

Brain volumes in late life: gender, hormone treatment, and estrogen receptor variants.

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Table 1. Characteristics of the 582 participants according to gender and women's use of HT.

| Characteristic | Males (N=287) | Females (N=295) | | |
|---|---|----------------------------------|---------------------|---------------------|
| | | Never HT | Past HT | Current HT |
| | Median (Interquartile range: 25th – 75th percentile) | | | |
| Age (years) | 71 (68 to 74) [†] | 71 (68 to 75) [‡] | 70 (68 to 72) | 68 (67 to 71) |
| Body Mass Index (kg/m ²) | 25.6 (23.7 to 27.4) [†] | 24.1 (22.0 to 26.7) [‡] | 23.9 (21.6 to 26.3) | 23.2 (21.1 to 25.5) |
| | N (%) | N (%) | N (%) | N (%) |
| ≥ 12 years of education | 126 (43.9) [†] | 45 (26.0) [‡] | 12 (20.0) | 29 (46.8) |
| Living alone | 17 (5.9) [†] | 59 (34.1) | 15 (25.0) | 14 (22.6) |
| High alcohol consumption (≥ 24 g each day) | 100 (34.8) [†] | 9 (5.2) | 4 (6.6) | 5 (8.1) |
| Smoking history (10 pack year) | 98 (34.2) [†] | 32 (18.5) | 15 (25.0) | 15 (24.2) |
| Current depressive symptoms (CES-D ≥16) | 58 (20.2) [†] | 58 (33.5) | 24 (40.0) | 17 (27.4) |
| Lifetime major depressive disorder ^a | 37 (14.0) [†] | 54 (34.4) | 25 (45.5) | 28 (46.7) |
| Low global cognitive function (MMSE≤24) | 15 (5.2) [†] | 21 (12.1) | 6 (10.0) | 3 (4.8) |
| History of cardiovascular disease | 58 (20.2) | 36 (20.8) [‡] | 8 (13.3) | 6 (9.7) |
| Hypertension (≥ 160/95mm Hg or treatment) | 138 (48.1) | 86 (49.7) [‡] | 27 (45.0) | 17 (27.4) |
| Diabetes (fasting glucose ≥ 7.0mmol/l or treatment) | 37 (12.9) [†] | 12 (6.9) [‡] | 1 (1.7) | 0 (0.0) |

| | | | | |
|---|------------------------|------------------------|-----------------------|-----------------------|
| Hypercholesterolemia | 79 (27.6) [†] | 67 (38.7) | 25 (41.7) | 21 (33.9) |
| Anticholinergic medication | 7 (2.4) [†] | 9 (5.2) [‡] | 2 (3.3) | 9 (14.5) |
| Current user of ≥3 medications | 94 (32.8) [†] | 72 (44.5) [‡] | 20 (33.3) | 20 (32.3) |
| Carrier of the <i>APOE</i> ε4 allele | 61 (21.3) | 42 (24.3) | 14 (23.3) | 10 (16.1) |
| Median (Interquartile range: 25th – 75th percentile) | | | | |
| Volume of grey matter, cm ³ | 684 (643 to 729) | 631 (598 to 662) | 630 (608 to 661) | 623 (594 to 659) |
| Ratio of grey matter to ICV | 54.5 (53.4 to 56.4) | 55.2 (53.8 to 56.9) | 55.9 (54.6 to 57.9) | 54.8 (53.2 to 55.9) |
| Volume of white matter volume, cm ³ | 374 (346 to 407) | 339 (315 to 362) | 334 (314 to 360) | 342 (327 to 365) |
| Ratio of white matter to ICV | 29.8 (28.5 to 31.4) | 29.6 (28.3 to 31.0) | 29.3 (28.3 to 30.3) | 30.4 (28.7 to 31.4) |
| Total volume of hippocampus, mm ³ | 5964 (5510 to 6481) | 5653 (5109 to 6011) | 5619 (5136 to 6114) | 5572 (5231 to 6048) |
| Ratio of hippocampus to ICV | 4.7 (4.3 to 5.3) | 4.9 (4.5 to 5.3) | 5.0 (4.2-5.3) | 4.9 (4.5-5.4) |
| Midsagittal total corpus callosum area, mm ² | 609 (546 to 670) | 591 (524 to 651) | 574 (534 to 652) | 596 (527 to 671) |
| Ratio of corpus callosum to ICV | 0.48 (0.43 to 0.54) | 0.52 (0.47 to 0.57) | 0.51 (0.46 to 0.58) | 0.52 (0.46 to 0.60) |
| Total volume of WML, cm ³ | 0.8 (0.3 to 3.2) | 0.60 (0.2 to 2.1) | 0.80 (0.2 to 2.4) | 0.45 (0.2 to 2.1) |
| Volume of WML transformed (log ₁₀) | -0.09 (-0.51 to 0.51) | -0.21 (-0.68 to 0.32) | -0.09 (-0.68 to 0.39) | -0.34 (-0.68 to 0.32) |
| | N (%) | N (%) | N (%) | N (%) |
| Participants with no detectable WML | 10 (3.5) | 11 (6.4) | 3 (5.0) | 2 (3.2) |

^aData were missing for 23 men and women. [†]Significantly different between genders at $p \leq 0.10$. [‡]Significantly different between women according to their use or not of HT at $p \leq 0.10$.

Table 2. Linear regression models for the association between brain measures^a and gender or use of HT.

| Model | N | Grey Matter | White Matter | Hippocampus | Corpus Callosum | White Matter Lesions |
|---|-----|-----------------------|---------------------|--------------------|-----------------------|----------------------|
| | | Beta (SE), p | Beta (SE), p | Beta (SE), p | Beta (SE), p | Beta (SE), p |
| <u>Age-adjusted</u> | | | | | | |
| Women, never HT | 173 | 1 | 1 | 1 | 1 | 1 |
| Women, past HT | 60 | 0.40 (0.38), 0.28 | -0.44 (0.30), 0.14 | 0.02 (0.10), 0.83 | -0.01 (0.01), 0.34 | 0.12 (0.11), 0.28 |
| Women, current HT | 62 | -0.94 (0.38), 0.01* | 0.18 (0.30), 0.54 | -0.06 (0.10), 0.60 | -0.003 (0.01), 0.84 | 0.08 (0.11), 0.51 |
| Men | 287 | -0.68 (0.24), 0.005** | 0.23 (0.19), 0.22 | -0.09 (0.06), 0.16 | -0.03 (0.01), 0.001** | -0.02 (0.008), 0.78 |
| <u>Multivariable-adjusted^b</u> | | | | | | |
| Women, never HT | 173 | 1 | 1 | 1 | 1 | 1 |
| Women, past HT | 60 | 0.38 (0.37), 0.31 | -0.47, (0.30), 0.11 | 0.007 (0.10), 0.94 | -0.01 (0.01), 0.30 | 0.14 (0.11), 0.22 |
| Women, current HT | 62 | -1.11 (0.38), 0.003** | 0.32 (0.30), 0.29 | -0.09 (0.10), 0.39 | -0.003 (0.01), 0.84 | 0.13 (0.11), 0.24 |
| Men | 287 | -0.75 (0.24), 0.002** | 0.28 (0.20), 0.15 | -0.10 (0.07), 0.11 | -0.03 (0.01), 0.001** | 0.008 (0.08), 0.92 |

^aAll brain measures are given as a percentage of total intracranial volume (ICV), except for the volume of white matter lesions, which were adjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications

*p<0.05; **p≤0.005

Table 3. Linear regression models for the multivariable-adjusted association^a between ESR polymorphisms and brain measures^b in women.

| Model | N | Grey Matter | White Matter | Hippocampus | Corpus Callosum | White Matter Lesions |
|-----------------------------|-----|--------------------|--------------------|---------------------|---------------------|----------------------|
| | | Beta (SE), p-value | Beta (SE), p-value | Beta (SE), p | Beta (SE), p | Beta (SE), p-value |
| <u>ESR1</u> | | | | | | |
| <i>rs2234693</i> : C allele | 205 | 1 | 1 | 1 | 1 | 1 |
| TT | 90 | -0.29 (0.33), 0.38 | 0.21 (0.24), 0.38 | 0.10 (0.08), 0.22 | 0.006 (0.01), 0.54 | 0.26 (0.10), 0.008* |
| <i>rs9340799</i> : G allele | 171 | 1 | 1 | 1 | 1 | 1 |
| AA | 124 | -0.16 (0.31), 0.60 | 0.26 (0.22), 0.24 | 0.11 (0.07), 0.14 | 0.0003 (0.01), 0.98 | 0.13 (0.09), 0.18 |
| <u>ESR2</u> | | | | | | |
| <i>rs1271572</i> : T allele | 206 | 1 | 1 | 1 | 1 | 1 |
| GG | 89 | -0.20 (0.33), 0.55 | -0.09 (0.24), 0.72 | -0.001 (0.08), 0.99 | -0.003 (0.01), 0.81 | 0.01 (0.10), 0.91 |
| <i>rs4986938</i> : A allele | 202 | 1 | 1 | 1 | 1 | 1 |
| GG | 93 | 0.48 (0.33), 0.15 | 0.09 (0.24), 0.73 | 0.12 (0.08), 0.12 | 0.01 (0.01), 0.31 | -0.04 (0.10), 0.66 |
| <i>rs1256049</i> : A allele | 26 | 1 | 1 | 1 | 1 | 1 |
| GG | 269 | -0.26 (0.55), 0.64 | -0.24 (0.40), 0.55 | 0.11 (0.13), 0.41 | -0.02 (0.02), 0.24 | -0.03 (0.17), 0.86 |

^aAll brain measures are given as a percentage of total intracranial brain volume, except for the volume of white matter lesions, which were adjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications.

* $p < 0.05$; ** $p \leq 0.005$

Table 4. Linear regression models for the association between ESR1 variants and white matter lesions^a in women, stratified by HT.

| | Hormone Treatment | | | | | |
|---|-------------------|----------------------|------|---------------------|---------|--------------------|
| | Never | | Past | | Current | |
| | N | Beta (SE), p-value | N | Beta (SE), p-value | N | Beta (SE), p-value |
| <u>Age-adjusted</u> | | | | | | |
| <i>rs2234693</i> : C allele | 53 | 1 | 43 | 1 | 42 | 1 |
| TT | 120 | 0.40 (0.13), 0.002** | 17 | -0.42 (0.21), 0.08 | 20 | 0.35 (0.21), 0.10 |
| <i>rs9340799</i> : G allele | 71 | 1 | 27 | 1 | 26 | 1 |
| AA | 102 | 0.21 (0.12), 0.09 | 33 | -0.47 (0.21), 0.03* | 36 | 0.42 (0.19), 0.03* |
| <u>Multivariable-adjusted^b</u> | | | | | | |
| <i>rs2234693</i> : C allele | 53 | 1 | 43 | 1 | 42 | 1 |
| TT | 120 | 0.38 (0.13), 0.003** | 17 | -0.18 (0.25), 0.48 | 20 | 0.43 (0.20), 0.04* |
| <i>rs9340799</i> : G allele | 71 | 1 | 27 | 1 | 26 | 1 |
| AA | 102 | 0.19 (0.12), 0.12 | 33 | -0.30 (0.21), 0.17 | 36 | 0.45 (0.19), 0.02* |

^aAdjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications.

*p<0.05; **p≤0.005

Supplementary Table 1. Linear regression model for the association between ESR1 polymorphisms and brain measures^a in men.

| Model | N | Grey Matter | White Matter | Hippocampus | Corpus Callosum | White Matter Lesions |
|---|-----|--------------------|--------------------|-------------------|--------------------|----------------------|
| | | Beta (SE), p | Beta (SE), p | Beta (SE), p | Beta (SE), p | Beta (SE), p |
| <u>Age-adjusted</u> | | | | | | |
| <i>rs2234693</i> : C allele | 79 | 1 | 1 | 1 | 1 | 1 |
| TT | 208 | -0.33 (0.33), 0.31 | -0.04 (0.28), 0.89 | 0.05 (0.10), 0.60 | -0.02 (0.01), 0.07 | -0.01 (0.10), 0.91 |
| <i>rs9340799</i> : G allele | 114 | 1 | 1 | 1 | 1 | 1 |
| AA | 173 | -0.31 (0.30), 0.30 | 0.18 (0.26), 0.47 | 0.05 (0.09), 0.58 | -0.01 (0.01), 0.36 | -0.008 (0.09), 0.93 |
| <u>Multivariable-adjusted^b</u> | | | | | | |
| <i>rs2234693</i> : C allele | 79 | 1 | 1 | 1 | 1 | 1 |
| TT | 208 | -0.35 (0.32), 0.28 | -0.04 (0.28), 0.89 | 0.06 (0.09), 0.50 | -0.02 (0.01), 0.07 | -0.007 (0.10), 0.94 |
| <i>rs9340799</i> : G allele | 114 | 1 | 1 | 1 | 1 | 1 |
| AA | 173 | -0.36 (0.30), 0.23 | 0.20 (0.26), 0.45 | 0.05 (0.09), 0.60 | -0.01 (0.01), 0.36 | 0.004 (0.09), 0.97 |

^aAll brain measures are given as a percentage of total intracranial brain volume, except for the volume of white matter lesions, which were adjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications

Supplementary Table 2. Linear regression model for the association between ESR2 polymorphisms and brain measures^a in men.

| Model | N | Grey Matter | White Matter | Hippocampus | Corpus Callosum | White Matter Lesions |
|---|-----|--------------------|-------------------|--------------------|--------------------|----------------------|
| | | Beta (SE), p | Beta (SE), p | Beta (SE), p | Beta (SE), p | Beta (SE), p |
| <u>Age-adjusted</u> | | | | | | |
| <i>rs1271572</i> : T allele | 196 | 1 | 1 | 1 | 1 | 1 |
| GG | 91 | -0.09 (0.31), 0.79 | 0.16 (0.27), 0.55 | 0.01 (0.09), 0.90 | 0.00 (0.01), 0.95 | -0.06 (0.09), 0.53 |
| <i>rs4986938</i> : A allele | 176 | 1 | 1 | 1 | 1 | 1 |
| GG | 111 | 0.36 (0.30), 0.23 | 0.02 (0.26), 0.93 | 0.09 (0.09), 0.30 | 0.00 (0.01), 0.99 | -0.05 (0.09), 0.57 |
| <i>rs1256049</i> : A allele | 23 | 1 | 1 | 1 | 1 | 1 |
| GG | 264 | -0.77 (0.57), 0.19 | 0.49 (0.50), 0.33 | -0.16 (0.18), 0.38 | -0.02 (0.02), 0.29 | -0.23 (0.17), 0.18 |
| <u>Multivariable-adjusted^b</u> | | | | | | |
| <i>rs1271572</i> : T allele | 196 | 1 | 1 | 1 | 1 | 1 |
| GG | 91 | -0.18 (0.31), 0.56 | 0.16 (0.30), 0.56 | -0.02 (0.09), 0.82 | 0.00 (0.01), 0.99 | -0.04 (0.09), 0.70 |
| <i>rs4986938</i> : A allele | 176 | 1 | 1 | 1 | 1 | 1 |
| GG | 111 | 0.43 (0.30), 0.16 | 0.02 (0.26), 0.93 | 0.09 (0.09), 0.27 | 0.00 (0.01), 0.98 | -0.07 (0.09), 0.44 |
| <i>rs1256049</i> : A allele | 23 | 1 | 1 | 1 | 1 | 1 |
| GG | 264 | -0.68 (0.57), 0.23 | 0.51 (0.50), 0.30 | -0.14 (0.18), 0.43 | -0.02 (0.02), 0.31 | 0.27 (0.17), 0.11 |

^aAll brain measures are given as a percentage of total intracranial brain volume, except for the volume of white matter lesions, which were adjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications.

Supplementary Table 3. Linear regression model for the age-adjusted association between ESR polymorphisms and brain measures^a in women.

| Model | N | Grey Matter | White Matter | Hippocampus | Corpus Callosum | White Matter Lesions |
|-----------------------------|-----|--------------------|--------------------|--------------------|---------------------|----------------------|
| | | Beta (SE), p-value | Beta (SE), p-value | Beta (SE), p | Beta (SE), p | Beta (SE), p-value |
| <u>ESR1</u> | | | | | | |
| <i>rs2234693</i> : C allele | 205 | 1 | 1 | 1 | 1 | 1 |
| TT | 90 | -0.28 (0.33), 0.38 | 0.25 (0.24), 0.30 | 0.12 (0.08), 0.14 | 0.008 (0.01), 0.46 | 0.24 (0.10), 0.02* |
| <i>rs9340799</i> : G allele | 171 | 1 | 1 | 1 | 1 | 1 |
| AA | 124 | -0.13 (0.30), 0.66 | 0.29 (0.22), 0.20 | 0.12 (0.07), 0.11 | 0.00 (0.01), 0.98 | 0.11 (0.09), 0.23 |
| <u>ESR2</u> | | | | | | |
| <i>rs1271572</i> : T allele | 206 | 1 | 1 | 1 | 1 | 1 |
| GG | 89 | -0.16 (0.33), 0.64 | -0.17 (0.24), 0.49 | 0.00 (0.08), 0.99 | -0.003 (0.01), 0.81 | -0.004 (0.10), 0.97 |
| <i>rs4986938</i> : A allele | 202 | 1 | 1 | 1 | 1 | 1 |
| GG | 93 | 0.47 (0.33), 0.15 | 0.09 (0.25), 0.70 | 0.12 (0.08), 0.12 | 0.01 (0.01), 0.31 | -0.05 (0.10), 0.62 |
| <i>rs1256049</i> : A allele | 26 | 1 | 1 | 1 | 1 | 1 |
| GG | 269 | -0.32 (0.54), 0.55 | -0.12 (0.40), 0.76 | -0.10 (0.13), 0.46 | -0.02 (0.02), 0.32 | -0.04 (0.17), 0.80 |

^aAll brain measures are given as a percentage of total intracranial brain volume, except for the volume of white matter lesions, which were adjusted for the volume of white matter. *p<0.05