

Age at menopause and lifetime cognition _supplemental tables e-1 to e-5

Supplementary Table e-1. Estimates from multilevel models showing change in verbal memory with age and the mean difference in verbal memory between 43 and 69 years, by each covariate separately and mutually adjusted in (a) women with a natural menopause and (b) women with a surgical menopause.

	Model 1 Each covariate adjusted only for both age terms			Model 2 Fully adjusted		
	Regression coefficient	95% CI	p-value	Regression Coefficient	95% CI	p-value
a) Natural menopause (846 women, 2678 observations)						
Age (per yr): linear term				0.0095	-0.054,0.073	.8
Age (per yr): quadratic term				-0.0037	-0.0057,-0.0017	<.001
Age at period cessation (per yr)	0.17	-0.07,0.27	.001	0.095	0.020,0.17	.013
*HRT yes v. no	-0.33	-0.98,0.32	.3	-0.35	-1.00,0.28	.3
*BMI (per unit)	-0.44	-0.72,-0.15	.002	-0.23	-0.48,0.016	.07
*Smoker v. non-smoker	-0.87	-1.5,-0.24	.007	-0.21	-0.79,0.37	.5
Occupation class (per class)	-1.9	-2.2,-1.7	<.001	-0.55	-0.83,-0.28	<.001
Educational qualifications (per step)	2.4	2.1,2.6	<.001	1.3	1.0,1.6	<.001
Childhood cognitive ability (per 1 SD)	3.1	2.8,3.4	<.001	1.7	1.4,2.1	<.001
b) Surgical menopause (313 women, 965 observations)						
Age (per yr): linear term				0.25	0.12,0.37	<.001
Age (per yr): quadratic term				-0.011	-0.015,-0.0070	<.001
Age at period cessation (per yr)	0.15	0.057,0.24	.002	0.055	-0.028,0.14	.2
Bilateral oophorectomy v. hysterectomy	-0.46	-1.83,0.92	.5	-0.037	-1.11,1.03	.9
*HRT yes v.no	-0.78	-1.53,-0.32	.04	-0.73	-1.46,-0.012	.05
*BMI (per unit)	-0.30	-0.80,0.20	.2	0.043	-0.39,0.48	.8
*Smoker v. non-smoker	0.90	-0.83,2.6	.3	1.26	-0.40,2.98	.1
*Smoking status by age	-0.35	-0.62,-0.080	.011	-0.34	-0.60,-0.07	.01
*Smoking status by age ²	0.013	0.0034,0.022	.008	0.013	0.0033,0.022	.008
Occupation class (per class)	-1.8	-2.2,-1.4	<.001	-0.50	-0.93,-0.073	.02
Educational qualifications (per step)	2.3	1.9,2.7	<.001	1.22	0.76,1.69	<.001
Childhood cognitive ability (per 1 SD)	3.3	2.8,3.8	<.001	1.98	1.4,2.6	<.001

*included as time-varying covariates

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Supplementary Table e-2. Estimates from multilevel models showing change in processing speed with age and the mean difference in verbal memory between 43 and 69 years, by each covariable separately and mutually adjusted in (a) women with a natural menopause and (b) women with a surgical menopause

	Model 1 Each covariable adjusted only for both age terms			Model 2 Fully adjusted		
	Regression coefficient	95% CI	p-value	Regression coefficient	95% CI	p-value
a) Natural menopause (847 women, 2705 observations)						
Age (per yr): linear term				-9.0	-9.9,-8.1	<.001
Age (per yr): quadratic term				0.18	0.15,0.21	<.001
Age at period cessation (per yr)	0.77	-0.30,1.85	.2	0.64	-0.43,1.71	.2
*HRT yes v.no	-3.1	-12.1,5.8	.5	-3.7	-12.6,5.2	.4
*BMI (per unit)	-4.5	-8.0,-1.0	.01	-3.7	-7.2,-0.22	.04
*Smoker v. non-smoker	-0.21	-8.3,7.9	1.0	2.2	-6.3,10.3	.6
Occupation class (per class)	-4.6	-8.0,-1.3	.007	-0.19	-4.1,3.8	.9
Educational qualifications (per step)	6.6	3.5,9.6	<.001	3.9	0.015,7.8	.06
Childhood cognitive ability (per 1 SD)	3.8	-2.7,10.3	.2	0.058	-7.2,7.3	1.0
Childhood cognitive ability (per 1SD) by age	0.86	0.0055,1.72	.05	0.89	0.03,1.74	.04
Childhood cognitive ability (per 1SD) by age ²	-0.025	-0.051,-0.0021	.07	-0.025	-0.052,0.0014	.06
b) Surgical menopause (314 women, 980 observations)						
Age (per yr): linear term				-6.3	-10.7,-1.9	.005
Age (per yr): quadratic term				0.094	-0.45,0.23	.2
Age at period cessation (per yr)	0.46	-0.56,1.48	.4	0.43	-0.72,1.60	.5
Bilateral oophorectomy v. hysterectomy	0.8	-12.7,14.2	.9	-1.92	-16.9,13.1	.8
*HRT yes v. no	0.12	-10.2,10.5	1.0	0.71	-9.6,11.0	.9
*BMI (per unit)	1.6	-4.5,7.6	.6	2.1	-4.0,8.2	.5
*Smoker v. non-smoker	1.4	-11.1,13.9	.8	3.4	-9.3,16.1	.6
Occupation class (per class)	5.6	-2.5,13.6	.2	5.4	-3.9,14.8	.3
Occupation class (per class) by age	-1.5	-2.6,-0.32	.01	-1.0	-2.3,0.27	.1
Occupation class (per class) by age ²	0.046	0.011,0.082	.01	0.033	-0.0069,0.073	.1
Educational qualifications (per step)	3.8	-1.4,8.9	.1	3.4	-3.1,9.9	.3
Childhood cognitive ability (per 1 SD)	-5.4	-16.4,5.6	.3	-4.3	-17.5,8.9	.5
Childhood cognitive ability (per 1SD) by age	1.9	0.39,3.48	.01	1.3	-0.46,3.0	.1
Childhood cognitive ability (per 1SD) by age ²	-0.059	-0.11,-0.011	.02	-0.038	-0.093,0.016	.2

*included as time-varying covariables

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Supplementary Table e-3 Mean and standard deviation (SD) and regression coefficients (and 95% CI) for verbal memory at various ages by menopausal characteristics.

	Verbal memory age 43	Verbal memory age 53	Verbal memory age 60-64	Verbal memory age 69
	Mean (SD)	Mean (SD)	Mean (SD)	
Age at period cessation (years)				
27-39	23.7 (6.4)	24.0 (5.7)	24.4 (5.6)	22.1 (6.5)
40-44	25.0 (6.2)	23.7 (5.6)	24.7 (5.6)	21.8 (5.5)
45-49	25.4 (6.6)	24.7 (6.3)	24.9 (6.3)	22.7 (6.4)
50-52	25.8 (6.4)	25.1 (6.6)	25.4 (6.5)	23.7 (6.0)
53-55	27 (6.1)	25.8 (5.8)	25.7 (5.7)	24.1 (5.7)
56-62	26.9 (6.4)	25.2 (6.2)	25.7 (5.8)	23.9 (5.7)
Total sample	1192	1202	937	871
Regression coeff. (95% CI) (adj type)	0.17 (0.09, 0.25)	0.14 (0.06, 0.22)	0.13 (0.04, 0.22)	0.16 (0.07, 0.25)
p-value (trend) adjusting for type of menopause	<.001	<.001	.005	.001
Menopause type				
Natural menopause	26.1 (6.5)	25 (6.2)	25.3 (6.2)	23.5 (5.9)
Hysterectomy	25.0 (6.3)	24.5 (5.6)	24.9 (5.5)	22.2 (6.5)
Bilateral oophorectomy	24.6 (6.2)	25.0 (6.7)	25.2 (6.2)	23.0 (6.2)
Total sample	1192	1202	937	871
Regression coeff. 95% CI				
Bilateral oophorectomy v. natural menopause	-1.5 (-2.7, -0.37)	-0.02 (-1.1, 1.1)	-0.17 (-1.5, 1.1)	-0.50 (-1.8, 0.78)
Hysterectomy or unilateral oophorectomy v. natural menopause	-1.1 (-2.1, -1.0)	-0.46 (-1.44, 0.52)	-0.41 (-1.5, 0.67)	-1.3 (-2.4, -0.19)
P-value	.007	.6	.8	.07
Age at natural menopause (years)				
<45	25.8 (6.8)	23.9 (6.1)	25.8 (6.5)	22.7 (5.7)
45-49	25.0 (6.7)	24.0 (6.1)	24.5 (6.4)	22.7 (6.1)
50-52	26.0 (6.5)	25.2 (6.5)	25.3 (6.5)	23.6 (6.0)
53-55	27.0 (6.1)	25.8 (5.9)	25.7 (5.7)	24.2 (5.8)
56-62	26.9 (6.3)	25.2 (6.1)	25.8 (5.9)	23.8 (5.5)
Total sample	860	883	691	634
Regression coeff. (95% CI)	0.17 (0.06, 0.28)	0.15 (0.05, 0.26)	0.10 (-0.02, 0.22)	0.14 (0.02, 0.25)
p-value (trend)	.003	.004	.1	.02
Age at hysterectomy or unilateral oophorectomy (years)				
<40	23.7 (6.1)	23.8 (5.2)	24.2 (5.5)	22.0 (6.6)
40-44	24.7 (6.3)	23.6 (5.5)	24.3 (5.2)	21.2 (5.9)
45-49	27.5 (5.3)	27.4 (5.2)	26.5 (5.6)	23.1 (6.9)
≥50	26.6 (8.3)	23.5 (7.5)	27.3 (6.1)	27.3 (7.0)
Regression coeff. (95% CI)	0.24 (0.08, 0.40)	0.19 (0.04, 0.33)	0.21 (0.06, 0.37)	0.25 (0.06, 0.44)
p-value (trend)	.004	.011	.007	.011
Age at bilateral oophorectomy (years)				
<40	23.3 (6.6)	25.1 (7.0)	23.9 (5.9)	21.4 (4.8)
40-44	24.3 (5.4)	23.8 (5.7)	24.5 (4.9)	23.9 (4.8)
45-49	25.0 (6.6)	25.2 (7.1)	25.3 (6.8)	22.4 (7.1)
≥50	24.8 (5.9)	25.2 (6.5)	25.6 (6.1)	23.9 (6)
Regression coeff. (95% CI)	0.10 (-0.06, 0.27)	0.05 (-0.14, 0.25)	0.09 (-0.13, 0.31)	0.10 (-0.11, 0.31)
p-value for trend	.3	.6	.4	.4

Age at period cessation is based on months since birth, and regression coefficients per year

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Supplementary Table e-4. Mean and standard deviation (SD) and regression coefficients (and 95% CI) for processing speed at various ages by menopausal characteristics

	Processing speed age 43	Processing speed age 53	Processing speed age 60-64	Processing speed age 69
	Mean (SD)	Mean (SD)	Mean (SD)	
Age at period cessation (years)				
27-39	357.0 (71.9)	286.5 (71.6)		264.1 (75.8)
40-44	350.7 (79.2)	288.6 (80.7)	267.3 (69.5)	273.5 (91.6)
45-49	354.2 (77.1)	286.1 (74.4)	265.3 (70.0)	268.7 (77.6)
50-52	350.1 (72.1)	286.8 (75.3)	277.6 (74.1)	268.7 (68.7)
53-55	360.5 (74.3)	287.7 (71.4)	269.2 (74.3)	259.4 (69.1)
56-62	359.6 (73.0)	299.4 (84.8)	284.2 (81.0)	281.1 (79.0)
Total sample	1224	1211	948	877
Regression coeff. (95% CI) (adj. for menopause type)	0.56 (-0.38,1.5)	0.64 (-0.32,1.6)	0.9 (-0.18,2.0)	0.8 (-0.32,1.9)
p-value for trend	.2	.2	.1	.2
Type of menopause				
Natural menopause	353.4 (75.5)	287.4 (76.0)	273.0 (75.3)	266.1 (74.2)
Hysterectomy	356.6 (72.8)	292.8 (73.5)	272.6 (71.0)	269.5 (84.9)
Bilateral oophorectomy	358.4 (72.2)	286.1 (75.1)	265.0 (63.6)	277.9 (67.1)
Total sample	1224	1211	948	877
Bilateral oophorectomy v. natural menopause	5.0 (-8.1,18.1)	-1.3 (-14.9,12.4)	-8.0 (-23.6,7.7)	11.8 (-4.3,27.9)
Hysterectomy or unilateral oophorectomy v. natural menopause	3.1 (-8.4,14.6)	5.4 (-6.5,17.4)	-0.4 (-13.3,12.5)	3.4 (-10.2,17.1)
P-value (categories)	.7	.6	.6	.3
Age at natural menopause (years)				
<45	336.1 (82.8)	282.7 (83.3)	268.8 (81.9)	261.6 (76.7)
45-49	351.7 (78.7)	284.0 (73.0)	262.5 (68.2)	266.6 (80.3)
50-52	350.8 (73.0)	288.1 (76.2)	278.7 (75.7)	264.9 (69.3)
53-55	360.5 (74.9)	286.5 (72.5)	269.5 (75.0)	258.8 (69.8)
56-62	357.7 (73.3)	296.4 (85.2)	285.0 (82.4)	282.0 (80.6)
Total sample	880	889	699	637
Regression coeff. (95% CI)	1.2 (-0.08,2.5)	0.56 (-0.72,1.8)	1.3 (-0.24,2.8)	0.78 (-0.67,2.2)
p-value for trend	.07	.4	.1	.3
Age at hysterectomy (years)				
<40	367.4 (70.2)	289.1 (72.7)	277.2 (75.2)	264.9 (82.1)
40-44	353.5 (77.3)	296.5 (76.5)	266.6 (65.1)	276.0 (102.6)
45-49	348.3 (69.8)	293.2 (74.0)	273.1 (75.9)	264.2 (64.5)
≥50	333.4 (67.7)	293.9 (66.3)	274.5 (65.0)	281.7 (36.1)
	198	186	152	143
Regression coeff. (95% CI)	-1.8 (-3.6,0.48)	0.10 (-1.8,2.0)	-0.09 (-2.1,1.9)	0.81 (-1.7,3.3)
p-value for trend	.06	.9	.9	.5
Age at bilateral oophorectomy (years)				
<40	327.6 (71.3)	285.9 (70.8)	251.2 (62.9)	259.9 (51.7)
40-44	366.3 (73.1)	264.9 (82.1)	256.6 (48.9)	294.9 (53.0)
45-49	368.1 (76.2)	288.9 (81.4)	269.9 (72.7)	281.3 (78.9)
≥50	356.3 (66.0)	290.6 (67.8)	267.2 (59.8)	275.6 (63.6)
	146	136	97	97
Regression coeff. (95% CI)	1.6 (-0.34,3.5)	1.5 (-0.63,3.7)	1.4 (-0.87,3.6)	.78 (-1.5,3.1)
p-value for trend	.1	.2	.2	.5

Age at period cessation is based on months since birth, adjusted for type of menopause, and regression coefficients per year

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Supplementary Table e-5. Mean difference in a) verbal memory score and b) processing speed score at age 69 by ever use of HRT, length of use and years since last use by type of period cessation. Adjusted for all covariates

	Natural menopause Adj. for covariabless (n=568-587) Column 1			Hysterectomy Adj. for covariables (n=96-100) Column 2			Bilateral oophorectomy Adj. for covariables (n=66-68) Column 3			Bilateral oophorectomy Additionally adjusted for verbal memory / processing speed at age 43 (n=63-67) Column 4		
	Reg coeff	95% CI	p-value	Reg coeff	95% CI	p-value	Reg coeff	95% CI	p-value	Reg coeff	95% CI	p-value
a)Verbal memory												
HRT ever (yes v.no)	-0.55	-1.4,0.28	.2	-1.1	-4.1,1.8	.5	4.7	-0.63,10.0	.08	5.1	0.24,9.9	.04
Length of HRT use (yrs)			.4			.3			.2			.2
> 10 years	-0.90	-2.6,0.76		-1.8	-5.6,2.0		4.9	-0.94,10.7		5.0	-0.34,10.3	
7-10 years	-0.80	-2.0,0.44		0.91	-2.9,4.7		3.4	-2.4,9.2		3.6	-1.8,9.0	
3-6 years	-0.96	-2.2,0.25		-2.9	-6.6,0.86		4.8	-0.87,10.4		5.7	0.53,10.8	
< 3 years	0.0013	-1.2,1.2		-1.0	-5.2,3.2		7.3	0.39,14.2		6.1	-0.21,12.3	
Not used HRT	Ref			Ref								
Last use of HRT			.3			.7			.2			.2
In the last year	-1.4	-3.1,0.35		-0.70	-4.8,3.4		6.5	0.04,13.1		5.9	-0.11,11.9	
1-5 years ago	0.24	-1.5,2.0		-1.5	-7.6,4.4		3.0	-3.2,9.2		3.2	-2.6,8.9	
➢ 5 years ago	-0.52	-1.4,0.38		-1.8	-4.9,1.3		4.3	-1.2,9.8		4.9	-0.13,10.0	
Never used HRT	Ref			Ref								
b)Processing speed												
HRT ever (yes v.no)	-5.1	-16.6,6.3	.4	-0.81	-41.7,40.1	1.0	53.0	-18.7,124.6	.1	79.1	12.7,145.5	.02
Length of HRT use (yrs)			.9			.9			.03			.007
> 10 years	-4.1	-26.6,18.5		-7.6	-59.7,44.4		71.9	-2.8,146.5		100.3	31.6,169.1	
7-10 years	-2.2	-19.2,14.7		-12.3	-63.7,39.1		49.4	-24.9,123.7		64.9	-2.7,132.5	
3-6 years	-4.0	-20.7,12.8		-5.6	-55.3,44.2		23.6	-48.8,96.1		52.3	-15.4,120.1	
< 3 years	-8.5	-24.8,7.8		16.3	-40.0,72.5		102.4	13.7,191.1		121.8	41.1,202.4	
Not used HRT	Ref			Ref			ref			ref		
Last use of HRT			.6			.4			<.001			<.001
In the last year	0.86	-22.6,24.4		20.3	-33.4,74.0		101.3	26.9,175.7		120.2	52.7,187.8	
1-5 years ago	6.5	-17.4,30.3		-41.4	-120.4,37.5		100.2	29.6,170.9		121.2	57.1,185.2	
➢ 5 years ago	-6.8	-19.3,5.7		-9.3	-50.6,31.9		29.1	-34.1,92.2		48.8	-9.1,106.7	
Never used HRT	Ref			Ref			ref			ref		