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Impact of a premature menopause on cognitive function in later life

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Objective To determine whether premature menopause (≤40 years) can have long-lasting effects on later-life cognition and investigate whether this association varies depending on the type of menopause and use of hormone treatment (HT).

Design Population-based cohort study.

Setting The French Three-City Study.

Population Four thousand eight hundred and sixty-eight women aged at least 65 years.

Methods Multivariable-adjusted logistic regression models were used to determine the association between age at menopause, type of menopause (surgical, natural), and the use of menopausal HT and later-life cognitive function.

Main outcome measures Performance on a cognitive test battery (at baseline and over 7 years) and clinical dementia diagnosis.

Results Menopause at or before the age of 40 years, both premature bilateral ovariectomy and premature ovarian failure (non-surgical loss of ovarian function), was associated with worse verbal fluency (OR 1.56, 95%CI 1.12–1.87, $P = 0.004$) and visual memory (OR 1.39, 95%CI 1.09–1.77, $P = 0.007$) in later life. HT at the time of premature menopause appeared beneficial for later-life visual memory but increased the risk of poor verbal fluency. Type of menopause was not significantly associated with cognitive function. Premature menopause was associated with a 30% increased risk of decline in psychomotor speed and global cognitive function over 7 years.

Conclusion Both premature surgical menopause and premature ovarian failure were associated with long-term negative effects on cognitive function, which are not entirely offset by menopausal HT. In terms of surgical menopause, these results suggest that the potential long-term effects on cognitive function should form part of the risk/benefit ratio when considering ovariectomy in younger women.

Keywords Cognition, dementia, hormone treatment, ovariectomy, premature menopause.

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Introduction

Menopause signals the end of spontaneous ovarian function and a woman's reproductive life. Endocrine changes accompanying the menopause include a gradual albeit erratic decline in estrogen levels over several years,[1] which drop to a low level in the postmenopause.[2] These changes in estrogen levels have been speculated to account for the increased reporting of memory complaints during this period.[3,4] In support of this, experimental evidence indicates that estrogen has neuroprotective and neurotrophic effects[5] and, after the menopause, brain atrophy in women accelerates at a faster rate than in men.[6] Although it remains under debate,[7,8] positive correlations between endogenous estrogen levels and cognitive function[9,10] have been reported, and supplementing estrogen through hormone treatment (HT) may help reduce cognitive decline and dementia risk in postmenopausal women.[11,12]

Women with a bilateral ovariectomy before the natural onset of menopause (surgical menopause) experience an abrupt drop in estrogen levels.[13] Studies have found a significant decline in cognitive performance post-surgery, but those that have compared cognitive function in women with surgical versus natural menopause report mixed findings.[14–16] It may be that the effects are only transient or that age at menopause is a more important factor. Age at surgical menopause was directly correlated with verbal memory performance in one study[16] and another study reported that surgical menopause after 50 years did not increase the risk of global impairment.[17] No subsequent study has attempted to replicate these findings and it remains unknown whether any negative effects of an early menopause could be offset by menopausal HT. There is some evidence to suggest that short-term HT at the time of surgical menopause may be beneficial,[18,19] but there is less evidence for naturally menopausal women[20] and very few studies have taken into account age at natural menopause. Another limitation is the definition of surgical menopause, which has often included women with a hysterectomy in the absence of an ovariectomy.[21–23]

This study aims to determine whether a younger age at menopause has long-lasting effects on cognition, based on performance on a short cognitive test battery administered at baseline and over follow-up. The potential modifying effects of type of menopause, natural or surgical, as well as menopausal HT were also examined. We hypothesise that a younger age at menopause, in particular surgical menopause, will be associated with worse later-life cognition, but the use of HT at the time of menopause will help offset these effects.

Methods

Participants

The recruitment of participants to the Three-City Study cohort has been described in detail previously.[24] In brief, non-institutionalised individuals living in one of three French cities (Montpellier, Bordeaux or Dijon) and aged at least 65 years were recruited between 1999 and 2001 by random selection from the electoral rolls. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and all participants provided written informed consent.

Of the 5526 women recruited who were free of dementia at baseline, 84 did not report an age at menopause, 239 women were missing data concerning at least one of the other key characteristics (type of menopause, use of HT at the menopause), 232 had incomplete baseline cognitive testing and a further 103 women were missing data concerning key covariates (including current use of HT). This left a total of 4868 women for analysis. Compared with the analysed sample, excluded participants were older and had a higher frequency of depressive symptoms, activity limitations and comorbidity ($P < 0.003$) and they were more likely to have poorer cognitive function at baseline ($P \leq 0.03$). Excluded participants were also more likely to have menopause at an earlier age ($P = 0.001$).

Cognitive measures and dementia diagnosis

A short neuropsychological battery of valid, reliable and widely used tests[25–28] assessing different areas of cognitive functioning (as detailed previously[29]) were administered by trained staff at baseline and at each follow-up (2, 4 and 7 years). These tests are considered important diagnostic tools and can be used to help distinguish normal age-related changes from those associated with more severe conditions. The Mini-Mental State Examination (MMSE) is one of the most commonly used tests to measure global cognitive function[30] and is designed to detect more serious cognitive defects. Benton's Visual Retention Test (BVRT) requires participants to identify correctly a line drawing from one they were shown previously, and thus assesses visual memory.[31] Isaacs Set Test provided a measure of verbal fluency or semantic access, as participants were given 30 seconds to generate as many words as possible within a given semantic category (animals, colours, fruits and cities).[32] Semantic memory refers to memory for generic, over-learned information, including memory for word names. The Trail Making Tests A (TMTA) and B (TMTB) are timed visual motor tasks where participants have to connect consecutively numbered circles (TMTA) or alternate number and letter circles (TMTB). TMTA assesses psychomotor speed and attention, and TMTB assesses executive function.[33] Executive function tasks are considered to be higher order cognitive function tasks which require more complex thought processes. Given the non-normal distribution of scores on the cognitive tests and as described previously,[34] low cognitive performance at baseline was defined as scoring in the lowest quintile for each cognitive test or the highest quintile for the timed TMTA and TMTB (Table S1). This enabled the identification of women with the poorest cognitive function on each of the tasks. Cognitive decline was evaluated by calculating the change in test scores between each of the follow-ups and the baseline score. Substantial decline was defined as those in the lowest quintile of the difference in score (greatest decline) over follow-up or in the highest quintile for TMTA and TMTB, and the time of decline was recorded as the date of the first follow-up examination at which substantial decline was noted.

At baseline and each follow-up interview, dementia diagnoses were made based on a three-step procedure.[24,35] This involved a trained psychologist undertaking a complete neuropsychological examination which assessed various domains of cognitive function, and then the gathering of information related to the severity of cognitive disorders, physical activity limitations and magnetic resonance images or computed tomography scans, if these were available. All participants suspected of having dementia were examined by a neurologist. The potential dementia cases were then reviewed by a national panel of dementia experts, who were neurologists not associated with the 3C study. These neurologists used all of the existing information to reach a consensus on a diagnosis of dementia, which was made according to DSM-IV revised criteria and etiology. The date of the follow-up interview in which the diagnosis of dementia was made, was recorded as the date of dementia onset.

Menopausal characteristics and hormone treatment

Women reported their age at menopause, which was defined as 1 year without menses.[36] They were also asked to state whether they had undergone a hysterectomy and/or bilateral ovariectomy and, if so, at what age this had occurred. The participants were also asked to state whether their menopause was natural, surgical, i.e. the result of a bilateral ovariectomy or due to another procedure (e.g. radiation or chemotherapy).

Women were grouped according to their age and type of menopause and these groups were defined based on standard definitions used in the literature.[37] The average age of menopause is around 50 years in the Western world.[38] An 'early menopause' is defined as occurring between the ages of 41 and 45 years and could be natural or surgically induced. 'Premature surgical menopause' refers to a bilateral ovariectomy at or before 40 years of age and 'premature ovarian failure' refers to non-surgical loss of ovarian function at or before 40 years. The more general term 'premature menopause' refers to menopause at or before 40 years of age, without taking into account whether this was surgically induced or resulted from premature ovarian failure.

At 4 years follow-up, 12% of the women recruited from the Montpellier centre were also administered a separate questionnaire, which contained several questions that had already been asked at baseline, such as their age at menopause, type of menopause and ever having had a hysterectomy or ovariectomy. The overall concordance in responses was very high, suggesting that these data were valid.[39]

Women recorded current and past use of HT and detailed information related to the type and the duration of treatment. Current treatment use was validated by presentation of the prescription or the medication itself and photos of the standard prescribed treatments aided in the recall of past HT. Specific questions also focused on women's use of HT at the time of menopause, which was defined as any estrogen-containing treatment started within 2 years of the amenorrhoea, and used for at least 1 year.

Covariates

Women responded to detailed questionnaires which covered socio-demographic, lifestyle and health information. Information relevant to the current study included the participant's age, education level, alcohol consumption, smoking status and living situation. The Rosow and Breslau mobility and the Instrumental Activities of Daily Living scales[40,41] were used to assess activity limitations among the participants, which was defined as being unable to complete one or more activities from both scales. The presence of depressive symptoms was assessed with the Centre for Epidemiology Studies Depression Scale (CES-D).[42] Genotyping of Apolipoprotein E $\varepsilon 4$ (*APOE*-$\varepsilon 4$) was performed in Lille, France (http://www.pasteur-lille.fr/fr/recherche/plateformes/amouyel_plat.html). Comprehensive medical questionnaires as well as complete drug inventories and fasting blood samples were used to obtain information on the overall health of the participants. In this study we defined chronic illness as having one or more of the following: diabetes (fasting glucose ≥7.0 mmol/l or treatment), thyroid problems, asthma, vascular diseases (including angina pectoris, myocardial infarction, stroke, cardiovascular surgery, bradycardia or palpitations), hypertension (resting blood pressure ≥160/95 mm Hg or treated) or hypercholesterolemia (total cholesterol ≥6.2 mmol/l).

Statistical analysis

The association between baseline socio-demographic, lifestyle and health variables, and menopausal characteristics and cognitive function was examined using *t*-tests, analysis of variance (ANOVA) and chi-squared tests as appropriate. Multivariable logistic regression models were used to examine the association between age at menopause and poor cognitive performance at baseline. Consecutive covariate adjustment was made to determine whether any specific factors strongly influenced the results. The association between type of menopause was then examined, as well as the age at menopause when stratified by type of menopause, in multivariable logistic regression analysis.

Cox proportional hazards models with delayed entry were used to assess the association between age or type of menopause and the incidence of dementia. To avoid the problem of non-proportionality in dementia risk with age, age itself was taken as the basic time scale, and birth as the time origin.[43] Similar Cox models were also used to determine the longitudinal association between menopausal characteristics and the 7-year risk of cognitive decline. The Cox model helps minimise selection bias due to cohort attrition by taking into account all the information available until time of censoring, due to loss to follow-up, death, or the time when cognitive decline was observed. This approach was chosen due to the nature of the

Table 1. Characteristics of the 4868 participants according to their age at menopause

Characteristic	Age at menopause (years)				*P*
	>50 *n* = 2005	46–50 *n* = 1871	41–45 *n* = 621	≤40 *n* = 371	
	Mean (SD)				
Age (years)	73.9 (5.4)	74.2 (5.4)	74.6 (5.5)	74.1 (5.2)	0.02
	%				
≥12 years' schooling	25.5	22.8	21.1	18.1	0.005
Married or living with others	47.6	48.0	51.9	50.9	0.20
≥24 g alcohol each day	4.4	4.1	4.4	4.4	0.97
Heavy smoker (10 pack years)	3.6	4.3	3.6	5.4	0.34
Physical activity limitations	9.2	8.6	9.0	14.3	0.007
Chronic illness*	46.5	46.5	52.2	51.2	0.03
Depressive symptoms (CES-D ≥16)	27.7	29.0	30.1	33.4	0.13
Anticholinergic medication	8.8	9.1	9.5	11.6	0.40
At least one Apoe-ε4 allele	20.8	18.6	19.4	20.4	0.45
Current use of hormone treatment	15.4	13.8	11.8	12.1	0.07
Used hormone treatment at menopause**	22.1	18.1	18.8	28.8	<0.001
Type of menopause					
Natural	90.8	83.2	59.0	27.0	<0.001
Surgical menopause (bilateral ovariectomy)	4.8	8.1	18.5	36.6	

*Includes cerebro- and cardio-vascular disease, more than one chronic illnesses (high blood pressure, high cholesterol, diabetes, thyroid problems, asthma), or cancer diagnosed within the last 2 years.
**Started HT at the menopause or within 2 years around the time of the menopause and used for a minimum of 1 year.

repeated cognitive tests, which results in learning effects. It was preferred over mixed model analysis, which might be more sensitive to fluctuating and small changes in cognitive scores over time. Furthermore, the use of this model was in keeping with prior analysis of cognition in this cohort, and thus ensures consistency across studies.

In all these analyses, adjustment was made for baseline cognitive function, in addition to the other covariates described previously. For incident dementia, APOE-ε4 was also included as a covariate in the models, given that it is known to be a strong risk factor. SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for all of the statistical analyses with a significance level of $P < 0.05$.

Results

Participant characteristics

The characteristics of the 4868 women in this study are given in Table 1, according to their age at menopause. Natural menopause was reported by 79% of the women, 10% had a surgical menopause and 11% of women reported menopause due to other causes (radiation, chemotherapy or unknown). Fewer than one in seven women was a current user of HT and over a fifth of women used HT at the menopause. Transdermal estradiol was the most commonly used treatment (78% currently and 67% at the menopause) and only a small proportion of women used unopposed estradiol (13.3 and 22.4% of women with a natural and surgical menopause, respectively). The median duration of HT use was 10 years (IQR 4–15 years). Around 7.6% of women in the study had a premature menopause (at or before the age of 40 years) and a further 12.8% an early menopause (between the ages of 41 and 45 years). Women with premature menopause were significantly more likely to use HT at the menopause and to have undergone a surgical menopause, rather than having experienced premature ovarian failure. Participant characteristics that were found to be associated with age at menopause at the conservative level of $P < 0.15$, were considered potentially confounding factors in subsequent analysis given that they could also influence cognitive function.

Association between age at menopause and cognitive function

Multivariable logistic regression analyses were used to examine the association between age at menopause and cognitive function (Table 2). In comparison with women

Table 2. Multivariable logistic regression models for the association between age at menopause and cognitive performance (n = 4868)

Age at menopause (years)	*n*	Verbal fluency Isaacs ≤40		Visual memory BVRT ≤10		Psychomotor speed TMTA ≥68		Executive function TMTB ≥135		Global function MMSE < 26	
		OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Minimally-adjusted model*											
After 50	2005	Reference		Reference		Reference		Reference		Reference	
46–50	1871	1.06 (0.91–1.23)	0.48	1.05 (0.91–1.21)	0.51	1.05 (0.90–1.22)	0.53	1.10 (0.94–1.28)	0.23	1.04 (0.88–1.24)	0.64
41–45	621	1.15 (0.93–1.42)	0.21	1.16 (0.95–1.41)	0.14	1.17 (0.95–1.43)	0.14	1.19 (0.96–1.47)	0.12	1.12 (0.88–1.42)	0.36
40 or before	371	1.51 (1.18–1.95)	0.001	1.43 (1.13–1.82)	0.003	1.15 (0.89–1.49)	0.29	1.22 (0.94–1.59)	0.14	1.24 (0.93–1.65)	0.14
Multivariable adjusted model**											
After 50	2005	Reference		Reference		Reference		Reference		Reference	
46–50	1871	1.06 (0.91–1.24)	0.44	1.05 (0.91–1.21)	0.50	1.06 (0.91–1.24)	0.44	1.10 (0.95–1.30)	0.19	1.05 (0.88–1.25)	0.58
41–45	621	1.14 (0.92–1.41)	0.25	1.16 (0.95–1.41)	0.15	1.16 (0.94–1.43)	0.17	1.18 (0.95–1.47)	0.14	1.11 (0.87–1.41)	0.40
40 or before	371	1.56 (1.12–1.87)	0.004	1.39 (1.09–1.77)	0.007	1.07 (0.83–1.39)	0.59	1.16 (0.88–1.51)	0.29	1.19 (0.89–1.58)	0.25

*Models are adjusted for recruitment centre, age and education level.
**Models are adjusted for recruitment centre, age, education level, physical limitations, chronic illness, depression, use of HT at the menopause and current HT use.

Table 3. Multivariable-adjusted association* between age at menopause and cognitive performance according to type of menopause**

Type of menopause	*n*	Verbal fluency Isaacs ≤40		Visual memory BVRT ≤10		Psychomotor speed TMTA ≥68		Executive function TMTB ≥135		Global function MMSE < 26	
		OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Natural	3842	Reference		Reference		Reference		Reference		Reference	
Surgical	499	0.87 (0.69–1.10)	0.25	1.20 (0.97–1.47)	0.09	0.91 (0.72–1.14)	0.40	0.85 (0.67–1.09)	0.20	0.83 (0.64–1.09)	0.18
Natural menopause, >50 years	1820	Reference		Reference		Reference		Reference		Reference	
Natural menopause, 46–50 years	1556	1.10 (0.93–1.30)	0.27	1.05 (0.90–1.22)	0.58	1.01 (0.86–1.20)	0.89	1.14 (0.96–1.34)	0.13	1.10 (0.91–1.32)	0.33
Early natural menopause, 41–45 years	366	1.07 (0.82–1.40)	0.63	1.10 (0.86–1.41)	0.45	1.08 (0.83–1.41)	0.55	1.08 (0.83–1.42)	0.56	1.21 (0.90–1.63)	0.21
Premature ovarian failure, ≤40 years	100	2.24 (1.44–3.48)	0.0004	1.77 (1.16–2.72)	0.009	1.13 (0.71–1.79)	0.62	1.02 (0.62–1.69)	0.93	1.44 (0.88–2.37)	0.15
Surgical menopause, >50 years	96	Reference		Reference		Reference		Reference		Reference	
Surgical menopause, 46–50 years	152	1.51 (0.70–3.28)	0.29	1.10 (0.61–1.98)	0.76	1.34 (0.66–2.71)	0.42	0.93 (0.44–2.00)	0.86	0.86 (0.40–1.86)	0.71
Early surgical menopause, 41–45 years	115	2.64 (1.23–5.67)	0.01	1.32 (0.71–2.44)	0.38	1.74 (0.85–3.57)	0.13	2.07 (0.99–4.33)	0.05	0.99 (0.45–2.18)	0.99
Premature surgical menopause, ≤40 years	136	2.70 (1.28–5.68)	0.009	1.62 (0.90–2.92)	0.11	1.56 (0.77–3.13)	0.21	1.78 (0.86–3.66)	0.12	1.34 (0.64–2.79)	0.44

*Models are adjusted for recruitment centre, age, education level, physical limitations, chronic illness, depression, use of HT at the menopause and current HT use.
**The 527 women with menopause due to other causes were excluded from this analysis.

who experienced menopause after the age of 50 years, those with a premature menopause had a more than 40% increased risk of poor performance on the tasks assessing verbal fluency and visual memory, whereas no significant associations were found for menopause between the ages of 41 and 50 years. These associations remained highly significant even after multivariable adjustment.

Association between type of menopause and cognitive function

We then investigated whether there was an overall association between the type of menopause and later life cognitive function (Table 3). No significant associations were found with any of the cognitive tests, although there was a weak trend for surgical menopause to be associated with worse visual memory. In stratified analysis, both premature ovarian failure and premature surgically menopause were associated with a more than two-fold increased risk of poor verbal fluency. There was also an increased risk for women who underwent early surgical menopause. In terms of visual memory, premature ovarian failure was associated with a significantly increased risk of poor performance, compared with a natural menopause after 50 years, and there was a similar trend for premature surgical menopause, although this failed to reach significance. Given the similarity of results, the type of menopause was not considered in the subsequent analyses.

Potential modifying effect of hormone treatment

When the potential modifying effect of using HT at the time of premature menopause was examined, there was some evidence that it might be beneficial for visual memory but could increase the risk of poor verbal fluency (Table 4). Women with a premature menopause had a significantly increased risk of poor visual memory if they did not use menopausal HT only; however with respect to verbal fluency, the use of menopausal HT appeared to increase the risk of poor performance. A statistical interaction term examining the modifying effect of type of menopause on the association between age at menopause and cognitive function was not significant; however, in the case of verbal fluency and executive function, there was a non-significant trend (P = 0.08 and P = 0.06, respectively).

Association between age at menopause and cognitive decline over 7 years

Cox regression models were used to investigate the association between age of menopause and the 7-year risk of cognitive decline (Table 5), adjusting for the same covariates as detailed previously, as well as baseline cognitive function. This analysis was based on 3739 women who were assessed for dementia over follow-up, and/or for those without a diagnosis of dementia but who had complete

Table 4. The multivariable-adjusted association* between cognitive performance and age at menopause, taking into account HT use at the time of premature menopause (n = 4868)

Age at menopause	n	Verbal fluency Isaacs ≤40		Visual memory BVRT ≤10		Psychomotor speed TMTA ≥68		Executive function TMTB ≥135		Global function MMSE < 26	
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
After 50	2005	Reference		Reference		Reference		Reference		Reference	
46–50	1871	1.07 (0.92–1.26)	0.37	1.05 (0.91–1.21)	0.53	1.06 (0.91–1.23)	0.48	1.10 (0.94–1.29)	0.22	1.05 (0.89–1.26)	0.55
41–45	621	1.19 (0.95–1.49)	0.13	1.14 (0.93–1.39)	0.22	1.15 (0.92–1.43)	0.21	1.16 (0.93–1.45)	0.20	1.13 (0.88–1.46)	0.33
40 or before											
Without HT	264	1.33 (0.97–1.82)	0.08	1.46 (1.10–1.95)	0.01	1.07 (0.78–1.46)	0.69	0.99 (0.77–1.38)	0.97	1.21 (0.85–1.72)	0.28
With HT	107	2.41 (1.54–3.75)	0.001	1.08 (0.69–1.67)	0.74	1.05 (0.65–1.68)	0.84	1.50 (0.93–2.41)	0.09	1.29 (0.78–1.67)	0.33

*Models are adjusted for recruitment centre, age, education level, physical limitations, chronic illness, depression, current HT use and type of menopause.

Table 5. Multivariable-adjusted Cox regression models* for the 7-year risk of cognitive decline according to age at menopause and type of menopause (n = 3739)

	Verbal fluency Isaacs decline ≥10		Visual memory BVRT decline ≥3		Psychomotor speed TMTA decline ≤11		Executive function TMTB decline ≤57		Global function MMSE decline ≥3		Risk of dementia**	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Age at menopause												
After 50	Reference		Reference		Reference		Reference		Reference		Reference	
46–50	1.07 (0.93–1.23)	0.37	1.01 (0.87–1.17)	0.89	1.14 (0.99–1.30)	0.06	1.06 (0.91–1.25)	0.45	0.96 (0.82–1.13)	0.69	1.23 (0.92–1.64)	0.16
41–45	0.95 (0.77–1.16)	0.60	0.96 (0.78–1.19)	0.73	1.04 (0.86–1.25)	0.70	1.06 (0.85–1.32)	0.61	0.83 (0.66–1.04)	0.58	1.13 (0.77–1.67)	0.52
40 or before	1.05 (0.80–1.36)	0.74	1.10 (0.85–1.45)	0.45	1.36 (1.09–1.71)	0.01	1.10 (0.82–1.47)	0.54	1.35 (1.05–1.74)	0.02	1.23 (0.76–2.00)	0.40
Type of menopause* **												
Natural	Reference		Reference		Reference		Reference		Reference		Reference	
Surgical	0.97 (0.78–1.22)	0.82	1.08 (0.87–1.34)	0.50	1.10 (0.90–1.34)	0.37	1.07 (0.84–1.37)	0.56	1.13 (0.90–1.43)	0.29	0.83 (0.51–1.36)	0.83

*Models are adjusted for baseline cognitive function, recruitment centre, age, education level, physical limitations, chronic illness, depression, use of HT at the menopause and current HT use.
**Also adjusted for APOE-ε4.
***The 527 women with menopause due to other causes were excluded from this analysis.

cognitive testing. Compared with the analysed sample, the participants lost from the follow-up had a lower education level (P = 0.002), and a higher frequency of depressive symptoms (P = 0.03) and activity limitations (P = 0.02). They were also more likely to have lower scores on the tests of verbal fluency (P = 0.02) and executive function (P = 0.04) at baseline. There was no significant difference however, in terms of the other cognitive tests, other covariates and, importantly, the key exposures of interest—age and type of menopause and HT use.

Of the 3739 women remaining in the longitudinal analysis, 10.5% were defined as having dementia over follow-up. Premature menopause was associated with a 35% increased risk for substantial decline in psychomotor speed and global cognitive function, but there was no significant association with the risk of dementia. Sensitivity analysis was performed by excluding baseline cognitive function in these longitudinal models (as it may result in over-adjustment), and similar results were observed. No significant associations were found between type of menopause and the risk of cognitive decline and dementia, and associations did not vary according to the use of menopausal HT (data not shown).

Discussion

Main findings

We found no significant difference in cognitive function between older postmenopausal women who reported a surgical versus non-surgical menopause. However premature menopause, both premature ovarian failure at ≤40 years and premature surgical menopause at ≤40 years, was independently associated with an increased risk of poor verbal fluency and visual memory in later life, only partly supporting our initial hypothesis. Over the 7-year follow-up, premature menopause was associated with an increased risk of decline in psychomotor speed and global decline. We found no strong evidence that using HT at the time of premature menopause could help counteract the negative effects on cognition, with some evidence that it may be beneficial for visual memory but could increase the risk of poor verbal fluency.

Strengths and limitations

Data concerning age and type of menopause, and menopausal HT were both self-reported and retrospectively assessed, which could lead to recall errors, particularly with an elderly population. However, women demented at baseline were excluded from the analysis and we found high reproducibility in responses at different time-points for a sub-sample of participants.[39] Furthermore, sensitivity analysis using groups with slightly different age at menopause (≤42, 43–48, 49–53 and >53 years) gave very similar findings. The most ideal design would follow women throughout their reproductive life and into old age, where their risk of cognitive decline and dementia could be assessed, but such a study would be very time-consuming and costly. Other study limitations include bias from participant exclusion, which included a higher proportion of women with poor cognitive function and an early menopause, thus reducing the overall power of this study. There is also the potential for follow-up bias, in that women with premature and/or surgical menopause may have had an increased risk of dying before 65 years and thus would not have been included in the study. It should also be noted that data from the 1946 British birth cohort actually found that higher cognitive scores during childhood were associated with a later age at menopause.[44] As we could not control for childhood cognition, it remains possible that this could account, in part, for the associations observed in our study.

Strengths of this analysis relate to the 3C study design, which followed a large population of community-based and well-characterised women prospectively over 7 years. Participants provided detailed information concerning their age and type of menopause, and their use of HT at the menopause and later in life. Different cognitive tasks and dementia were assessed at baseline and three times during follow-up. The size of the data set and the vast information relating to each participant also enabled us to adjust for a wide range of covariates, which could potentially confound the association between age at menopause and later-life cognitive function.

Interpretation

Previous studies on the potential association between menopause age and later-life cognition have reported either null associations[45,46] or small positive correlations,[15,29,47] but none of these studies was stratified by the type of menopause. Two small studies of women with surgical menopause found a decline in cognitive function immediately after surgery,[48,49] and this was supported by a small prospective study examining global cognition.[50] In an unadjusted analysis of women with a mean age of 52 years, 27 surgically menopausal women had a worse verbal memory than did 76 naturally menopausal women, and verbal memory was negatively correlated with age at surgery.[16] However, studies investigating cognitive function in older women have reported no long-lasting effects from surgical menopause,[14,15] suggesting that, as we have found here, it may only be surgical menopause at a young age which is detrimental for later-life cognition. In a large study of over 4000 women, surgical menopause was associated with an increased risk of cognitive impairment and dementia, with a linear trend for increasing risk with younger age and no significant association after 50 years.[17,51] This is supported by the largest study in this field, where bilateral ovariectomy was not associated with dementia risk overall but specifically with early onset dementia (40–49 years). However, they could not investigate potential associations with surgical menopause at a later age and their analysis was unadjusted.[52] Neither of these studies investigated other cognitive domains, long-term cognitive decline or the potential effects of a premature ovarian failure. Our findings thus add to this work and suggest that premature menopause is associated with worse later-life cognitive function, particularly verbal fluency and visual memory. Over the 7-year follow-up, a decline in global cognitive function and psychomotor speed was also observed with premature menopause.

In recent years there has been considerable debate surrounding the use of HT. While observational studies provided some evidence that HT could be beneficial,[53] results of the largest clinical trial showed that HT given to older postmenopausal women could have a detrimental effect on cognitive function and dementia risk.[54–56] However, it is possible that there is a 'critical window' whereby estrogen treatment needs to be administered shortly after menopause to have the greatest neuroprotective effects.[57] Short-term estrogen treatment immediately following surgical menopause was shown to help prevent the cognitive decline observed post-surgery.[48,49] Likewise, surgically menopausal women who used HT until 50 years of age had no increased risk of global cognitive impairment or dementia.[17] However, this finding has yet to be replicated. In a study of 428 women aged at least 60 years, early HT initiation (either before 56 years or within 5 years of an ovariectomy) was associated with better global cognition and faster psychomotor speed, but that study did not differentiate between the types of menopause.[58] Our findings suggest that for women with a premature menopause, HT started within 2 years of the menopause may be beneficial for later-life visual memory specifically. Surprisingly, however, for verbal fluency, menopausal HT was actually associated with worse cognitive function. A study of 885 older women reported an association between ovariectomy and worse executive function among current HT users only.[14] While they controlled for menopause age and past HT that study did not specifically examine HT use at the time of menopause. Our findings could possibly be explained by changes in other endogenous hormone levels as a result of exogenous HT, or specific characteristics related to the type and duration of treatment.

Conclusion

With the aging population and the projected increase in the number of postmenopausal women worldwide, it is important to have a better understanding of the long-term effects of a premature menopause on later-life cognitive function and the potential benefit from using menopausal HT. Our results add to the current literature providing evidence that both premature surgical menopause and premature ovarian failure can have long-lasting negative effects on cognitive function in later life. In terms of surgical menopause, these results suggest that further caution should be used when recommending ovariectomy in younger women, and the potential long-term effects on cognitive function are a component of the risk/benefit ratio associated with such surgery. Speculatively, our findings could be explained by a premature decline in estrogen exposure at a time when estrogen would have greatest neuroprotective effects. We could then expect that supplementing estrogen in the form of exogenous estrogen-based HT at the time of premature menopause would help counteract the negative effects of cognitive function, but we failed to find strong supporting evidence for this. Further work in other large population-based studies could examine in detail specific characteristics related to the duration, dose and type of HT used at the menopause.

Disclosure of interests

We declare that we have no conflicts of interest.

Contribution to authorship

JR and MLA contributed to the conception and design of the study, HA, OR, CB and KR contributed to the acquisition of data; JR, JS, IC and MLA were involved with the analysis and interpretation of data. JR and MLA drafted the article and all authors revised it critically and approved the final version. All authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the analysis.

Details of ethics approval

The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre on 10 June 1999 (No. 99-28).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cognitive functions assessed at baseline and follow-up. ■

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