

eTable 1. Reproductive history assessments.

Type of exposure	Exposure	Data	Instrument	Questions/ Criteria
Women				
Endogenous estrogen exposures	Menopausal status	Categorical (pre-, peri-, post-menopausal)	Menopause Questionnaire, clinical evaluation based on the Stages of Reproductive Aging Workshop (STRAW) criteria, and hormone laboratory assessments	Participants were classified as: pre-menopausal (regular cyclist); peri-menopausal (irregular cyclers with an interval of amenorrhea ≥ 60 days or ≥ 2 skipped cycles); or post-menopausal (absence of menstrual cycle for 12 or more months).
	Menopause type	Categorical (spontaneous or induced)	Semi-structured Interviews and Menopause Questionnaire	“Have you received any medical treatment that caused or precipitated menopause (hysterectomy, oophorectomy)?”
	Age at menarche (years)	Continuous and categorical (<13 and ≥ 13 years)	Menopause Questionnaire	“At what age did you have your first menstrual period?”
	Age at menopause (years)	Continuous and categorical (<51 and ≥ 51 years)	Menopause Questionnaire	“What was the date of your last menstrual cycle?”; “Are you post-menopausal (was your last period over 1 year ago)?” If Yes, “At what age did you consider yourself post-menopausal?”

	Number of children	Continuous and categorical (0, 1, ≥ 2)	Menopause Questionnaire	"How many biological children do you have?"
	Number of pregnancies	Continuous	Menopause Questionnaire	"How many times have you been pregnant?" For 1 or more pregnancies, participants were asked to provide the number of births, miscarriages, and abortions. Number of pregnancies was determined by the sum of children, abortions, and miscarriages.
	Age at first birth (years)	Continuous	Menopause Questionnaire	"At what age did you give birth to your first child?"
	Reproductive span (years)	Continuous and categorical (<39 and ≥ 39 years)	n.a.	Calculated as the difference between age at menarche and age at menopause
Exogenous estrogen exposures	Menopause Hormone Therapy (HT) usage	Categorical (never users, past users, current users)	Semi-structured interviews and Menopause Questionnaire	"Are you currently on HT?" "Have you been on HT for menopause?"
	Duration of HT usage (years)	Continuous	Semi-structured interviews and Menopause Questionnaire	"How long have you been on HT?" or "How long were you on HT?"
	Hormonal Contraceptives (HC) usage	Categorical (never users, past users, current users)	Semi-structured interview and Menopause Questionnaire	"Have you taken/are you currently taking birth control?" Participants were asked to specify type/brand/dose, and if IUD, to indicate whether hormonal or non-hormonal.

	Duration of HC usage (years)	Continuous	Semi-structured interviews and Menopause Questionnaire	"How long were you on HC?"
Men				
Endogenous testosterone exposures	Andropause status	Categorical (pre-, post-andropause)	Andropause Questionnaire, clinical diagnosis based on the Aging Male Symptoms (AMS) Scale, hormone laboratory assessments	Participants were classified as pre-andropause or post-andropause
Exogenous testosterone exposure	Testosterone Therapy (TT) usage	Categorical (never users, past users, current users)	Andropause Questionnaire	"Are you currently or have you been on TT?"
Other	Number of children	Continuous and categorical (0, 1, \geq 2)	Andropause Questionnaire	"How many biological children do you have?"
	Age at first birth (years)	Continuous	Andropause Questionnaire	"How old were you when your first biological child was born?"

eTable 2. Associations between menopause status and gray matter volume (GMV)

Ke	Coordinates (x, y, z)	Z	*P _{SVC}	P voxel-level	Side	Anatomical location	BA
Menopause status effects							
78	69, -16, -8	3.00	0.049	<0.001	Right	Inferior temporal gyrus	21
67	55, 24, -4	2.93	0.059	0.001	Right	Inferior frontal gyrus	38
Pre-menopause vs men							
30	42, -46, -14	5.09	0.022	<0.001	Right	Fusiform gyrus	37
69	-27, -44, -21	4.95	0.011	<0.001	Left	Fusiform gyrus	37
57	-26, -4, -24	4.91	0.014	<0.001	Left	Amygdala	
23	22, 21, -4	4.82	0.047	<0.001	Right	Putamen	
Peri-menopause vs men							
8470	26, -46, -18	7.78	<0.001	<0.001	Right	Fusiform gyrus	37
	27, -39, -22	7.64		<0.001	Right	Fusiform gyrus	37
	27, 0, -24	7.60		<0.001	Right	Parahippocampal gyrus	36
	25, -2, -21	7.42		<0.001	Right	Parahippocampal gyrus	28
	28, -16, -18	5.84		0.001	Right	Hippocampus	36
8199	-27, -48, -18	7.43	<0.001	<0.001	Left	Fusiform gyrus	37

	-27, -4, -21	7.15		<0.001	Left	Amygdala	
	-26, -5, -16	7.05		<0.001	Left	Parahippocampal gyrus	36
	-40, -38, -22	7.10		<0.001	Left	Fusiform gyrus	37
	-21, -5, -18	5.75		<0.001	Left	Parahippocampal gyrus	28
1962	-32, 14, 8	5.81	<0.001	<0.001	Left	Insula	
	-14, -22, 6	6.80		<0.001	Left	Thalamus	
1306	-1, -60, 43	5.69	<0.001	<0.001	Left	Precuneus	7
198	-8, 34, -8	5.15	0.003	<0.001	Left	Anterior cingulate gyrus	11
48	-18, 51, 32	5.18	0.016	<0.001	Left	Superior frontal gyrus	9
44	51, -36, 9	5.18	0.017	<0.001	Right	Superior temporal gyrus	22
22	10, -22, 6	5.00	0.025	<0.001	Right	Thalamus	
Post-menopause vs men							
1041	26, -46, -18	7.64	0.001	<0.001	Right	Fusiform gyrus	37
	27, -39, -22	7.40		<0.001	Right	Fusiform gyrus	37
1193	-26, -46, -20	7.15	0.001	<0.001	Left	Fusiform gyrus	37
	-31, -5, -40	5.98		<0.001	Left	Inferior temporal gyrus	20
800	-24, -6, -32	6.99		<0.001	Left	Amygdala	
	-27, -3, -40	5.98		<0.001	Left	Entorhinal cortex	36

863	26, -3, -22	6.93	0.007	<0.001	Right	Amygdala	
	28, -16, -18	6.32		<0.001	Right	Hippocampus	
	27, 0, -24	6.84		<0.001	Right	Parahippocampal gyrus	36
200	30,-8,-39	5.58		<0.001	Right	Inferior temporal gyrus	20
195	24, 9, -6	5.09	0.003	<0.001	Right	Putamen	
121	-21, 8, -8	4.98	0.024	<0.001	Left	Putamen	
106	-5, 37, -9	4.18	<i>0.067</i>	<0.001	Left	Anterior cingulate gyrus	32
	-27, 36, -14	4.02		<0.001	Left	Inferior orbital gyrus	11

*Small volume corrected (SVC) $p < 0.05$, adjusted by age and total intracranial volume. Clusters showing borderline significance are in italics.

Abbreviations: BA, Brodmann area; Ke, cluster extent.

GMV was extracted from the peak association clusters and from the medial temporal lobe clusters in bold, for further examinations.

eTable 3. Associations between number of children and gray matter volume (GMV)

Ke	Coordinates (x, y, z)	Z	*P_{SVC}	P voxel- level	Side	Anatomical location	BA
92	44, 18, 10	3.75	0.005	<0.001	Right	Inferior frontal gyrus	45
40	46, 39, 6	3.60	0.008	<0.001	Right	Inferior frontal gyrus	45
62	48, -51, 13	3.52	0.010	<0.001	Right	Middle temporal gyrus	21
46	-28, 50, 16	3.40	0.032	<0.001	Left	Middle frontal gyrus	46
24	44, -32, -18	3.38	0.016	<0.001	Right	Inferior temporal gyrus	20
21	-36, 2, -42	3.24	0.021	0.001	Left	Inferior temporal gyrus	20

*Small volume corrected (SVC) $p < 0.05$, adjusted by age and total intracranial volume.

Abbreviations: BA, Brodmann area; Ke, cluster extent.

GMV was extracted from the peak association cluster in bold for further examinations.

eTable 4. Associations between exogenous estrogen exposures and gray matter volume (GMV)

Ke	Coordinates (x, y, z)	Z	*P_{svc}	P voxel- level	Side	Anatomical location	BA
Menopause hormone therapy use							
171	20, 27, 36	3.78	0.004	<0.001	Right	Superior frontal gyrus	9
	21, 38, 38	3.34		<0.001	Right	Superior frontal gyrus	9
77	54, 10, -24	3.65	0.006	<0.001	Right	Middle temporal gyrus	21
40	-40, -40, 38	3.52	0.010	<0.001	Left	Supramarginal gyrus	40
39	-10, 28, 36	3.49	0.011	<0.001	Left	Superior frontal gyrus	32
58	-42, -8, -34	3.49	0.011	<0.001	Left	Inferior temporal gyrus	20
34	22, 52, 14	3.46	0.012	<0.001	Right	Superior frontal gyrus	10
39	48, -39, 39	3.46	0.012	<0.001	Right	Supramarginal gyrus	40
42	-28, -66, -8	3.44	0.012	<0.001	Left	Fusiform gyrus	19
26	-26, 32, 28	3.37	0.015	<0.001	Left	Middle frontal gyrus	48
Hormonal contraceptive use							
547	-9, -61, 63	4.37	0.001	<0.001	Left	Precuneus	7
	-10, -60, 66	3.67		<0.001	Left	Precuneus	7

269	-38, -62, -14	4.22	0.001	<0.001	Left	Fusiform gyrus	37
787	52, -51, 24	4.14	0.001	<0.001	Right	Angular gyrus	22
	51, -57, 42	3.59		<0.001	Right	Angular gyrus	39
196	-56, -10, -16	4.06	0.001	<0.001	Left	Middle temporal gyrus	20
235	51, -34, 44	4.03	0.002	<0.001	Right	Supramarginal gyrus	40
752	-21, 54, 4	4.01	0.002	<0.001	Left	Superior frontal gyrus	11
	-32, 42, 24	3.80		<0.001	Left	Middle frontal gyrus	46
442	-48, -70, 32	4.00	0.003	<0.001	Left	Angular gyrus	39
	-48, -60, 46	3.45		<0.001	Left	Angular gyrus	39
541	39, 38, 30	3.92	0.003	<0.001	Right	Middle frontal gyrus	46
	42, 22, 40	3.76		<0.001	Right	Middle frontal gyrus	44
68	-42, -14, -39	3.84	0.004	<0.001	Left	Inferior temporal gyrus	20
169	-23, -51, 67	3.83	0.004	<0.001	Left	Precuneus	7
87	38, -58, 56	3.77	0.004	<0.001	Right	Angular gyrus	40
110	40, -10, -40	3.70	0.005	<0.001	Right	Inferior temporal gyrus	20

*Small volume corrected (SVC) $p < 0.05$, adjusted by age and total intracranial volume. Abbreviations: BA, Brodmann area; Ke, cluster extent. GMV were extracted from the peak association clusters in bold for further examinations.

eTable 5. Associations between reproductive history exposures and medial temporal lobe gray matter volume (GMV)

	Coeff.	95% C.I.	P	R sq.
Menopause status				
Men	Ref			0.425
Pre-menopause	-0.03	(-0.06, 0.00)	0.041	
Peri-menopause	-0.06	(-0.08, -0.03)	<0.001	
Post-menopause	-0.03	(-0.05, -0.01)	0.004	
Age at menarche				
Numeric	0.00	(0.00, 0.01)	0.481	0.387
<13	Ref			0.866
≥13	0.00	(-0.02, 0.01)	0.791	
Age at menopause				
Numeric	0.00	(0.00, 0.00)	0.579	0.504
<51	Ref			0.503
≥51	0.01	(-0.02, 0.03)	0.611	
Reproductive span				
Numeric	0.00	(0.00, 0.00)	0.737	0.494

<39	Ref			0.511
≥39	0.01	(-0.01, 0.03)	0.221	
Hysterectomy status	0.01	(-0.02, 0.03)	0.670	0.380
HT use	0.01	(-0.01, 0.03)	0.336	0.385
HC use	0.02	(0.00, 0.04)	0.017	0.406
Number of pregnancies	0.00	(0.00, 0.01)	0.312	0.381
Number of children (women)				
Numeric	0.01	(0.00, 0.01)	0.026	0.411
0	Ref			0.419
1	0.00	(-0.02, 0.03)	0.773	
≥2	0.02	(0.00, 0.04)	0.028	
Number of children (men)				
Numeric	0.00	(-0.02, 0.01)	0.872	0.582
0	Ref			0.585
1	0.02	(-0.06, 0.10)	0.665	
≥2	0.01	(-0.04, 0.05)	0.818	

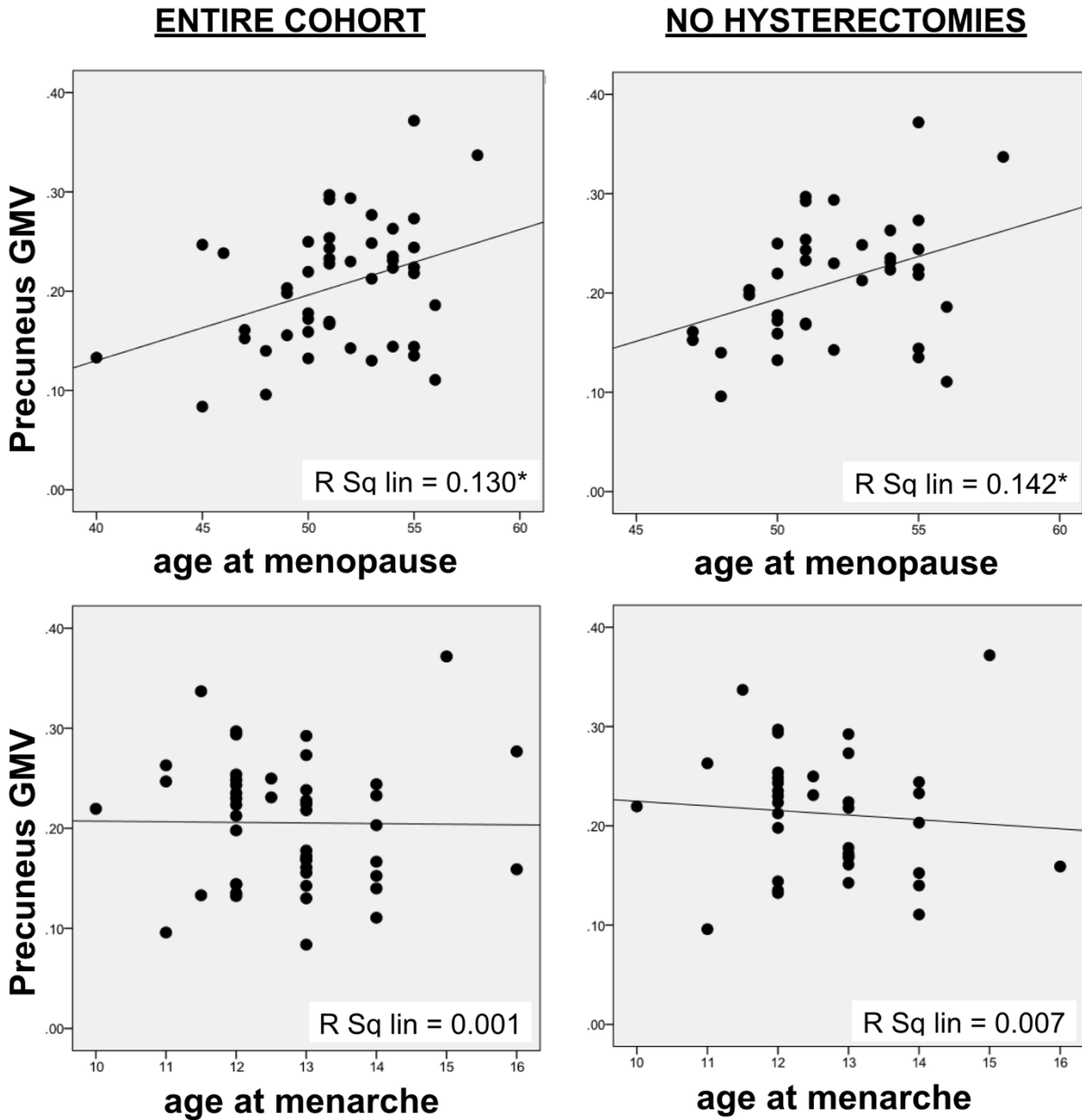
Fully adjusted data. Significant results are in bold.

eTable 6. Associations between regional gray matter volume (GMV) and cognitive measures

	Memory				Global cognition			
	Coeff.	95% CI	P	R sq.	Coeff.	95% CI	P	R sq.
Inferior frontal gyrus	0.02	(0.00, 0.04)	0.102	0.030	0.00	(-0.03, 0.04)	0.776	0.003
Inferior temporal gyrus	0.02	(0.00, 0.04)	0.016	0.063	0.02	(0.00, 0.05)	0.122	0.030
Medial temporal lobe	2.46	(0.19, 4.72)	0.034	0.036	1.78	(0.32, 3.24)	0.018	0.047
Precuneus	0.00	(-0.02, 0.02)	0.698	0.004	0.00	(-0.03, 0.03)	0.874	0.003
Superior frontal gyrus	0.00	(-0.01, 0.02)	0.602	0.008	0.00	(-0.03, 0.02)	0.798	0.007

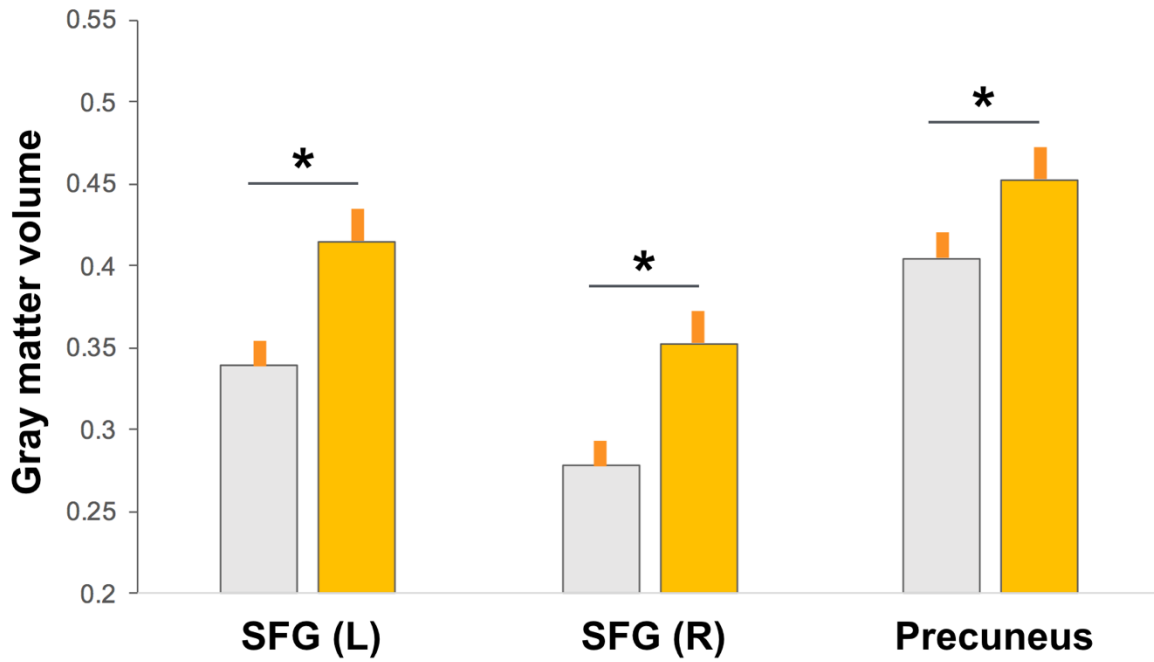
Significant results are in bold; trends are in italics. Regional GMV measures were extracted from the peak association cluster for each exposure, e.g. inferior temporal gyrus for menopause status; precuneus for reproductive span and HC use; inferior frontal gyrus for number of children; and superior frontal gyrus for HT use (**eTables 2-4**). MTL GMV was extracted from the clusters yielding significant differences in the analysis of post-menopause status vs. men (**eTable 2**).

eFigure 1. Effects of age at menopause and age at menarche on GMV



Associations of precuneus gray matter volume (GMV), expressed in units of GM density, with (top) age at menopause, years, and (bottom) age at menarche, years; *p<0.05.

eFigure 2. Effects of hormonal contraceptive and menopausal hormonal therapy use on GMV



GMV measures are mean (SEM), expressed in units of GM density, adjusted by age and total intracranial volume; * $p < 0.05$.

Graphs display GMV differences between participants who never took hormonal contraceptives or HT (gray) and those who took both hormonal contraceptives and later on, HT (yellow), in left (L) and right (R) superior frontal gyrus, and precuneus.