

# Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women



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## ABSTRACT

**Objective:** To determine the association between age at surgical menopause and both cognitive decline and Alzheimer disease (AD) pathology in 2 longitudinal cohorts.

**Methods:** Female subjects from 2 longitudinal studies of cognitive decline (Religious Orders Study and Rush Memory and Aging Project) were included (total  $n = 1,884$ ). The primary analysis examined the association between age at surgical menopause and decline in a global cognition score. Secondary analyses examined additional outcomes: 1) decline in 5 cognitive subdomains and 2) a global measure of the burden of AD pathology. In exploratory analyses, we examined the effect of hormone replacement therapy (HRT). We adjusted all models for age, education, smoking, and cohort and stratified by surgical vs natural menopause.

**Results:** For the 32% of subjects with surgical menopause, earlier age at menopause was associated with faster decline in global cognition ( $p = 0.0007$ ), specifically episodic memory ( $p = 0.0003$ ) and semantic memory ( $p = 0.002$ ). Earlier age at menopause was also associated with increased AD neuropathology ( $p = 0.038$ ), in particular neuritic plaques ( $p = 0.013$ ). HRT use for at least 10 years, when administered within a 5-year perimenopausal window, was associated with decreased decline in global cognition. No associations were seen in women who had natural menopause.

**Conclusions:** Early age at surgical menopause was associated with cognitive decline and AD neuropathology. Ongoing studies should clarify the potential effect of HRT on this relationship.

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## GLOSSARY

**AD** = Alzheimer disease; **HRT** = hormone replacement therapy; **MAP** = Memory and Aging Project; **NINCDS-ADRDA** = National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; **ROS** = Religious Orders Study.

As the general population ages, cognitive decline is a major public health concern.<sup>1</sup> Gonadal hormones may play an important modulatory function in this process. In fact, in a series of epidemiologic observations, interventional studies, and animal models, a neuroprotective role of estrogen, among other hormones, has emerged.<sup>2-4</sup>

There has been strong interest in the potential influence of menopause and the associated decrease in ovarian production of estradiol on subsequent cognitive function. An earlier age at menopause,<sup>5,6</sup> particularly surgical menopause,<sup>7-9</sup> has been associated with increased risk of dementia and cognitive decline in some but not all<sup>10,11</sup> studies.<sup>12-14</sup> In general, prior studies of surgical menopause examined the risk of developing Alzheimer disease (AD) or dementia but did not assess intermediate phenotypes, such as change in performance on detailed cognitive testing or development of the neuropathologic features associated with AD.

We leveraged data from 2 prospective cohort studies of aging and dementia that include organ donation at death to test the hypothesis that earlier age at surgical menopause increases the rate of cognitive decline. In addition, we examined the relation of surgical menopause to the neuropathologic changes associated with AD.

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**METHODS Subjects.** Subjects were women from 2 longitudinal studies of cognitive decline. The Religious Orders Study (ROS), started in 1994, enrolled older Catholic priests, nuns, and brothers from about 40 groups in 12 states. Participants were free of known dementia at enrollment. Participants agreed to annual clinical evaluations, and signed both an informed consent and an Anatomic Gift Act form donating their brains at time of death.<sup>15</sup>

The Memory and Aging Project (MAP), started in 1997, enrolled older men and women in the Chicago area free of known dementia at enrollment. Participants also agreed to annual clinical evaluations and signed both an informed consent and an Anatomic Gift Act form.<sup>15,16</sup> The follow-up rate of ROS and MAP survivors exceeds 90%, and the autopsy rate exceeds 80%. Both cohorts, previously described in detail,<sup>17,18</sup> share a large core of identical phenotypic data, allowing efficient merging for joint analyses.<sup>19,20</sup>

Analyses are based on 1,884 female participants who completed the baseline evaluation between January 1994 and August 2012 and for whom reproductive data were available. The clinical evaluation was repeated annually for up to 18 years with examiners blinded to previously collected data. It included a medical history, neurologic examination, and cognitive function assessment.

**Standard protocol approvals, registrations, and patient consents.** ROS and MAP were approved by the institutional review board of Rush University Medical Center. Additionally, retrospective analysis of the data was approved by the Partners Healthcare Institutional Review Board.

**Hormonal variables.** At baseline, subjects were asked about exogenous hormone use, dates of use, age at menarche and menopause, and whether menopause had occurred naturally or been induced surgically (table e-1 on the *Neurology*<sup>®</sup> Web site at www.neurology.org). Data on type of surgery (hysterectomy or unilateral or bilateral oophorectomy) were not available. Ten subjects were excluded because they provided highly unlikely ages at menopause (<20 or >60 years), and 4 due to unlikely ages at menarche (>30 years). We calculated the duration of reproductive period by subtracting age at menarche from age at menopause.<sup>10</sup> We verified current hormone replacement therapy (HRT) use by inventory of prescription bottles during participant interviews, with an agreement of 93%. We calculated total duration of HRT use; in current HRT users, this was censored at study entry.

**Measures of cognitive function.** A battery of 19 tests was administered annually to each participant by trained examiners. We used the Mini-Mental State Examination only for descriptive purposes,<sup>21</sup> and excluded another test because of an extremely skewed distribution. We combined the remaining 17 tests to form a global cognition score,<sup>19</sup> and categorized them into 5 cognitive domains: 1) episodic memory (7 tests), 2) semantic memory (3 tests), 3) working memory (3 tests), 4) perceptual speed (2 tests), and 5) visuospatial ability (2 tests). Summary measures were created for each domain and for the global cognition score, using averaged sums of *z* scores (detailed in table e-2 and prior publications<sup>22-24</sup>).

**Classification of dementia and AD.** The clinical diagnosis of dementia and AD was made by a clinician with expertise in the evaluation of older persons for dementia based on the criteria of the Joint Working Group of the National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) following a detailed clinical evaluation.<sup>25</sup> These criteria require a history of cognitive decline and evidence of impairment in memory and cognition. Clinical diagnoses were implemented in a 2-step process as

previously detailed.<sup>26</sup> The diagnosis of clinical AD was confirmed pathologically in 90% of autopsied participants.<sup>26</sup> Participants meeting criteria for dementia at the baseline clinical evaluation were excluded from analyses.

**Neuropathologic measures.** Brain autopsies were available for 600 women. Brains were removed at 12 predetermined sites across the United States, using standardized autopsy procedures and postmortem data collection.<sup>15,27,28</sup> We obtained counts for the following markers of AD pathology: neuritic plaques, diffuse plaques, and neurofibrillary tangles. We standardized the raw counts from 5 brain regions by dividing each person's count by the SD for that count and formed a global pathology summary score by averaging the standardized scores. We used the square root of the score to minimize the skewed distribution. A pathologic diagnosis of AD was also made, based on National Institute on Aging-Reagan criteria.<sup>29</sup>

**Statistical analysis.** Demographic and reproductive characteristics of women undergoing natural and surgical menopause are described using means and SDs for continuous variables and frequency and proportions for categorical variables. We compared these variables across studies using 2 independent sample *t* tests,  $\chi^2$  tests, and Fisher exact test, when warranted.

Our primary analysis examined the association between age at menopause and longitudinal decline in the global cognition composite score. For all longitudinally collected cognitive variables, we performed mixed models of cognitive decline, adjusting for age at enrollment, years of education, study (ROS vs MAP), and smoking (pack-years at study baseline). Similar analyses examined change in 5 cognitive domains. Menopausal type (natural vs surgical) was an effect modifier in the relationship between age at menopause and decline in global cognition ( $p = 0.016$ ); therefore, all analyses were stratified by menopausal type.

We next examined the association between age at menopause and AD-related neuropathologic outcomes using multivariate linear regression adjusted for age at death, years of education, smoking, and study.

Finally, in exploratory analyses of the association between other reproductive variables and cognitive decline, we performed the analyses detailed above, including as independent variables age at menarche, duration of reproductive period, and HRT use (ever/never, and duration). In order to evaluate the effects of HRT use within the perimenopausal "window of opportunity,"<sup>31,32</sup> we categorized ever-use of HRT as whether it occurred within 5 years of menopause, or 5 or more years after menopause.<sup>30</sup> We categorized the duration of HRT use as lasting 10 or more years vs fewer than 10 years, similar to prior studies.<sup>30</sup>

We performed all tests using SAS software, version 9.3 (SAS Institute, Cary, NC).

**RESULTS Cohort characteristics.** Cohort characteristics are listed in table 1. The 1,884 female subjects considered in these analyses had a mean age of 78 years at enrollment (range 53–100 years), and one-third of women reported having undergone surgical menopause. These women were less likely to be Caucasian, had a higher body mass index, and reported both a younger mean menopausal age (42 vs 49 years) and a greater use of HRT (53% vs 27%) than women who had undergone natural menopause. More women in MAP (35%) than in ROS (28%) reported surgical menopause ( $p = 0.003$ ). Among all HRT users ( $n = 632$ ),

**Table 1** Comparison of subject characteristics in women with natural vs surgical menopause in 2 largely postmenopausal longitudinal cohorts (Rush University)

	Natural menopause, n = 1,277 (68%)	Surgical menopause, n = 607 (32%)	p Value
Age at baseline, y, mean (SD)	78.3 (8.0)	77.4 (7.7)	0.0148
Years of education, mean (SD)	15.8 (3.5)	15.4 (3.7)	0.0170
<b>Race</b>			
% Caucasian	93	86	
<b>Ethnicity</b>			
% Hispanic	6	6	<0.0001
<b>Smoking</b>			
Pack-years at baseline, mean (range)	5.6 (15.6)	6.5 (15.8)	0.2375
Ever smoked, %	23.3	26.1	0.1860
Baseline body mass index, kg/m <sup>2</sup> , mean (SD)	26.8 (5.5)	28.2 (6.1)	<0.0001
<b>Reproductive history, mean (SD)</b>			
Age at menarche	13.1 (1.5)	12.8 (1.6)	<0.0001
Age at menopause	49.1 (5.3)	42.7 (7.2)	<0.0001
Duration of reproductive period	36.1 (5.5)	29.9 (7.4)	<0.0001
Number of surviving children (MAP only, n = 1,092)	2.48 (1.9)	2.80 (2.1)	0.0117
<b>Hormone replacement therapy use</b>			
Ever use of HRT, %			<0.0001
Within 5 years of menopause	17.2	41.6	
At least 5 years after menopause	9.5	11.3	
No HRT	72.5	46.3	
Current users of HRT (n = 678 nonmissing), n (%)	99 (28)	108 (34)	0.0950
<b>Duration of HRT use, y, mean (SD)<sup>a</sup></b>			
Within 5 years of menopause	12.7 (12.2)	18.6 (15.1)	<0.0001
At least 5 years after menopause	6.3 (6.5)	10.1 (9.6)	0.0018
<b>Types of HRT used, among HRT users, %<sup>b</sup></b>			
Oral	87.4	92.5	
Injection	6.7	7.5	
Vaginal cream or suppository	12.6	5.6	
Skin patch	6.2	5.9	

Abbreviations: HRT = hormone replacement therapy; MAP = Memory and Aging Project.

<sup>a</sup> Censored at study entry.

<sup>b</sup> Some individuals used more than one type.

71% reported HRT use within 5 years of menopause, with a mean duration of more than 13 years. As more than 96% of HRT users reported oral use, all HRT types were collapsed together.

**Age at menopause and cognitive decline.** In our primary analysis examining the association of menopause with cognitive decline, earlier age at surgical menopause was associated with a steeper slope of global cognitive decline ( $p = 0.0007$ ) (table 2). Their coefficients indicate that the effect of each year of earlier surgical menopause on the rate of cognitive decline was equivalent to the effect associated with 6 months of aging

(age at menopause  $\times$  time:  $0.0024 \times 10.5 =$  age  $\times$  time:  $-0.00503 \times 5$ ). When age at surgical menopause was categorized by quartiles, this association was also significant ( $p = 0.008$ ). These divergent estimated slopes are represented in the figure, centered on a woman with median age at study entry (78 years) and level of education (16 years). The figure illustrates the finding that women who were younger at the time of surgical menopause have a more rapid rate (steeper slope) of cognitive decline than women who were older at the time of surgery or than women undergoing natural menopause. Further, because the women who were younger at the time of surgery have a lower intercept

**Table 2** Inverse association between age at surgical menopause and risk of neurologic outcomes

	Estimate	p Value
<b>Longitudinal cognitive decline (n = 593)<sup>a</sup></b>		
Global cognition	0.0024	0.0007
<b>Domains</b>		
Episodic memory	0.0032	0.0003
Semantic memory	0.0025	0.0022
Working memory	0.0010	0.1219
Visuospatial ability	0.0012	0.0909
Perceptual speed	0.0009	0.2920
<b>Neuropathologic measures (n = 179)</b>		
Global AD pathology <sup>b</sup>	-0.0077	0.0379
Neuritic plaques	-0.0129	0.0131
Neurofibrillary tangles	-0.0062	0.1384
Diffuse plaques	-0.0032	0.4895
<b>Pathologic AD diagnosis by NIA-Reagan criteria<sup>c</sup></b>		
OR (95% CI) <sup>a</sup>	0.957 (0.92, 1.00)	0.053
<b>Clinical AD diagnosis (n = 592)<sup>d</sup></b>		
<b>AD by NINCDS-ADRDA criteria</b>		
Hazard ratio (95% CI)	0.988 (0.98, 1.00)	0.093

Abbreviations: AD = Alzheimer disease; CI = confidence interval; MAP = Memory and Aging Project; NIA = National Institute on Aging; NINCDS-ADRDA = National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; OR = odds ratio; ROS = Religious Orders Study.

<sup>a</sup>Mixed models, adjusted for age at enrollment, education (years), smoking (pack-years), and study (ROS vs MAP). A positive estimate indicates a less steep slope of cognitive decline. ORs are interpreted for each 1 year of increased age at surgical menopause.

<sup>b</sup>Multivariate regression, adjusted for age at death, education (years), smoking (pack-years), and study (ROS vs MAP). A negative estimate indicates lower neuropathologic scores.

<sup>c</sup>Logistic regression, adjusted for age at death, education (years), smoking (pack-years), and study (ROS vs MAP).

<sup>d</sup>Cox proportional hazards, adjusted for age at enrollment, education (years), smoking (pack-years), and study (ROS vs MAP).

at study entry, their cognitive decline may, on average, have started many years before, yielding a lower level of cognitive performance at study entry.

In secondary analyses, we examined the association of menopause with decline in 5 cognitive systems. Earlier age at surgical menopause was associated with a steeper slope of decline in episodic memory ( $p = 0.0003$ ) and semantic memory ( $p = 0.002$ ).

To address potential confounders, we added body mass index at study entry and race in the model and noted no decrease in the significance of the association between age at surgical menopause and outcome measures. We also included an interaction term for menopausal age and *APOE*  $\epsilon 4$  haplotype<sup>31</sup> and found no significant interaction with any cognitive outcome. Further, there was no association between age at surgical menopause and incident clinical AD by NINCDS-ADRDA criteria ( $p = 0.093$ ). Finally, there was no

significant association between age at natural menopause and any clinical outcome ( $p > 0.058$ ) (table e-3).

**Age at menopause and AD neuropathology.** We next examined the relation of menopause with AD pathology. Earlier age at surgical menopause was associated with a higher burden of the global measure of AD neuropathology ( $p = 0.038$ ). In secondary analyses of the 3 individual markers of AD pathology (neuritic amyloid plaques, neurofibrillary tangles, and diffuse amyloid plaques), the strongest association was with neuritic amyloid plaques ( $p = 0.013$ ). There was no association between age at natural menopause and any neuropathologic outcome (table e-3).

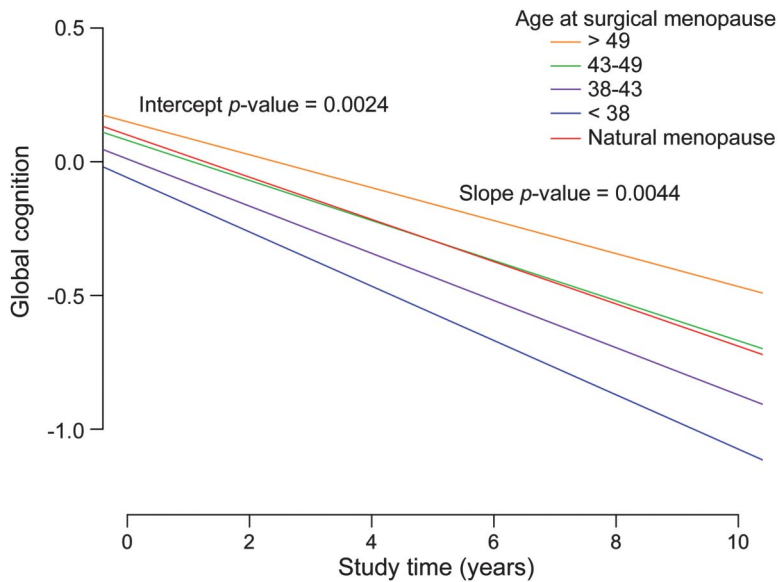
**HRT use and cognitive decline.** We next assessed the role of HRT, when used within a perimenopausal 5-year "window of opportunity," for women who had experienced surgical menopause (table 3). HRT use for at least 10 years was associated with decreased slope of decline in global cognition ( $p = 0.023$ ). Additionally, it was associated with less decline in episodic memory ( $p = 0.026$ ), semantic memory ( $p = 0.033$ ), and visuospatial ability ( $p = 0.021$ ). We further examined duration of HRT as a continuous variable, and it was not associated with decline in global cognition ( $p = 0.055$ ) but was associated with more gentle slopes of cognitive decline in episodic memory, visuospatial memory, and perceptual speed ( $p < 0.020$  for all).

Given these findings, we assessed whether duration of HRT use, when taken within 5 years of menopause, modulated some of the association between earlier surgical menopause on the slope of cognitive decline using a mediation analysis. When we included duration of HRT use in the statistical model, there was a 13.5% change in the estimate of the association between age at surgical menopause and decline in global cognition, suggesting that longer HRT use did attenuate some of the detrimental effects of early surgical menopause (table e-4).

When HRT was initiated beyond 5 years from surgical menopause, there was no association between duration of HRT use and any cognitive outcome. There were also no associations between HRT use and any cognitive outcome in the natural menopause group. Finally, there were no associations between any HRT use and AD pathology ( $p > 0.05$ ).

**Duration of reproductive period and cognitive decline.** In women who had undergone surgical menopause, a shorter reproductive period was associated with increased risk for decline in global cognition ( $p = 0.0003$ ). When we considered cognitive domains, shorter duration of reproductive period was not only associated with greater declines in episodic ( $p = 0.0002$ ) and semantic memory ( $p = 0.0020$ ), but also in

**Figure** Earlier surgical menopause is associated with worse slope of cognitive decline



Estimated slope of decline in global cognition according to age at surgical menopause, categorized by quantile, for a woman with the median age at enrollment (78 years) and educational level (16 years) of the Religious Orders Study and Memory and Aging Project cohorts. The x-axis is study time, and the y-axis is the change in global cognitive performance from the baseline at study entry. An earlier age at surgical menopause is associated with both a steeper slope of decline during the study and a lower intercept, which suggests that a substantial amount of decline has occurred prior to study enrollment. The slope of cognitive decline for women undergoing natural menopause at any age is included as a reference.

visuospatial ability ( $p = 0.048$ ). Additionally, a shorter reproductive period was associated with increased risk of global AD-related pathology ( $p = 0.023$ ) and neuritic plaques ( $p = 0.007$ ) (table e-3). Interestingly, this association was not seen in persons with natural menopause despite an overlap in the duration of reproductive period (surgical menopause: mean 42.7 years, SD 7.2; natural menopause: mean 49.1 years, SD 5.3). We found no association between age at menarche or number of surviving children (MAP study only) with any of the outcome measures.

**DISCUSSION** In this study of 1,884 women followed longitudinally for up to 18 years, earlier age at surgical menopause was associated with a steeper slope of decline in cognition as well as a greater level of AD neuropathology in women who survived free of dementia to a mean age of 78 years. Duration of reproductive period (years between menarche and menopause) showed similar associations. Additionally, when HRT was administered within a 5-year perimenopausal window, HRT use for 10 years or more was associated with decreased decline in cognition but not AD neuropathology. We did not find the same associations for women who had undergone natural menopause.

Prior studies have pointed to an association between surgical menopause and risk of cognitive

decline. In fact, the Mayo Clinic Cohort Study of Oophorectomy and Aging reported an almost doubled risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause, as well as a trend of increasing risk of cognitive impairment and dementia with younger age at the time of oophorectomy or at the time of estrogen deficiency.<sup>7</sup> Similarly, in a Danish cohort, earlier age at bilateral oophorectomy was associated with an increased risk of early-onset dementia,<sup>8</sup> and, in a Chinese study, unilateral oophorectomy prior to menopause was associated with worse word recall.<sup>9</sup> Nonetheless, not all studies have yielded the same conclusions.<sup>12</sup> Here, we extend these prior findings by examining the relation of surgical menopause to the intermediate phenotypes of cognitive decline and to quantitative measures of AD pathology.

Some caution must be taken in attributing causation to the associations noted in this study, as a confounding factor could lead to both increased risk of early gynecologic surgery as well as dementia. Nonetheless, during the years corresponding to the reproductive period of our study population, gynecologic surgeries were performed for more heterogeneous indications than they are today. Additionally, in the Mayo Clinic cohort, there was no effect of indication for gynecologic surgery on the association between surgical menopause and risk of dementia.<sup>12</sup>

The lack of association between age at natural menopause and cognitive outcomes was consistent with some,<sup>32</sup> but not all studies.<sup>33</sup> Indeed, several groups have found a negative effect of earlier age at natural menopause on cognitive function, specifically when menopause occurred before 47 years of age.<sup>34,35</sup> We found no effect of natural menopause occurring before or after age 47 (data not shown). Reasons for this difference may include demographic, educational, sample size, study design, or other factors.

In the decade since the Women's Health Initiative Memory Study raised concerns for an increased risk of stroke or cognitive decline associated with HRT initiated in women of older age,<sup>32</sup> a perimenopausal window of opportunity has been implicated, during which exogenous hormones may be protective against cognitive decline but beyond which, possibly due to estrogen receptor downregulation, treatment may be neutral or harmful.<sup>12,32,36-38</sup> In this study, when we examined HRT used within a 5-year perimenopausal window, HRT use for 10 years or more appeared to have a small protective effect against cognitive decline. Interestingly, we did not find an association with AD neuropathology, suggesting either that we were underpowered to assess an effect of HRT use on AD pathology, or that HRT's protective effects may occur independently of neuropathologic changes. Caution must be taken in interpreting our findings

**Table 3** Association between duration of HRT exposure, when administered within a 5-year window of surgical menopause, and outcomes

	Categorical analysis: HRT use for 10 years or more vs <10 years		Continuous analysis: Duration of HRT use, y	
	Estimate	p Value	Estimate	p Value
<b>Longitudinal cognitive decline (n = 233)<sup>a</sup></b>				
Global cognition	0.0341	0.0230	0.0010	0.0547
<b>Domains</b>				
Episodic memory	0.0442	0.0263	0.0016	0.0191
Semantic memory	0.0315	0.0332	0.0008	0.1138
Working memory	0.0179	0.1106	0.0002	0.5614
Visuospatial ability	0.0328	0.0212	0.0013	0.0101
Perceptual speed	0.0181	0.3186	0.0014	0.0179
<b>Neuropathologic measures (n = 61)</b>				
Global AD pathology <sup>b</sup>	-0.0325	0.7691	0.00018	0.9575
Neuritic plaques	0.0018	0.9908	0.0015	0.7622
Neurofibrillary tangles	-0.1366	0.2438	-0.0018	0.6210
Diffuse plaques	0.0786	0.5524	0.0024	0.5613
<b>Pathologic AD diagnosis (NIA-Reagan criteria)<sup>c</sup></b>				
OR (95% CI) <sup>a</sup>	1.053 (0.356-3.114)	0.9252	1.014 (0.980-1.049)	0.4362
<b>Clinical AD diagnosis (n = 592)<sup>d</sup></b>				
<b>AD by NINCDS-ADRDA criteria</b>				
Hazard ratio (95% CI)	0.917 (0.744-1.131)	0.4188	0.999 (0.988-1.009)	0.8053

Abbreviations: AD = Alzheimer disease; CI = confidence interval; HRT = hormone replacement therapy; MAP = Memory and Aging Project; NIA = National Institute on Aging; NINCDS-ADRDA = National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; OR = odds ratio; ROS = Religious Orders Study.

Analyses examined HRT duration as a categorical variable (10 years or more vs less than 10 years) and as a continuous variable.

<sup>a</sup>Mixed models, adjusted for age at enrollment, education (years), smoking (pack-years), and study (ROS vs MAP). A positive estimate indicates a less steep slope of cognitive decline. ORs are interpreted for each 1 year of increased age at surgical menopause.

<sup>b</sup>Multivariate regression, adjusted for age at death, education (years), smoking (pack-years), and study (ROS vs MAP). A negative estimate indicates lower neuropathologic scores.

<sup>c</sup>Logistic regression, adjusted for age at death, education (years), smoking (pack-years), and study (ROS vs MAP).

<sup>d</sup>Cox proportional hazards, adjusted for age at enrollment, education (years), smoking (pack-years), and study (ROS vs MAP).

in light of this window of opportunity hypothesis, however, given small effect sizes in our group, changing patterns of HRT use in the decades since this cohort's menopausal transition, the important limitations of our study, and discrepancies between observational and interventional studies.<sup>12</sup>

The study has unique strengths, including long duration of follow-up of almost 600 women with surgical menopause, which includes both detailed annual cognitive testing and neuropathologic measures for the deceased individuals, with very high rates of clinical follow-up and autopsy leading to good internal validity. The first important limitation was the retrospective and patient-reported nature of the reproductive exposures. It was not possible to stratify the surgical menopause group according to whether women had undergone

unilateral or bilateral oophorectomy or hysterectomy. Physiologically, this is important because only bilateral oophorectomy is associated with abrupt cessation of all ovarian estrogenic production.<sup>12</sup> The prevalence of surgical menopause in this study (32%) was higher than in other reports (e.g., 25% among women aged 70 to 74 years<sup>39</sup>), raising the possibility of recall biases,<sup>40</sup> changing surgical practices, or other biases within our sample. Second, the requirement that individuals be "cognitively normal" at enrollment could have led to a selection bias, by excluding from the cohort individuals experiencing early cognitive sequelae from an early age at menopause. Thus, the inclusion into the surgical menopause group of women who may not have undergone bilateral oophorectomy, and hence rapid estrogen decline, as well the exclusion of women who did not

survive free of dementia to their later years, likely led us to underestimate the association between surgical menopause and cognitive decline. Finally, we could not control for other midlife predictors of cognitive decline, such as body mass index (which was only available at study entry), or for their interaction with gonadal function.

Our findings add to an emerging literature suggesting that midlife hormonal changes may leave a lasting trace on cognition. Ongoing evaluation of the impact of current reproductive practices, including HRT, on longitudinal cognitive decline is warranted.

### AUTHOR CONTRIBUTIONS

Drs. Bove and De Jager contributed to the study concept and design. E. Secor and Dr. Chibnik contributed to the analysis and interpretation of data. Drs. Bennett, Barnes, and Schneider contributed to the acquisition of data and interpretation of results. Drs. Bove, Chibnik, Barnes, Schneider, Bennett, and De Jager and E. Secor contributed to drafting/ revising the manuscript.

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### DISCLOSURE

R. Bove, E. Secor, L. Chibnik, and L. Barnes report no disclosures. J. Schneider has served as a consultant for AVID Radiopharmaceuticals, Eli Lilly Inc., and GE Healthcare. D. Bennett has served as consultant for Danone, Inc., Dr. Wilmar Schwabe GmbH & Co. KG Pharmaceuticals, Eli Lilly, Inc., Enzymotic Ltd., and has received research support from Danone, Inc., and GE Healthcare. P.L. De Jager has served as consultant for Merck Serono and Teva Neuroscience, received speaker fees from Biogen Idec, and received research support from Biogen Idec. Go to [Neurology.org](http://Neurology.org) for full disclosures.

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## This Week's *Neurology*<sup>®</sup> Podcast



### **Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women (See p. 222)**

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the January 21, 2014, issue of *Neurology*. In the second segment, Dr. Jeff Burns talks with Drs. Riley Bove and Philip De Jager about their paper on the influence of age at surgical menopause on cognitive decline and Alzheimer pathology in older women. Dr. Adam Numis reads our e-Pearl of the week about parechovirus and neurologic disease. In the next part of the podcast, Dr. Binit Shah focuses his interview

with Dr. Anthony Lang on non-neurodegenerative causes of parkinsonism - drug-induced; structural: NPH, stroke, tumor; psychogenic. Disclosures can be found at [www.neurology.org](http://www.neurology.org).

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