSub    | -0.005 | 0.018 | -0.274 | 0.784           | 0.835           | -0.009 |
|                     | DigitSpan    | 0.044  | 0.026 | 1.664  | 0.096           | 0.174           | 0.082  |
|                     | TrailA       | -0.027 | 0.022 | -1.263 | 0.207           | 0.325           | -0.046 |
|                     | TrailB       | -0.039 | 0.021 | -1.864 | 0.062           | 0.118           | -0.068 |
| Hysterectomy        | PairsMatch   | -0.001 | 0.008 | -0.151 | 0.880           | 0.915           | -0.001 |
|                     | ReactionTime | 0.005  | 0.007 | 0.659  | 0.510           | 0.617           | 0.005  |
|                     | SymbolSub    | 0.015  | 0.014 | 1.079  | 0.281           | 0.399           | 0.017  |
|                     | DigitSpan    | -0.072 | 0.024 | -2.995 | <b>0.003</b>    | <b>0.008</b>    | -0.073 |
|                     | TrailA       | -0.014 | 0.017 | -0.833 | 0.405           | 0.514           | -0.014 |
|                     | TrailB       | 0.007  | 0.016 | 0.459  | 0.646           | 0.742           | 0.008  |
| Age at Hysterectomy | PairsMatch   | -0.015 | 0.008 | -1.917 | 0.055           | 0.107           | -0.028 |
|                     | ReactionTime | 0.008  | 0.007 | 1.153  | 0.249           | 0.361           | 0.017  |
|                     | SymbolSub    | -0.022 | 0.015 | -1.509 | 0.131           | 0.225           | -0.045 |
|                     | DigitSpan    | 0.008  | 0.024 | 0.348  | 0.728           | 0.800           | 0.016  |
|                     | TrailA       | -0.015 | 0.018 | -0.878 | 0.380           | 0.502           | -0.029 |
|                     | TrailB       | -0.004 | 0.017 | -0.210 | 0.834           | 0.881           | -0.007 |
| N Childbirth        | PairsMatch   | 0.023  | 0.004 | 5.607  | <b>2.07e-08</b> | <b>1.05e-07</b> | 0.025  |
|                     | ReactionTime | 0.038  | 0.004 | 9.282  | <b>1.68e-20</b> | <b>4.44e-19</b> | 0.041  |
|                     | SymbolSub    | -0.027 | 0.009 | -3.006 | <b>0.003</b>    | <b>0.008</b>    | -0.026 |

# SUPPLEMENTARY MATERIAL

|                           |              |           |       |        |                 |                 |        |
|---------------------------|--------------|-----------|-------|--------|-----------------|-----------------|--------|
| N Childbirth <sup>2</sup> | DigitSpan    | -0.019    | 0.016 | -1.171 | 0.242           | 0.359           | -0.016 |
|                           | TrailA       | -0.043    | 0.011 | -4.119 | <b>3.81e-05</b> | <b>1.44e-04</b> | -0.038 |
|                           | TrailB       | 0.009     | 0.010 | 0.848  | 0.396           | 0.514           | 0.008  |
|                           | PairsMatch   | -0.010    | 0.004 | -2.451 | <b>0.014</b>    | <b>0.035</b>    | -0.011 |
|                           | ReactionTime | -0.037    | 0.004 | -9.037 | <b>1.62e-19</b> | <b>3.57e-18</b> | -0.040 |
|                           | SymbolSub    | -0.014    | 0.011 | -1.281 | 0.200           | 0.320           | -0.011 |
| Age last Birth            | DigitSpan    | 0.001     | 0.018 | 0.068  | 0.946           | 0.960           | 0.001  |
|                           | TrailA       | -0.011    | 0.013 | -0.841 | 0.400           | 0.514           | -0.008 |
|                           | TrailB       | -0.030    | 0.012 | -2.367 | <b>0.018</b>    | <b>0.042</b>    | -0.022 |
|                           | PairsMatch   | 0.009     | 0.003 | 3.084  | <b>0.002</b>    | <b>0.006</b>    | 0.017  |
|                           | ReactionTime | -0.001    | 0.003 | -0.316 | 0.752           | 0.814           | -0.002 |
|                           | SymbolSub    | 0.002     | 0.005 | 0.429  | 0.668           | 0.753           | 0.005  |
| Age first Birth           | DigitSpan    | 0.025     | 0.008 | 2.936  | <b>0.003</b>    | <b>0.009</b>    | 0.049  |
|                           | TrailA       | 0.017     | 0.006 | 2.906  | <b>0.004</b>    | <b>0.010</b>    | 0.034  |
|                           | TrailB       | 0.018     | 0.006 | 3.234  | <b>0.001</b>    | <b>0.004</b>    | 0.038  |
|                           | PairsMatch   | 0.022     | 0.003 | 7.484  | <b>7.23e-14</b> | <b>6.36e-13</b> | 0.041  |
|                           | ReactionTime | 0.022     | 0.003 | 8.052  | <b>8.20e-16</b> | <b>1.08e-14</b> | 0.044  |
|                           | SymbolSub    | 0.033     | 0.005 | 6.398  | <b>1.60e-10</b> | <b>1.24e-09</b> | 0.069  |
| Miscarriage & Termination | DigitSpan    | 0.050     | 0.009 | 5.734  | <b>1.00e-08</b> | <b>5.30e-08</b> | 0.096  |
|                           | TrailA       | 0.046     | 0.006 | 7.650  | <b>2.07e-14</b> | <b>1.96e-13</b> | 0.089  |
|                           | TrailB       | 0.049     | 0.006 | 8.622  | <b>6.90e-18</b> | <b>1.01e-16</b> | 0.101  |
|                           | PairsMatch   | -0.014    | 0.013 | -1.137 | 0.256           | 0.367           | -0.014 |
|                           | ReactionTime | 0.015     | 0.012 | 1.291  | 0.197           | 0.320           | 0.016  |
|                           | SymbolSub    | 0.012     | 0.019 | 0.639  | 0.523           | 0.627           | 0.014  |
| Stillbirth                | DigitSpan    | 0.031     | 0.038 | 0.814  | 0.416           | 0.523           | 0.033  |
|                           | TrailA       | 0.008     | 0.022 | 0.364  | 0.716           | 0.794           | 0.009  |
|                           | TrailB       | -0.021    | 0.021 | -0.979 | 0.328           | 0.446           | -0.023 |
|                           | PairsMatch   | -0.004    | 0.069 | -0.058 | 0.954           | 0.961           | -0.004 |
|                           | ReactionTime | -0.012    | 0.066 | -0.175 | 0.861           | 0.902           | -0.012 |
|                           | SymbolSub    | -0.005    | 0.124 | -0.037 | 0.970           | 0.970           | -0.005 |
| Current HT use            | DigitSpan    | -0.216    | 0.226 | -0.953 | 0.341           | 0.459           | -0.226 |
|                           | TrailA       | -0.247    | 0.144 | -1.714 | 0.087           | 0.159           | -0.265 |
|                           | TrailB       | -0.399    | 0.139 | -2.862 | <b>0.004</b>    | <b>0.011</b>    | -0.443 |
|                           | PairsMatch   | -0.032    | 0.010 | -3.335 | <b>0.001</b>    | <b>0.003</b>    | -0.027 |
|                           | ReactionTime | 0.013     | 0.009 | 1.404  | 0.160           | 0.265           | 0.011  |
|                           | SymbolSub    | -0.008    | 0.016 | -0.513 | 0.608           | 0.704           | -0.008 |
| Past HT use               | DigitSpan    | 0.038     | 0.031 | 1.238  | 0.216           | 0.332           | 0.019  |
|                           | TrailA       | 0.038     | 0.019 | 2.004  | <b>0.045</b>    | 0.090           | 0.021  |
|                           | TrailB       | -0.030    | 0.018 | -1.656 | 0.098           | 0.174           | -0.017 |
|                           | PairsMatch   | -0.034    | 0.006 | -5.885 | <b>4.00e-09</b> | <b>2.29e-08</b> | -0.047 |
|                           | ReactionTime | 0.020     | 0.005 | 3.707  | <b>2.10e-04</b> | <b>0.001</b>    | 0.031  |
|                           | SymbolSub    | -0.032    | 0.010 | -3.166 | <b>0.002</b>    | <b>0.005</b>    | -0.049 |
| Age HT initiation         | DigitSpan    | 0.005     | 0.018 | 0.303  | 0.762           | 0.817           | 0.005  |
|                           | TrailA       | 0.012     | 0.012 | 0.995  | 0.320           | 0.443           | 0.010  |
|                           | TrailB       | -0.051    | 0.011 | -4.534 | <b>5.79e-06</b> | <b>2.47e-05</b> | -0.048 |
|                           | PairsMatch   | -4.23e-04 | 0.004 | -0.101 | 0.920           | 0.941           | -0.001 |
|                           | ReactionTime | 0.009     | 0.004 | 2.129  | <b>0.033</b>    | 0.072           | 0.016  |
|                           | SymbolSub    | 0.021     | 0.008 | 2.817  | <b>0.005</b>    | <b>0.013</b>    | 0.043  |
|                           | DigitSpan    | 0.028     | 0.013 | 2.163  | <b>0.031</b>    | 0.067           | 0.052  |

# SUPPLEMENTARY MATERIAL

|                       |              |        |       |         |                 |                 |        |
|-----------------------|--------------|--------|-------|---------|-----------------|-----------------|--------|
| Age HT rel. Menopause | TrailA       | 0.004  | 0.009 | 0.445   | 0.656           | 0.746           | 0.007  |
|                       | TrailB       | 0.016  | 0.009 | 1.764   | 0.078           | 0.145           | 0.029  |
|                       | PairsMatch   | -0.001 | 0.005 | -0.134  | 0.893           | 0.921           | -0.001 |
|                       | ReactionTime | -0.003 | 0.005 | -0.691  | 0.489           | 0.598           | -0.006 |
|                       | SymbolSub    | 0.005  | 0.009 | 0.520   | 0.603           | 0.704           | 0.009  |
| Duration HT use       | DigitSpan    | -0.016 | 0.015 | -1.039  | 0.299           | 0.419           | -0.030 |
|                       | TrailA       | 0.004  | 0.011 | 0.339   | 0.735           | 0.801           | 0.007  |
|                       | TrailB       | 0.021  | 0.011 | 2.018   | <b>0.044</b>    | 0.089           | 0.040  |
|                       | PairsMatch   | -0.004 | 0.004 | -0.990  | 0.322           | 0.443           | -0.008 |
|                       | ReactionTime | 0.005  | 0.004 | 1.152   | 0.249           | 0.361           | 0.009  |
| Current HC use        | SymbolSub    | -0.009 | 0.008 | -1.175  | 0.240           | 0.359           | -0.018 |
|                       | DigitSpan    | 0.007  | 0.013 | 0.590   | 0.555           | 0.660           | 0.014  |
|                       | TrailA       | 0.011  | 0.009 | 1.193   | 0.233           | 0.353           | 0.020  |
|                       | TrailB       | -0.018 | 0.009 | -2.046  | <b>0.041</b>    | 0.084           | -0.034 |
|                       | PairsMatch   | 0.047  | 0.017 | 2.769   | <b>0.006</b>    | <b>0.014</b>    | 0.021  |
| Past HC use           | ReactionTime | 0.152  | 0.016 | 9.328   | <b>1.09e-20</b> | <b>3.59e-19</b> | 0.062  |
|                       | SymbolSub    | 0.150  | 0.028 | 5.462   | <b>4.73e-08</b> | <b>2.23e-07</b> | 0.067  |
|                       | DigitSpan    | 0.185  | 0.051 | 3.628   | <b>2.86e-04</b> | <b>0.001</b>    | 0.066  |
|                       | TrailA       | 0.158  | 0.031 | 5.053   | <b>4.36e-07</b> | <b>1.98e-06</b> | 0.067  |
|                       | TrailB       | 0.173  | 0.030 | 5.775   | <b>7.74e-09</b> | <b>4.25e-08</b> | 0.078  |
| Age HC initiation     | PairsMatch   | 0.014  | 0.006 | 2.349   | <b>0.019</b>    | <b>0.044</b>    | 0.018  |
|                       | ReactionTime | 0.092  | 0.006 | 16.023  | <b>9.64e-58</b> | <b>1.27e-55</b> | 0.116  |
|                       | SymbolSub    | 0.100  | 0.011 | 9.009   | <b>2.16e-19</b> | <b>4.07e-18</b> | 0.111  |
|                       | DigitSpan    | 0.111  | 0.019 | 5.887   | <b>3.99e-09</b> | <b>2.29e-08</b> | 0.107  |
|                       | TrailA       | 0.083  | 0.013 | 6.338   | <b>2.35e-10</b> | <b>1.73e-09</b> | 0.079  |
| Duration HC use       | TrailB       | 0.098  | 0.013 | 7.764   | <b>8.39e-15</b> | <b>8.52e-14</b> | 0.105  |
|                       | PairsMatch   | -0.017 | 0.003 | -6.007  | <b>1.89e-09</b> | <b>1.19e-08</b> | -0.030 |
|                       | ReactionTime | -0.028 | 0.003 | -10.586 | <b>3.51e-26</b> | <b>1.55e-24</b> | -0.053 |
|                       | SymbolSub    | -0.052 | 0.005 | -10.966 | <b>6.07e-28</b> | <b>4.01e-26</b> | -0.103 |
|                       | DigitSpan    | -0.062 | 0.009 | -7.153  | <b>8.82e-13</b> | <b>7.28e-12</b> | -0.109 |
| Duration HC use       | TrailA       | -0.035 | 0.006 | -6.217  | <b>5.11e-10</b> | <b>3.37e-09</b> | -0.063 |
|                       | TrailB       | -0.042 | 0.005 | -7.841  | <b>4.60e-15</b> | <b>5.52e-14</b> | -0.079 |
|                       | PairsMatch   | 0.004  | 0.003 | 1.470   | 0.141           | 0.237           | 0.008  |
|                       | ReactionTime | 0.008  | 0.002 | 3.424   | <b>0.001</b>    | <b>0.002</b>    | 0.018  |
|                       | SymbolSub    | 0.038  | 0.004 | 8.900   | <b>5.81e-19</b> | <b>9.59e-18</b> | 0.086  |
| Duration HC use       | DigitSpan    | 0.043  | 0.008 | 5.482   | <b>4.26e-08</b> | <b>2.08e-07</b> | 0.087  |
|                       | TrailA       | 0.038  | 0.005 | 7.803   | <b>6.18e-15</b> | <b>6.80e-14</b> | 0.081  |
|                       | TrailB       | 0.029  | 0.005 | 6.227   | <b>4.80e-10</b> | <b>3.33e-09</b> | 0.064  |

Abbreviation: PairMatch = Pair Matching Test. ReactionTime = Reaction Time Test. SymbolSub = Symbol Substitution Test. DigitSpan = Digit Span Test. Trail A & B = Trail Making Test A & B. N = Number. HT = Hormone Therapy. HC = Hormonal Contraceptive. S.E. = Standard Error. FDR = False Discovery Rate. Significant results are highlighted in bold.



**Table S11| Associations between female-specific factors and late life cognition after adjustment for APOE  $\epsilon 4$  genotype.**

| Model               | Test         | beta   | S.E.  | t      | p               | pFDR         | d      |
|---------------------|--------------|--------|-------|--------|-----------------|--------------|--------|
| Reproductive Span   | PairsMatch   | 0.002  | 0.004 | 0.662  | 0.508           | 0.612        | 0.004  |
|                     | ReactionTime | 0.008  | 0.003 | 2.444  | <b>0.015</b>    | <b>0.038</b> | 0.016  |
|                     | SymbolSub    | 0.015  | 0.006 | 2.414  | <b>0.016</b>    | <b>0.041</b> | 0.030  |
|                     | DigitSpan    | 0.037  | 0.011 | 3.404  | <b>0.001</b>    | <b>0.002</b> | 0.070  |
|                     | TrailA       | 0.006  | 0.008 | 0.836  | 0.403           | 0.537        | 0.011  |
|                     | TrailB       | 0.008  | 0.007 | 1.080  | 0.280           | 0.425        | 0.015  |
| Age at Menarche     | PairsMatch   | 0.002  | 0.002 | 0.934  | 0.350           | 0.503        | 0.005  |
|                     | ReactionTime | -0.004 | 0.002 | -1.680 | 0.093           | 0.195        | -0.008 |
|                     | SymbolSub    | 0.006  | 0.004 | 1.335  | 0.182           | 0.324        | 0.013  |
|                     | DigitSpan    | 0.004  | 0.008 | 0.524  | 0.600           | 0.666        | 0.008  |
|                     | TrailA       | 0.013  | 0.005 | 2.521  | <b>0.012</b>    | <b>0.032</b> | 0.025  |
|                     | TrailB       | 0.007  | 0.005 | 1.490  | 0.136           | 0.264        | 0.015  |
| Age at Menopause    | PairsMatch   | 0.004  | 0.004 | 1.072  | 0.284           | 0.426        | 0.007  |
|                     | ReactionTime | 0.007  | 0.003 | 2.029  | <b>0.043</b>    | 0.098        | 0.013  |
|                     | SymbolSub    | 0.017  | 0.006 | 2.640  | <b>0.008</b>    | <b>0.024</b> | 0.033  |
|                     | DigitSpan    | 0.040  | 0.011 | 3.744  | <b>1.82e-04</b> | <b>0.001</b> | 0.076  |
|                     | TrailA       | 0.011  | 0.008 | 1.398  | 0.162           | 0.301        | 0.019  |
|                     | TrailB       | 0.011  | 0.007 | 1.468  | 0.142           | 0.272        | 0.020  |
| Oophorectomy        | PairsMatch   | 0.011  | 0.010 | 1.147  | 0.251           | 0.400        | 0.011  |
|                     | ReactionTime | -0.021 | 0.009 | -2.301 | <b>0.021</b>    | 0.051        | -0.022 |
|                     | SymbolSub    | 0.041  | 0.017 | 2.369  | <b>0.018</b>    | <b>0.045</b> | 0.045  |
|                     | DigitSpan    | -0.039 | 0.030 | -1.328 | 0.184           | 0.324        | -0.039 |
|                     | TrailA       | 0.031  | 0.020 | 1.498  | 0.134           | 0.264        | 0.031  |
|                     | TrailB       | 0.017  | 0.020 | 0.881  | 0.378           | 0.515        | 0.018  |
| Age at Oophorectomy | PairsMatch   | -0.017 | 0.010 | -1.638 | 0.101           | 0.209        | -0.030 |
|                     | ReactionTime | -0.006 | 0.010 | -0.624 | 0.533           | 0.622        | -0.012 |
|                     | SymbolSub    | -0.005 | 0.020 | -0.278 | 0.781           | 0.825        | -0.010 |
|                     | DigitSpan    | 0.038  | 0.030 | 1.270  | 0.204           | 0.339        | 0.072  |
|                     | TrailA       | -0.030 | 0.024 | -1.266 | 0.206           | 0.339        | -0.051 |
|                     | TrailB       | -0.049 | 0.023 | -2.128 | <b>0.033</b>    | 0.079        | -0.087 |
| Hysterectomy        | PairsMatch   | -0.004 | 0.009 | -0.487 | 0.626           | 0.683        | -0.002 |
|                     | ReactionTime | 0.003  | 0.008 | 0.384  | 0.701           | 0.752        | 0.003  |
|                     | SymbolSub    | 0.020  | 0.015 | 1.290  | 0.197           | 0.339        | 0.022  |
|                     | DigitSpan    | -0.071 | 0.028 | -2.571 | <b>0.010</b>    | <b>0.029</b> | -0.071 |
|                     | TrailA       | 0.002  | 0.018 | 0.130  | 0.897           | 0.932        | 0.002  |
|                     | TrailB       | 0.026  | 0.017 | 1.512  | 0.130           | 0.264        | 0.028  |
| Age at Hysterectomy | PairsMatch   | -0.011 | 0.009 | -1.230 | 0.219           | 0.357        | -0.020 |
|                     | ReactionTime | 0.006  | 0.008 | 0.674  | 0.501           | 0.612        | 0.011  |
|                     | SymbolSub    | -0.031 | 0.016 | -1.959 | <b>0.050</b>    | 0.110        | -0.065 |

# SUPPLEMENTARY MATERIAL

|                           |              |        |       |        |                 |                 |        |
|---------------------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| N Childbirth              | DigitSpan    | 0.002  | 0.027 | 0.087  | 0.931           | 0.952           | 0.005  |
|                           | TrailA       | -0.022 | 0.019 | -1.132 | 0.258           | 0.404           | -0.041 |
|                           | TrailB       | -0.017 | 0.018 | -0.909 | 0.364           | 0.511           | -0.033 |
|                           | PairsMatch   | 0.025  | 0.004 | 5.701  | <b>1.19e-08</b> | <b>7.73e-08</b> | 0.028  |
|                           | ReactionTime | 0.032  | 0.004 | 7.434  | <b>1.06e-13</b> | <b>1.55e-12</b> | 0.036  |
|                           | SymbolSub    | -0.031 | 0.010 | -3.052 | <b>0.002</b>    | <b>0.008</b>    | -0.028 |
| N Childbirth <sup>2</sup> | DigitSpan    | -0.009 | 0.018 | -0.528 | 0.598           | 0.666           | -0.008 |
|                           | TrailA       | -0.046 | 0.012 | -3.975 | <b>7.06e-05</b> | <b>2.91e-04</b> | -0.040 |
|                           | TrailB       | 0.008  | 0.011 | 0.711  | 0.477           | 0.597           | 0.007  |
|                           | PairsMatch   | -0.012 | 0.004 | -2.712 | <b>0.007</b>    | <b>0.021</b>    | -0.013 |
|                           | ReactionTime | -0.031 | 0.004 | -7.098 | <b>1.27e-12</b> | 1.19e-11        | -0.035 |
|                           | SymbolSub    | -0.011 | 0.013 | -0.864 | 0.387           | 0.522           | -0.008 |
| Age last Birth            | DigitSpan    | -0.010 | 0.020 | -0.530 | 0.596           | 0.666           | -0.008 |
|                           | TrailA       | -0.011 | 0.015 | -0.725 | 0.468           | 0.595           | -0.007 |
|                           | TrailB       | -0.033 | 0.014 | -2.324 | <b>0.020</b>    | <b>0.049</b>    | -0.023 |
|                           | PairsMatch   | 0.011  | 0.003 | 3.444  | <b>0.001</b>    | <b>0.002</b>    | 0.021  |
|                           | ReactionTime | -0.002 | 0.003 | -0.796 | 0.426           | 0.557           | -0.005 |
|                           | SymbolSub    | 0.000  | 0.005 | 0.069  | 0.945           | 0.960           | 0.001  |
| Age first Birth           | DigitSpan    | 0.027  | 0.009 | 2.916  | <b>0.004</b>    | <b>0.012</b>    | 0.054  |
|                           | TrailA       | 0.016  | 0.006 | 2.514  | <b>0.012</b>    | <b>0.032</b>    | 0.032  |
|                           | TrailB       | 0.012  | 0.006 | 2.000  | <b>0.046</b>    | 0.102           | 0.025  |
|                           | PairsMatch   | 0.023  | 0.003 | 7.173  | <b>7.39e-13</b> | <b>8.06e-12</b> | 0.043  |
|                           | ReactionTime | 0.020  | 0.003 | 6.545  | <b>5.97e-11</b> | <b>4.92e-10</b> | 0.039  |
|                           | SymbolSub    | 0.031  | 0.005 | 5.689  | <b>1.29e-08</b> | <b>7.73e-08</b> | 0.066  |
| Miscarriage & Termination | DigitSpan    | 0.051  | 0.010 | 5.264  | <b>1.43e-07</b> | <b>7.56e-07</b> | 0.097  |
|                           | TrailA       | 0.046  | 0.006 | 7.166  | <b>7.93e-13</b> | <b>8.06e-12</b> | 0.090  |
|                           | TrailB       | 0.044  | 0.006 | 7.247  | <b>4.37e-13</b> | <b>5.24e-12</b> | 0.091  |
|                           | PairsMatch   | -0.020 | 0.014 | -1.411 | 0.158           | 0.299           | -0.020 |
|                           | ReactionTime | 0.012  | 0.013 | 0.888  | 0.375           | 0.515           | 0.012  |
|                           | SymbolSub    | 0.015  | 0.021 | 0.707  | 0.480           | 0.597           | 0.017  |
| Stillbirth                | DigitSpan    | 0.028  | 0.043 | 0.639  | 0.523           | 0.616           | 0.029  |
|                           | TrailA       | 0.014  | 0.023 | 0.594  | 0.552           | 0.634           | 0.015  |
|                           | TrailB       | -0.015 | 0.023 | -0.652 | 0.515           | 0.612           | -0.017 |
|                           | PairsMatch   | -0.001 | 0.080 | -0.018 | 0.986           | 0.986           | -0.001 |
|                           | ReactionTime | 0.037  | 0.075 | 0.494  | 0.621           | 0.683           | 0.040  |
|                           | SymbolSub    | -0.004 | 0.135 | -0.030 | 0.976           | 0.984           | -0.005 |
| Current HT use            | DigitSpan    | -0.169 | 0.259 | -0.654 | 0.513           | 0.612           | -0.176 |
|                           | TrailA       | -0.274 | 0.157 | -1.747 | 0.081           | 0.172           | -0.296 |
|                           | TrailB       | -0.280 | 0.152 | -1.839 | 0.066           | 0.143           | -0.312 |
|                           | PairsMatch   | -0.031 | 0.011 | -2.861 | <b>0.004</b>    | <b>0.014</b>    | -0.026 |
|                           | ReactionTime | 0.012  | 0.010 | 1.126  | 0.260           | 0.404           | 0.010  |
|                           | SymbolSub    | -0.010 | 0.018 | -0.555 | 0.579           | 0.659           | -0.009 |
|                           | DigitSpan    | 0.032  | 0.035 | 0.927  | 0.354           | 0.503           | 0.016  |

# SUPPLEMENTARY MATERIAL

|                       |              |        |       |        |                 |                 |        |
|-----------------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| Past HT use           | TrailA       | 0.041  | 0.021 | 2.008  | <b>0.045</b>    | 0.102           | 0.023  |
|                       | TrailB       | -0.025 | 0.020 | -1.288 | 0.198           | 0.339           | -0.015 |
|                       | PairsMatch   | -0.033 | 0.006 | -5.152 | <b>2.58e-07</b> | <b>1.26e-06</b> | -0.047 |
|                       | ReactionTime | 0.025  | 0.006 | 4.170  | <b>3.05e-05</b> | <b>1.30e-04</b> | 0.039  |
|                       | SymbolSub    | -0.030 | 0.011 | -2.777 | <b>0.005</b>    | <b>0.018</b>    | -0.047 |
|                       | DigitSpan    | 0.007  | 0.020 | 0.353  | 0.724           | 0.771           | 0.006  |
| Age HT initiation     | TrailA       | 0.008  | 0.013 | 0.615  | 0.538           | 0.623           | 0.007  |
|                       | TrailB       | -0.053 | 0.012 | -4.324 | <b>1.53e-05</b> | <b>6.75e-05</b> | -0.049 |
|                       | PairsMatch   | -0.003 | 0.005 | -0.737 | 0.461           | 0.591           | -0.006 |
|                       | ReactionTime | 0.005  | 0.005 | 1.188  | 0.235           | 0.378           | 0.010  |
|                       | SymbolSub    | 0.019  | 0.008 | 2.365  | <b>0.018</b>    | <b>0.045</b>    | 0.040  |
|                       | DigitSpan    | 0.015  | 0.014 | 1.041  | 0.298           | 0.442           | 0.028  |
| Age HT rel. Menopause | TrailA       | 0.001  | 0.010 | 0.095  | 0.924           | 0.952           | 0.002  |
|                       | TrailB       | 0.007  | 0.010 | 0.765  | 0.444           | 0.575           | 0.014  |
|                       | PairsMatch   | -0.004 | 0.005 | -0.816 | 0.414           | 0.547           | -0.008 |
|                       | ReactionTime | 0.001  | 0.005 | 0.187  | 0.852           | 0.892           | 0.002  |
|                       | SymbolSub    | 0.010  | 0.010 | 1.081  | 0.280           | 0.425           | 0.021  |
|                       | DigitSpan    | -0.007 | 0.017 | -0.427 | 0.669           | 0.724           | -0.014 |
| Duration HT use       | TrailA       | 0.011  | 0.012 | 0.965  | 0.335           | 0.485           | 0.021  |
|                       | TrailB       | 0.030  | 0.011 | 2.574  | <b>0.010</b>    | <b>0.029</b>    | 0.055  |
|                       | PairsMatch   | -0.004 | 0.005 | -0.884 | 0.377           | 0.515           | -0.008 |
|                       | ReactionTime | 0.004  | 0.005 | 0.981  | 0.326           | 0.479           | 0.009  |
|                       | SymbolSub    | -0.013 | 0.009 | -1.505 | 0.132           | 0.264           | -0.025 |
|                       | DigitSpan    | 0.009  | 0.014 | 0.666  | 0.506           | 0.612           | 0.018  |
| Current HC use        | TrailA       | 0.013  | 0.010 | 1.280  | 0.201           | 0.339           | 0.023  |
|                       | TrailB       | -0.013 | 0.010 | -1.383 | 0.167           | 0.306           | -0.025 |
|                       | PairsMatch   | 0.050  | 0.018 | 2.692  | <b>0.007</b>    | <b>0.022</b>    | 0.022  |
|                       | ReactionTime | 0.135  | 0.018 | 7.696  | <b>1.41e-14</b> | <b>3.10e-13</b> | 0.055  |
|                       | SymbolSub    | 0.151  | 0.029 | 5.161  | <b>2.46e-07</b> | <b>1.25e-06</b> | 0.068  |
|                       | DigitSpan    | 0.203  | 0.056 | 3.645  | <b>2.68e-04</b> | <b>0.001</b>    | 0.074  |
| Past HC use           | TrailA       | 0.162  | 0.033 | 4.866  | <b>1.15e-06</b> | <b>5.21e-06</b> | 0.070  |
|                       | TrailB       | 0.195  | 0.032 | 6.134  | <b>8.64e-10</b> | <b>6.34e-09</b> | 0.089  |
|                       | PairsMatch   | 0.018  | 0.007 | 2.650  | <b>0.008</b>    | <b>0.024</b>    | 0.022  |
|                       | ReactionTime | 0.092  | 0.006 | 14.549 | <b>6.34e-48</b> | <b>8.37e-46</b> | 0.114  |
|                       | SymbolSub    | 0.103  | 0.012 | 8.586  | <b>9.30e-18</b> | <b>3.07e-16</b> | 0.112  |
|                       | DigitSpan    | 0.119  | 0.021 | 5.695  | <b>1.26e-08</b> | <b>7.73e-08</b> | 0.116  |
| Age HC initiation     | TrailA       | 0.087  | 0.014 | 6.159  | <b>7.40e-10</b> | <b>5.75e-09</b> | 0.083  |
|                       | TrailB       | 0.103  | 0.014 | 7.591  | <b>3.25e-14</b> | <b>5.36e-13</b> | 0.111  |
|                       | PairsMatch   | -0.016 | 0.003 | -5.113 | <b>3.17e-07</b> | <b>1.50e-06</b> | -0.028 |
|                       | ReactionTime | -0.028 | 0.003 | -9.809 | <b>1.04e-22</b> | <b>4.59e-21</b> | -0.053 |
|                       | SymbolSub    | -0.050 | 0.005 | -9.878 | <b>5.52e-23</b> | <b>3.64e-21</b> | -0.100 |
|                       | DigitSpan    | -0.071 | 0.010 | -7.396 | <b>1.48e-13</b> | <b>1.96e-12</b> | -0.125 |
|                       | TrailA       | -0.032 | 0.006 | -5.334 | <b>9.68e-08</b> | <b>5.33e-07</b> | -0.058 |

## SUPPLEMENTARY MATERIAL

|                 |              |        |       |        |                 |                 |        |
|-----------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| Duration HC use | TrailB       | -0.043 | 0.006 | -7.603 | <b>2.98e-14</b> | <b>5.36e-13</b> | -0.082 |
|                 | PairsMatch   | 0.004  | 0.003 | 1.361  | 0.173           | 0.314           | 0.008  |
|                 | ReactionTime | 0.008  | 0.003 | 2.826  | <b>0.005</b>    | <b>0.016</b>    | 0.016  |
|                 | SymbolSub    | 0.036  | 0.005 | 7.877  | <b>3.45e-15</b> | <b>9.11e-14</b> | 0.082  |
|                 | DigitSpan    | 0.049  | 0.009 | 5.670  | <b>1.46e-08</b> | <b>8.39e-08</b> | 0.099  |
|                 | TrailA       | 0.035  | 0.005 | 6.745  | <b>1.55e-11</b> | <b>1.37e-10</b> | 0.075  |
|                 | TrailB       | 0.029  | 0.005 | 5.745  | <b>9.25e-09</b> | <b>6.43e-08</b> | 0.064  |

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Abbreviation: APOE = Apolipoprotein, PairMatch = Pair Matching Test, ReactionTime = Reaction Time Test, SymbolSub = Symbol Substitution Test, DigitSpan = Digit Span Test, Trail A & B = Trail Making Test A & B, N = Number, HT = Hormone Therapy, HC = Hormonal Contraceptive, S.E. = Standard Error, FDR = False Discovery Rate. Significant results are highlighted in bold.

**Table S12| Associations between proxies of estrogen exposure and late life cognition after exclusion of participants with diagnosed brain diseases, autoimmune diseases, metabolic disorders and cancer.**

| Model                 | Test         | beta      | S.E.  | t      | p               | pFDR            | d         |
|-----------------------|--------------|-----------|-------|--------|-----------------|-----------------|-----------|
| Current HT use        | PairsMatch   | -0.031    | 0.012 | -2.559 | <b>0.010</b>    | <b>0.022</b>    | -0.026    |
|                       | ReactionTime | 0.008     | 0.012 | 0.702  | 0.483           | 0.606           | 0.007     |
|                       | SymbolSub    | -0.026    | 0.020 | -1.297 | 0.195           | 0.304           | -0.024    |
|                       | DigitSpan    | 0.050     | 0.039 | 1.289  | 0.197           | 0.304           | 0.025     |
|                       | TrailA       | 0.025     | 0.023 | 1.101  | 0.271           | 0.366           | 0.014     |
|                       | TrailB       | -0.028    | 0.022 | -1.300 | 0.194           | 0.304           | -0.017    |
| Past HT use           | PairsMatch   | -0.032    | 0.007 | -4.369 | <b>1.25e-05</b> | <b>3.38e-05</b> | -0.045    |
|                       | ReactionTime | 0.030     | 0.007 | 4.382  | <b>1.17e-05</b> | <b>3.34e-05</b> | 0.047     |
|                       | SymbolSub    | -0.033    | 0.012 | -2.715 | <b>0.007</b>    | <b>0.015</b>    | -0.051    |
|                       | DigitSpan    | 0.009     | 0.023 | 0.375  | 0.707           | 0.749           | 0.007     |
|                       | TrailA       | 0.008     | 0.014 | 0.530  | 0.596           | 0.715           | 0.007     |
|                       | TrailB       | -0.054    | 0.014 | -3.958 | <b>7.56e-05</b> | <b>1.86e-04</b> | -0.050    |
| Age HT initiation     | PairsMatch   | -0.001    | 0.005 | -0.236 | 0.813           | 0.845           | -0.002    |
|                       | ReactionTime | -4.25e-05 | 0.005 | -0.008 | 0.994           | 0.994           | -8.05e-05 |
|                       | SymbolSub    | 0.014     | 0.009 | 1.537  | 0.124           | 0.224           | 0.029     |
|                       | DigitSpan    | 0.021     | 0.017 | 1.275  | 0.202           | 0.304           | 0.040     |
|                       | TrailA       | -0.005    | 0.011 | -0.426 | 0.670           | 0.747           | -0.009    |
|                       | TrailB       | 0.005     | 0.011 | 0.454  | 0.650           | 0.747           | 0.009     |
| Age HT rel. Menopause | PairsMatch   | -0.002    | 0.006 | -0.409 | 0.682           | 0.747           | -0.005    |
|                       | ReactionTime | 0.000     | 0.006 | -0.046 | 0.963           | 0.981           | -0.001    |
|                       | SymbolSub    | 0.014     | 0.011 | 1.243  | 0.214           | 0.304           | 0.028     |
|                       | DigitSpan    | -0.011    | 0.019 | -0.542 | 0.588           | 0.715           | -0.020    |
|                       | TrailA       | 0.017     | 0.013 | 1.249  | 0.212           | 0.304           | 0.030     |
|                       | TrailB       | 0.029     | 0.013 | 2.217  | <b>0.027</b>    | <i>0.050</i>    | 0.054     |
| Duration HT use       | PairsMatch   | -0.005    | 0.005 | -0.925 | 0.355           | 0.467           | -0.009    |
|                       | ReactionTime | 0.007     | 0.005 | 1.401  | 0.161           | 0.280           | 0.014     |
|                       | SymbolSub    | -0.014    | 0.010 | -1.385 | 0.166           | 0.280           | -0.026    |
|                       | DigitSpan    | 0.006     | 0.016 | 0.396  | 0.692           | 0.747           | 0.013     |
|                       | TrailA       | 0.010     | 0.011 | 0.901  | 0.367           | 0.472           | 0.018     |
|                       | TrailB       | -0.012    | 0.011 | -1.110 | 0.267           | 0.366           | -0.023    |
| Current HC use        | PairsMatch   | 0.044     | 0.019 | 2.263  | <b>0.024</b>    | <b>0.046</b>    | 0.019     |
|                       | ReactionTime | 0.149     | 0.018 | 8.096  | <b>5.72e-16</b> | <b>7.73e-15</b> | 0.061     |
|                       | SymbolSub    | 0.173     | 0.031 | 5.607  | <b>2.07e-08</b> | <b>7.98e-08</b> | 0.076     |
|                       | DigitSpan    | 0.194     | 0.058 | 3.336  | <b>0.001</b>    | <b>0.002</b>    | 0.077     |
|                       | TrailA       | 0.155     | 0.035 | 4.421  | <b>9.85e-06</b> | <b>2.96e-05</b> | 0.070     |
|                       | TrailB       | 0.221     | 0.033 | 6.611  | <b>3.87e-11</b> | <b>2.32e-10</b> | 0.106     |
| Past HC use           | PairsMatch   | 0.019     | 0.008 | 2.570  | <b>0.010</b>    | <b>0.022</b>    | 0.021     |
|                       | ReactionTime | 0.094     | 0.007 | 13.106 | <b>3.24e-39</b> | <b>1.75e-37</b> | 0.104     |
|                       | SymbolSub    | 0.103     | 0.013 | 7.756  | <b>8.96e-15</b> | <b>8.07e-14</b> | 0.106     |

# SUPPLEMENTARY MATERIAL

|                   |              |        |       |        |                 |                 |        |
|-------------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| Age HC initiation | DigitSpan    | 0.124  | 0.024 | 5.199  | <b>2.04e-07</b> | <b>7.33e-07</b> | 0.120  |
|                   | TrailA       | 0.094  | 0.016 | 6.014  | <b>1.83e-09</b> | <b>8.25e-09</b> | 0.091  |
|                   | TrailB       | 0.117  | 0.015 | 7.791  | <b>6.85e-15</b> | <b>7.40e-14</b> | 0.125  |
|                   | PairsMatch   | -0.014 | 0.003 | -4.158 | <b>3.21e-05</b> | <b>8.25e-05</b> | -0.025 |
|                   | ReactionTime | -0.029 | 0.003 | -9.178 | <b>4.45e-20</b> | <b>1.20e-18</b> | -0.055 |
|                   | SymbolSub    | -0.044 | 0.005 | -8.135 | <b>4.25e-16</b> | <b>7.65e-15</b> | -0.089 |
| Duration HC use   | DigitSpan    | -0.061 | 0.010 | -5.915 | <b>3.42e-09</b> | <b>1.42e-08</b> | -0.110 |
|                   | TrailA       | -0.031 | 0.006 | -4.902 | <b>9.54e-07</b> | <b>3.03e-06</b> | -0.057 |
|                   | TrailB       | -0.041 | 0.006 | -6.698 | <b>2.16e-11</b> | <b>1.46e-10</b> | -0.078 |
|                   | PairsMatch   | 0.001  | 0.003 | 0.397  | 0.692           | 0.747           | 0.002  |
|                   | ReactionTime | 0.007  | 0.003 | 2.502  | <b>0.012</b>    | <b>0.025</b>    | 0.015  |
|                   | SymbolSub    | 0.036  | 0.005 | 7.235  | <b>4.75e-13</b> | <b>3.67e-12</b> | 0.081  |
|                   | DigitSpan    | 0.049  | 0.009 | 5.166  | <b>2.43e-07</b> | <b>8.21e-07</b> | 0.099  |
|                   | TrailA       | 0.036  | 0.006 | 6.314  | <b>2.76e-10</b> | <b>1.49e-09</b> | 0.076  |
|                   | TrailB       | 0.033  | 0.005 | 6.074  | <b>1.26e-09</b> | <b>6.21e-09</b> | 0.073  |

Abbreviation: PairMatch = Pair Matching Test, ReactionTime = Reaction Time Test, SymbolSub = Symbol Substitution Test, DigitSpan = Digit Span Test, Trail A & B = Trail Making Test A & B, N = Number, HT = Hormone Therapy, HC = Hormonal Contraceptive, S.E. = Standard Error, FDR = False Discovery Rate. Significant results are highlighted in bold.

**Table S13| Detected extreme values of continuous female-specific factors using the median absolute deviation method.**

| Variable                      | Median | MAD  | Limits*       | Number extreme values |      |       |
|-------------------------------|--------|------|---------------|-----------------------|------|-------|
|                               |        |      |               | Low                   | High | Total |
| Age at Menarche               | 13     | 1.48 | 8.55 – 17.45  | 130                   | 920  | 1050  |
| Age at Menopause              | 50     | 4.45 | 36.66 – 63.34 | 2200                  | 24   | 2224  |
| Age at Bilateral Oophorectomy | 48     | 7.41 | 25.76 – 70.24 | 51                    | 0    | 51    |
| Age at Hysterectomy           | 44     | 7.41 | 21.76 – 66.24 | 26                    | 140  | 166   |
| Number of live Childbirths    | 2      | 1.48 | -2.45 – 6.45  | 0                     | 322  | 322   |
| Age at first Childbirth       | 25     | 4.45 | 11.66 – 38.34 | 1                     | 790  | 791   |
| Age at last Childbirth        | 30     | 4.45 | 16.66 – 43.34 | 7                     | 497  | 504   |
| Age started HT                | 48     | 4.45 | 34.66 – 61.34 | 1185                  | 115  | 1300  |
| Age last used HT              | 55     | 5.93 | 37.21 – 72.79 | 537                   | 0    | 537   |
| Age started HC                | 21     | 4.45 | 7.66 – 34.34  | 10                    | 3364 | 3374  |
| Age last used HC              | 31     | 7.41 | 8.76 – 53.24  | 2                     | 741  | 743   |

\*Limits of acceptable range of values. Abbreviations: HT = hormone therapy, HC = hormonal contraceptives, MAD = median absolute deviation.

**Table S14| Main effects of APOE  $\epsilon 4$  genotype on cognitive performance.**

| Model                  | Test         | beta   | S.E.  | t      | p               | pFDR            | d      |
|------------------------|--------------|--------|-------|--------|-----------------|-----------------|--------|
| APOE $\epsilon 4$      | PairsMatch   | -0.010 | 0.005 | -1.873 | 0.061           | 0.123           | -0.010 |
|                        | ReactionTime | -0.001 | 0.005 | -0.162 | 0.871           | 0.925           | -0.001 |
|                        | SymbolSub    | -0.046 | 0.009 | -4.974 | <b>6.59e-07</b> | <b>5.93e-06</b> | -0.053 |
|                        | DigitSpan    | -0.031 | 0.017 | -1.823 | 0.068           | 0.123           | -0.032 |
|                        | TrailA       | -0.014 | 0.011 | -1.267 | 0.205           | 0.284           | -0.014 |
|                        | TrailB       | -0.027 | 0.010 | -2.673 | <b>0.008</b>    | <b>0.027</b>    | -0.030 |
| 1x $\epsilon 4$ allele | PairsMatch   | -0.008 | 0.006 | -1.417 | 0.156           | 0.242           | -0.008 |
| 2x $\epsilon 4$ allele | PairsMatch   | -0.033 | 0.016 | -2.060 | <b>0.039</b>    | 0.118           | -0.012 |
| 1x $\epsilon 4$ allele | ReactionTime | -0.001 | 0.005 | -0.145 | 0.884           | 0.925           | -0.001 |
| 2x $\epsilon 4$ allele | ReactionTime | -0.001 | 0.015 | -0.094 | 0.925           | 0.925           | -0.001 |
| 1x $\epsilon 4$ allele | SymbolSub    | -0.037 | 0.010 | -3.840 | <b>1.23e-04</b> | <b>0.001</b>    | -0.042 |
| 2x $\epsilon 4$ allele | SymbolSub    | -0.145 | 0.027 | -5.276 | <b>1.33e-07</b> | <b>2.39e-06</b> | -0.057 |
| 1x $\epsilon 4$ allele | DigitSpan    | -0.034 | 0.018 | -1.964 | 0.049           | 0.123           | -0.086 |
| 2x $\epsilon 4$ allele | DigitSpan    | 0.005  | 0.049 | 0.109  | 0.913           | 0.925           | 0.005  |
| 1x $\epsilon 4$ allele | TrailA       | -0.011 | 0.011 | -0.962 | 0.336           | 0.432           | -0.028 |
| 2x $\epsilon 4$ allele | TrailA       | -0.045 | 0.032 | -1.401 | 0.161           | 0.242           | -0.040 |
| 1x $\epsilon 4$ allele | TrailB       | -0.020 | 0.011 | -1.852 | 0.064           | 0.123           | -0.055 |
| 2x $\epsilon 4$ allele | TrailB       | -0.111 | 0.031 | -3.619 | <b>2.96e-04</b> | <b>0.001</b>    | -0.107 |

Abbreviation: APOE = Apolipoprotein, PairMatch = Pair Matching Test, ReactionTime = Reaction Time Test, SymbolSub = Symbol Substitution Test, DigitSpan = Digit Span Test, Trail A & B = Trail Making Test A & B, N = Number, HT = Hormone Therapy, HC = Hormonal Contraceptive, S.E. = Standard Error, FDR = False Discovery Rate. Significant results are highlighted in bold.

**Table 15| Interactions between APOE  $\epsilon 4$  genotype and female-specific factors on late life cognition.**

| Model                                   | Test         | beta   | S.E.  | t      | p     | pFDR  |
|-----------------------------------------|--------------|--------|-------|--------|-------|-------|
| Reproductive Span * APOE $\epsilon 4$   | PairsMatch   | -0.002 | 0.002 | -0.783 | 0.434 | 0.867 |
|                                         | ReactionTime | 0.001  | 0.002 | 0.494  | 0.621 | 0.867 |
|                                         | SymbolSub    | 0.006  | 0.004 | 1.353  | 0.176 | 0.867 |
|                                         | DigitSpan    | 0.007  | 0.007 | 0.987  | 0.324 | 0.867 |
|                                         | TrailA       | -0.007 | 0.005 | -1.359 | 0.174 | 0.867 |
|                                         | TrailB       | 0.003  | 0.005 | 0.671  | 0.502 | 0.867 |
| Age at Menarche * APOE $\epsilon 4$     | PairsMatch   | 0.003  | 0.007 | 0.514  | 0.607 | 0.867 |
|                                         | ReactionTime | -0.005 | 0.006 | -0.752 | 0.452 | 0.867 |
|                                         | SymbolSub    | -0.001 | 0.012 | -0.047 | 0.963 | 0.983 |
|                                         | DigitSpan    | 0.008  | 0.020 | 0.394  | 0.693 | 0.897 |
|                                         | TrailA       | 0.003  | 0.014 | 0.218  | 0.828 | 0.966 |
|                                         | TrailB       | 0.007  | 0.013 | 0.499  | 0.617 | 0.867 |
| Age at Menopause * APOE $\epsilon 4$    | PairsMatch   | -0.004 | 0.007 | -0.598 | 0.550 | 0.867 |
|                                         | ReactionTime | 0.004  | 0.006 | 0.569  | 0.569 | 0.867 |
|                                         | SymbolSub    | -0.008 | 0.012 | -0.706 | 0.480 | 0.867 |
|                                         | DigitSpan    | 0.019  | 0.021 | 0.929  | 0.353 | 0.867 |
|                                         | TrailA       | -0.002 | 0.014 | -0.160 | 0.873 | 0.968 |
|                                         | TrailB       | 0.011  | 0.013 | 0.826  | 0.409 | 0.867 |
| Oophorectomy * APOE $\epsilon 4$        | PairsMatch   | -0.002 | 0.014 | -0.119 | 0.906 | 0.977 |
|                                         | ReactionTime | -0.029 | 0.013 | -2.210 | 0.027 | 0.596 |
|                                         | SymbolSub    | 0.023  | 0.021 | 1.098  | 0.272 | 0.867 |
|                                         | DigitSpan    | -0.028 | 0.043 | -0.653 | 0.514 | 0.867 |
|                                         | TrailA       | 0.031  | 0.024 | 1.322  | 0.186 | 0.867 |
|                                         | TrailB       | 0.013  | 0.023 | 0.553  | 0.580 | 0.867 |
| Age at Oophorectomy * APOE $\epsilon 4$ | PairsMatch   | -0.003 | 0.003 | -1.033 | 0.301 | 0.867 |
|                                         | ReactionTime | 0.005  | 0.003 | 1.997  | 0.046 | 0.755 |
|                                         | SymbolSub    | -0.001 | 0.005 | -0.220 | 0.826 | 0.966 |
|                                         | DigitSpan    | -0.008 | 0.008 | -0.974 | 0.330 | 0.867 |
|                                         | TrailA       | 0.004  | 0.006 | 0.798  | 0.425 | 0.867 |
|                                         | TrailB       | 0.004  | 0.005 | 0.821  | 0.411 | 0.867 |
| Hysterectomy * APOE $\epsilon 4$        | PairsMatch   | 0.090  | 0.082 | 1.097  | 0.273 | 0.867 |
|                                         | ReactionTime | -0.125 | 0.078 | -1.609 | 0.108 | 0.867 |
|                                         | SymbolSub    | 0.127  | 0.170 | 0.743  | 0.457 | 0.867 |
|                                         | DigitSpan    | -0.400 | 0.231 | -1.729 | 0.084 | 0.867 |
|                                         | TrailA       | 0.335  | 0.183 | 1.829  | 0.067 | 0.862 |
|                                         | TrailB       | 0.058  | 0.178 | 0.324  | 0.746 | 0.947 |
| Age at Hysterectomy * APOE $\epsilon 4$ | PairsMatch   | 0.002  | 0.003 | 0.697  | 0.486 | 0.867 |
|                                         | ReactionTime | -0.006 | 0.003 | -2.245 | 0.025 | 0.596 |
|                                         | SymbolSub    | -0.003 | 0.004 | -0.605 | 0.545 | 0.867 |
|                                         | DigitSpan    | 0.006  | 0.008 | 0.674  | 0.501 | 0.867 |



# SUPPLEMENTARY MATERIAL

|                                            |              |        |       |        |                 |              |
|--------------------------------------------|--------------|--------|-------|--------|-----------------|--------------|
| N Childbirth * <i>APOE</i> ε4              | TrailA       | -0.009 | 0.005 | -1.800 | 0.072           | 0.862        |
|                                            | TrailB       | -0.001 | 0.005 | -0.115 | 0.908           | 0.977        |
|                                            | PairsMatch   | -0.008 | 0.011 | -0.718 | 0.473           | 0.867        |
|                                            | ReactionTime | 0.039  | 0.011 | 3.589  | <b>3.32e-04</b> | <b>0.022</b> |
|                                            | SymbolSub    | 0.031  | 0.022 | 1.436  | 0.151           | 0.867        |
|                                            | DigitSpan    | 0.012  | 0.041 | 0.294  | 0.769           | 0.958        |
| N Childbirth <sup>2</sup> * <i>APOE</i> ε4 | TrailA       | -0.022 | 0.025 | -0.886 | 0.375           | 0.867        |
|                                            | TrailB       | -0.021 | 0.024 | -0.887 | 0.375           | 0.867        |
|                                            | PairsMatch   | 0.009  | 0.012 | 0.721  | 0.471           | 0.867        |
|                                            | ReactionTime | -0.046 | 0.012 | -3.831 | <b>1.28e-04</b> | <b>0.017</b> |
|                                            | SymbolSub    | -0.032 | 0.027 | -1.182 | 0.237           | 0.867        |
|                                            | DigitSpan    | -0.040 | 0.047 | -0.838 | 0.402           | 0.867        |
| Age last Birth * <i>APOE</i> ε4            | TrailA       | 0.015  | 0.031 | 0.477  | 0.633           | 0.867        |
|                                            | TrailB       | 0.001  | 0.030 | 0.047  | 0.963           | 0.983        |
|                                            | PairsMatch   | 0.043  | 0.021 | 2.054  | 0.040           | 0.755        |
|                                            | ReactionTime | 0.000  | 0.020 | -0.002 | 0.999           | 0.999        |
|                                            | SymbolSub    | 0.027  | 0.038 | 0.716  | 0.474           | 0.867        |
|                                            | DigitSpan    | 0.037  | 0.065 | 0.567  | 0.571           | 0.867        |
| Age first Birth * <i>APOE</i> ε4           | TrailA       | -0.002 | 0.045 | -0.045 | 0.964           | 0.983        |
|                                            | TrailB       | 0.042  | 0.043 | 0.962  | 0.336           | 0.867        |
|                                            | PairsMatch   | -0.005 | 0.021 | -0.234 | 0.815           | 0.966        |
|                                            | ReactionTime | 0.013  | 0.020 | 0.656  | 0.512           | 0.867        |
|                                            | SymbolSub    | -0.007 | 0.039 | -0.179 | 0.858           | 0.966        |
|                                            | DigitSpan    | -0.068 | 0.061 | -1.107 | 0.269           | 0.867        |
| Miscarriage & Termination * <i>APOE</i> ε4 | TrailA       | 0.004  | 0.047 | 0.092  | 0.927           | 0.983        |
|                                            | TrailB       | 0.009  | 0.046 | 0.205  | 0.837           | 0.966        |
|                                            | PairsMatch   | -0.025 | 0.019 | -1.271 | 0.204           | 0.867        |
|                                            | ReactionTime | 0.003  | 0.018 | 0.149  | 0.881           | 0.970        |
|                                            | SymbolSub    | -0.030 | 0.034 | -0.859 | 0.390           | 0.867        |
|                                            | DigitSpan    | 0.055  | 0.062 | 0.887  | 0.375           | 0.867        |
| Stillbirth * <i>APOE</i> ε4                | TrailA       | -0.015 | 0.041 | -0.374 | 0.709           | 0.908        |
|                                            | TrailB       | -0.016 | 0.039 | -0.414 | 0.679           | 0.896        |
|                                            | PairsMatch   | 0.020  | 0.019 | 1.062  | 0.288           | 0.867        |
|                                            | ReactionTime | 0.011  | 0.018 | 0.600  | 0.549           | 0.867        |
|                                            | SymbolSub    | 0.021  | 0.034 | 0.618  | 0.536           | 0.867        |
|                                            | DigitSpan    | 0.038  | 0.062 | 0.608  | 0.543           | 0.867        |
| Current HT use * <i>APOE</i> ε4            | TrailA       | -0.033 | 0.042 | -0.783 | 0.434           | 0.867        |
|                                            | TrailB       | -0.002 | 0.040 | -0.061 | 0.951           | 0.983        |
|                                            | PairsMatch   | -0.007 | 0.010 | -0.627 | 0.531           | 0.867        |
|                                            | ReactionTime | 0.007  | 0.010 | 0.741  | 0.459           | 0.867        |
|                                            | SymbolSub    | -0.018 | 0.017 | -1.067 | 0.286           | 0.867        |
|                                            | DigitSpan    | -0.025 | 0.034 | -0.737 | 0.461           | 0.867        |
|                                            | TrailA       | -0.014 | 0.020 | -0.711 | 0.477           | 0.867        |

# SUPPLEMENTARY MATERIAL

|                                        |              |        |       |        |       |       |
|----------------------------------------|--------------|--------|-------|--------|-------|-------|
| Past HT use * <i>APOE</i> ε4           | TrailB       | -0.010 | 0.019 | -0.530 | 0.596 | 0.867 |
|                                        | PairsMatch   | 0.003  | 0.006 | 0.459  | 0.646 | 0.867 |
|                                        | ReactionTime | 0.008  | 0.005 | 1.486  | 0.137 | 0.867 |
|                                        | SymbolSub    | -0.022 | 0.010 | -2.275 | 0.023 | 0.596 |
|                                        | DigitSpan    | -0.009 | 0.017 | -0.539 | 0.590 | 0.867 |
|                                        | TrailA       | 0.003  | 0.011 | 0.236  | 0.814 | 0.966 |
| Age HT initiation * <i>APOE</i> ε4     | TrailB       | -0.001 | 0.011 | -0.113 | 0.910 | 0.977 |
|                                        | PairsMatch   | -0.004 | 0.004 | -0.908 | 0.364 | 0.867 |
|                                        | ReactionTime | 0.003  | 0.004 | 0.712  | 0.476 | 0.867 |
|                                        | SymbolSub    | -0.012 | 0.008 | -1.518 | 0.129 | 0.867 |
|                                        | DigitSpan    | -0.003 | 0.013 | -0.239 | 0.811 | 0.966 |
|                                        | TrailA       | -0.006 | 0.010 | -0.634 | 0.526 | 0.867 |
| Age HT rel. Menopause * <i>APOE</i> ε4 | TrailB       | -0.002 | 0.009 | -0.248 | 0.804 | 0.966 |
|                                        | PairsMatch   | -0.002 | 0.004 | -0.458 | 0.647 | 0.867 |
|                                        | ReactionTime | 0.002  | 0.004 | 0.571  | 0.568 | 0.867 |
|                                        | SymbolSub    | -0.004 | 0.008 | -0.467 | 0.640 | 0.867 |
|                                        | DigitSpan    | -0.003 | 0.013 | -0.198 | 0.843 | 0.966 |
|                                        | TrailA       | 0.007  | 0.009 | 0.809  | 0.419 | 0.867 |
| Duration HT use * <i>APOE</i> ε4       | TrailB       | 0.000  | 0.009 | -0.031 | 0.975 | 0.983 |
|                                        | PairsMatch   | -0.005 | 0.005 | -1.067 | 0.286 | 0.867 |
|                                        | ReactionTime | 0.004  | 0.005 | 0.796  | 0.426 | 0.867 |
|                                        | SymbolSub    | 0.000  | 0.009 | -0.032 | 0.975 | 0.983 |
|                                        | DigitSpan    | -0.003 | 0.016 | -0.172 | 0.864 | 0.966 |
|                                        | TrailA       | 0.019  | 0.012 | 1.645  | 0.100 | 0.867 |
| Current HC use * <i>APOE</i> ε4        | TrailB       | 0.022  | 0.011 | 1.944  | 0.052 | 0.761 |
|                                        | PairsMatch   | 0.005  | 0.018 | 0.306  | 0.759 | 0.955 |
|                                        | ReactionTime | -0.008 | 0.017 | -0.454 | 0.650 | 0.867 |
|                                        | SymbolSub    | 0.066  | 0.028 | 2.354  | 0.019 | 0.596 |
|                                        | DigitSpan    | 0.064  | 0.054 | 1.178  | 0.239 | 0.867 |
|                                        | TrailA       | 0.001  | 0.032 | 0.041  | 0.968 | 0.983 |
| Past HC use * <i>APOE</i> ε4           | TrailB       | 0.048  | 0.031 | 1.546  | 0.122 | 0.867 |
|                                        | PairsMatch   | 0.003  | 0.006 | 0.479  | 0.632 | 0.867 |
|                                        | ReactionTime | -0.001 | 0.006 | -0.180 | 0.857 | 0.966 |
|                                        | SymbolSub    | 0.017  | 0.012 | 1.418  | 0.156 | 0.867 |
|                                        | DigitSpan    | 0.033  | 0.021 | 1.573  | 0.116 | 0.867 |
|                                        | TrailA       | 0.019  | 0.014 | 1.346  | 0.178 | 0.867 |
| Age HC initiation * <i>APOE</i> ε4     | TrailB       | 0.018  | 0.013 | 1.305  | 0.192 | 0.867 |
|                                        | PairsMatch   | 0.003  | 0.003 | 1.056  | 0.291 | 0.867 |
|                                        | ReactionTime | -0.001 | 0.003 | -0.218 | 0.827 | 0.966 |
|                                        | SymbolSub    | -0.003 | 0.006 | -0.518 | 0.605 | 0.867 |
|                                        | DigitSpan    | 0.008  | 0.010 | 0.791  | 0.429 | 0.867 |
|                                        | TrailA       | -0.006 | 0.007 | -0.799 | 0.424 | 0.867 |
|                                        | TrailB       | -0.006 | 0.007 | -0.804 | 0.421 | 0.867 |

## SUPPLEMENTARY MATERIAL

|                                            |              |        |       |        |       |       |
|--------------------------------------------|--------------|--------|-------|--------|-------|-------|
| Duration HC use * <i>APOE</i> $\epsilon 4$ | PairsMatch   | 0.004  | 0.003 | 1.186  | 0.236 | 0.867 |
|                                            | ReactionTime | -0.002 | 0.003 | -0.755 | 0.450 | 0.867 |
|                                            | SymbolSub    | -0.004 | 0.006 | -0.667 | 0.505 | 0.867 |
|                                            | DigitSpan    | 0.004  | 0.010 | 0.398  | 0.691 | 0.897 |
|                                            | TrailA       | -0.004 | 0.007 | -0.504 | 0.614 | 0.867 |
|                                            | TrailB       | -0.004 | 0.007 | -0.507 | 0.612 | 0.867 |

Abbreviation: APOE = Apolipoprotein. PairMatch = Pair Matching Test. ReactionTime = Reaction Time Test. SymbolSub = Symbol Substitution Test. DigitSpan = Digit Span Test. Trail A & B = Trail Making Test A & B. N = Number. HT = Hormone Therapy. HC = Hormonal Contraceptive. S.E. = Standard Error. FDR = False Discovery Rate. Significant results are highlighted in bold.

1. Foster HME, Celis-Morales CA, Nicholl BI, Petermann-Rocha F, Pell JP, Gill JMR *et al.* The effect of socioeconomic deprivation on the association between an extended measurement of unhealthy lifestyle factors and health outcomes: a prospective analysis of the UK Biobank cohort. *Lancet Public Health* 2018; **3**(12): e576-e585.