

# Reproductive Period and Risk of Dementia in Postmenopausal Women

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**A**FTER MENOPAUSE, ESTROGEN levels decrease dramatically in women. This decrease in endogenous estrogen is associated with increased risk of osteoporosis and cardiovascular disease.<sup>1-3</sup> Decreasing estrogen levels also have been hypothesized to be associated with increased risk of dementia. A relationship between estrogen levels and dementia is biologically plausible<sup>4-6</sup> and, if present, may have major implications for prevention or delay of dementia onset. In ovariectomized rats, estrogen increases choline acetyltransferase activity in the basal forebrain and hippocampus, regions in the brain that are acetylcholine-deficient in patients with Alzheimer disease (AD).<sup>4</sup> In addition, estrogen improves synapse formation on dendritic spines in the hippocampus of oophorectomized rats.<sup>5,7</sup> Estrogen also may improve cerebral blood flow and glucose metabolism, and it may act as an antioxidant.<sup>4,5,7,8</sup> Another mechanism by which estrogen may exert influence on development of dementia is by reducing risk of cardiovascular disease.<sup>9,10</sup> Several population-based studies reported lower prevalence and incidence of dementia and AD in postmenopausal women who used estrogen replacement therapy, suggesting that exogenous

**Context** Exogenous estrogen use may lower risk of dementia in postmenopausal women. A relationship between long-term exposure to endogenous estrogens and incident dementia has been hypothesized but not studied.

**Objective** To determine whether a longer reproductive period, as an indicator of longer exposure to endogenous estrogens, is associated with lower risk of dementia and Alzheimer disease (AD) in women who have natural menopause.

**Design and Setting** The Rotterdam Study, a population-based prospective cohort study conducted in the Netherlands.

**Participants** A total of 3601 women aged 55 years or older who did not have dementia at baseline (1990-1993) and had information on age at menarche, age at menopause, and type of menopause. Participants were reexamined in 1993-1994 and 1997-1999 and were continuously monitored for development of dementia.

**Main Outcome Measures** Incidence of dementia, based on *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria, and AD, based on National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria, compared by quartiles of reproductive period among women with natural menopause.

**Results** During 21046 person-years of follow-up (median follow-up, 6.3 years), 199 women developed dementia, including 159 who developed AD. After adjusting for age, dementia was not clearly associated with length of reproductive period. However, after adjusting for multiple covariates, women with natural menopause and more reproductive years had an increased risk of dementia (adjusted rate ratio [RR] for women with >39 reproductive years [highest quartile] compared with <34 reproductive years [lowest quartile], 1.78; 95% confidence interval [CI], 1.12-2.84). The adjusted RR per year of increase was 1.04 (95% CI, 1.01-1.08). For risk of AD, the adjusted RRs were 1.51 (95% CI, 0.91-2.50) and 1.03 (95% CI, 1.00-1.07), respectively. Risk of dementia associated with a longer reproductive period was most pronounced in APOE ε4 carriers (adjusted RR for >39 reproductive years compared with <34 reproductive years, 4.20 [95% CI, 1.97-8.92] for dementia and 3.42 [95% CI, 1.51-7.75] for AD), whereas in noncarriers, no clear association with dementia or AD was observed.

**Conclusion** Our findings do not support the hypothesis that a longer reproductive period reduces risk of dementia in women who have natural menopause.

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enous estrogen use may reduce risk of dementia.<sup>11-16</sup> These studies, however, have been criticized because of methodological limitations<sup>9,17-19</sup>; they also did not assess endogenous estrogen. Recently, 2 studies did not find a relationship be-

tween short-term measures of endogenous estrogen levels and cognitive decline in healthy elderly women,<sup>20,21</sup> but another study did observe that higher concentrations of bioavailable estradiol were associated with less cognitive de-

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cline.<sup>22</sup> To date, no studies have examined whether long-term exposure to endogenous estrogen is related to risk of dementia and AD. We examined whether number of reproductive years in women who had natural menopause was associated with risk of developing dementia and AD, using data from a large, population-based, prospective cohort study. We hypothesized that a longer reproductive period, as an indirect indicator of long-term exposure to endogenous estrogen, would be associated with lower risk of dementia and AD.

## METHODS

### The Rotterdam Study

The Rotterdam Study is a population-based, prospective cohort study of 3105 men and 4878 women aged 55 years or older residing in Ommoord (including those living in institutions), a suburb of Rotterdam, the Netherlands, that aims to assess the occurrence and determinants of chronic diseases in later life.<sup>23</sup> The Erasmus University Medical Ethics Committee approved the study, and written informed consent was obtained from all participants. In 1990-1993, trained research assistants visited all participants at home and obtained information on sociodemographic characteristics, medical history, current health status, medication use, and determinants for chronic diseases. The participants were invited to visit the research center for a clinical examination (including assessment of dementia) by the research physicians. Re-examinations took place in 1993-1994 and 1997-1999.

### Analytical Sample

The present analysis is based on 3601 women who did not have dementia at baseline and for whom data on age at menopause, age at menarche, and type of menopause were complete (85.4% of the 4219 women in the Rotterdam Study who were free of dementia at baseline).

### Dementia Diagnosis

The procedures of the baseline and follow-up examinations for the dementia diagnoses have been described in de-

tail elsewhere.<sup>24,25</sup> In a 3-step diagnostic procedure, the Mini-Mental State Examination<sup>26</sup> and the cognitive questions from the Geriatric Mental State Schedule<sup>27</sup> were administered to all participants during the home interview. Participants with Mini-Mental State Examination scores of less than 26 or Geriatric Mental State Schedule organic levels of more than 0 were invited to undergo a clinical examination by a research physician who administered the Cambridge Examination for Mental Disorders in the Elderly.<sup>28</sup> Participants in whom dementia was suspected were examined by a neurologist and tested by a neuropsychologist and, if possible, underwent brain nuclear magnetic resonance imaging (done in 20% of the participants diagnosed with dementia). If the diagnostic evaluation could not be completed, additional information was obtained from general practitioners' medical files. In addition to the 3-step diagnostic procedure, participants were continuously monitored for development of dementia through linkage of a general practitioners' medical record system to the database of the Rotterdam Study; this made it possible to obtain follow-up diagnoses for more than 99% of the cohort. Diagnoses of dementia and AD were made by a panel consisting of a neurologist, neuropsychologist, and research physician according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*<sup>29</sup>; diagnoses of possible and probable AD were made according to the National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.<sup>30</sup> Investigators who determined diagnoses were blinded to all other information about participants.

### Reproductive Period

Data on age at menarche, age at menopause, and type of menopause were collected during the baseline home interview. For the 2736 women (76.0%) who reported a natural menopause, age at menopause was defined as the age at which menses had not

occurred for at least 1 year. Reproducibility of age at menopause was determined in 913 women who reported age at natural menopause at baseline as well as during the first follow-up interview. Eighty-six percent of these women reported ages at menopause with a maximum deviation of  $\pm 2$  years. Forty-six percent provided the same age at both interviews. Reproductive period was defined as age at natural menopause minus age at menarche. Seven hundred sixteen women (19.9%) reported menopause occurring after gynecologic surgery; 103 (2.9%) reported menopause induced by drugs; and 46 (1.3%) reported menopause after radiation therapy. These women were considered as a separate group defined as having had artificial menopause. In 175 women, menopause had occurred after stopping oral contraceptive use. Although these women may have had a natural menopause, they were excluded from the analytic sample because age at menopause could not be verified. In addition, 13 women who reported highly unlikely ages at menopause (1 at age 20 years and 12 at age 60 years or older) were excluded from the analytic sample.

### Covariates

Information on educational level, smoking habits, number of children from live births, and ever use of hormone replacement therapy (HRT) for menopausal complaints was obtained during the home interview. At the research center, height and body weight were measured and intake of alcohol was assessed using a food frequency questionnaire.<sup>31</sup> Blood samples were drawn by venipuncture from nonfasting participants and apolipoprotein E (APOE) genotyping was performed on coded DNA samples without knowledge of dementia diagnosis, using standard methods.<sup>32</sup> Level of education was dichotomized as completion of primary education only vs higher education. Smoking status was categorized as current, former, or never. Use of HRT for menopausal complaints was categorized as ever vs never. (Only 82 women

were currently using estrogen and, of these, 49 had artificial menopause. Each quartile of reproductive period included 6 to 9 women taking estrogen. Since these small numbers would not alter the results, only ever vs never use was considered.) Apolipoprotein E genotype was categorized as presence of at least 1  $\epsilon 4$  allele vs no  $\epsilon 4$  alleles.

### Statistical Analyses

Data were analyzed using SAS Version 6.12 (SAS Institute Inc, Cary, NC). Crude age-specific incidence rates were calculated for women with natural menopause according to quartiles of reproductive years and for women with artificial menopause. Cox proportional hazards regression analysis was used to assess the relationship between number of reproductive years in women with natural menopause and risk of dementia and AD. Reproductive years were included in the model as a continuous variable and as dummy variables using quartiles. A fifth category was made for women with artificial menopause. The lowest quartile of reproductive years was used as the reference group in the analyses. Age was used as the time scale in the proportional hazards models.<sup>33</sup> Entry time was defined as age at study entry. Censoring age was defined as age at end of study, death, or onset of dementia, whichever came first. Age at onset of dementia was determined as the midpoint between the age of the participant when last known to be at risk for dementia and age at diagnosis (either through screening or through general practitioner records). All models were fully adjusted for age (time scale), level of education, smoking status, alcohol intake, body mass index (BMI), use of HRT, number of children, and APOE genotype. If data were missing on categorical variables, an extra category was added, whereas if data were missing on continuous variables, the mean value of the respective variable was imputed as calculated from all women in the Rotterdam Study who did not have dementia at baseline. Data were missing on education (n=7), alcohol intake (n=669), BMI (n=192), HRT use (n=82), num-

**Table 1.** Baseline Characteristics by Quartile of Reproductive Years in Women With Natural and Artificial Menopause

Characteristics	Reproductive Period, y (Range, 15-49 y)				Artificial Menopause (n = 865)
	<34 (n = 687)	34-36 (n = 672)	37-39 (n = 794)	>39 (n = 583)	
Reproductive period, mean (SD), y	29.7 (3.2)	35.1 (0.8)	37.9 (0.8)	41.6 (1.7)	32.1 (5.8)
Age at menopause, mean (SD), y	44.1 (3.5)	49.2 (1.8)	51.3 (1.6)	54.2 (1.9)	45.7 (5.6)
Age at menarche, mean (SD), y	14.4 (2.0)	14.1 (1.7)	13.4 (1.5)	12.6 (1.4)	13.5 (1.8)
Age at baseline, mean (SD), y	71.7 (9.5)	70.3 (9.4)	70.0 (9.5)	68.7 (8.8)	68.3 (8.3)
Level of education, %					
Completed primary education	34.9	28.7	28.8	24.1	29.7
Higher education	65.1	71.3	71.2	75.9	70.3
Smoking status, %					
Never	51.1	55.4	54.3	56.8	51.7
Former	28.5	25.6	27.3	27.6	30.5
Current	20.4	19.0	18.4	15.6	17.8
Alcohol intake, mean (SD), g/d	5.8 (8.5)	6.1 (9.2)	5.8 (8.3)	6.5 (9.3)	6.1 (9.8)
Body mass index, mean (SD), kg/m <sup>2</sup>	26.5 (4.0)	26.7 (4.1)	26.7 (4.1)	27.4 (4.0)	26.9 (3.8)
No. of children, mean (SD)	2.0 (1.7)	2.1 (1.7)	2.1 (1.8)	2.2 (1.7)	2.2 (1.7)
Use of hormone replacement therapy, %					
Never	90.5	91.7	90.6	91.4	84.9
Ever	9.5	8.3	9.4	8.6	15.1
Apolipoprotein E genotype, %					
No $\epsilon 4$ allele	70.3	74.7	73.0	71.3	73.3
At least 1 $\epsilon 4$ allele	29.7	25.3	27.0	28.7	26.7

ber of children (n=5), and APOE genotype (n=281). Finally, we examined the relationship between reproductive period in women with and without at least 1 APOE  $\epsilon 4$  allele.

### RESULTS

Of the 3601 women, 577 (16%) died during follow-up. The mean (SD) reproductive period of the women who died during follow-up was 34.7 (5.1) years and that of those who remained alive was 35.1 (5.2) years ( $P=.12$  using  $t$  test). Logistic regression analyses with adjustments for age and education showed that in women with natural menopause, reproductive years were not significantly associated with risk of death (relative risk per year increase, 1.00; 95% confidence interval [CI], 0.97-1.02). Also, women who had artificial menopause did not have a higher risk of death compared with women who had natural menopause (relative risk, 1.01; 95% CI, 0.79-1.29).

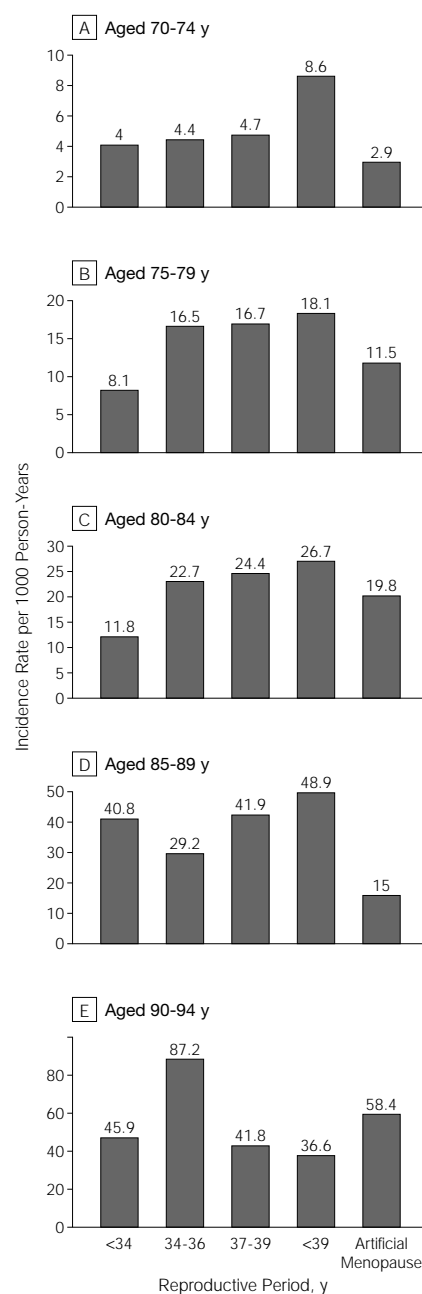
One participant with missing data on education developed dementia, as did 83 with missing data on alcohol intake, 31 with missing data on BMI, 13 with miss-

ing data on HRT use, and 22 with missing data on APOE genotype. None of the women with missing data on number of children developed dementia. Women with missing data on BMI, APOE genotype, or alcohol intake were older and, for alcohol intake, had a lower level of education. When adjusted for age, other characteristics of those with missing data did not differ from women with complete data. Quartile of reproductive period was not associated with missing data on either variable when adjusted for age.

The mean (SD) reproductive period in women with natural menopause was 35.9 (4.6) years. TABLE 1 presents the demographics of the study population by quartile of reproductive period in women with natural and artificial menopause. Age was inversely related to number of reproductive years. Women with more than 39 reproductive years (highest quartile) on average had higher levels of education, had a higher BMI, and were more often never smokers than women with fewer than 34 reproductive years (lowest quartile). Alcohol intake, number of children, use of HRT, and APOE genotype were similar across

strata of reproductive period in women with natural menopause. Women with artificial menopause were younger, had a younger age at menopause, and were more likely to have used HRT than

**Figure.** Crude Age-Specific Incidence Rates of Dementia by Quartile of Reproductive Period and Type of Menopause



Reproductive period was defined as age at natural menopause minus age at menarche.

women with natural menopause. Women who were excluded from the analytic sample because of incomplete data on reproductive period or type of menopause were older and less likely to have used HRT than women with complete data. The groups did not differ with respect to other covariates.

During 21 046 person-years of follow-up (median follow-up, 6.3 years; range, 0.0-9.4 years), 199 women were diagnosed as having dementia (159 with AD). Of the 3601 women in the study sample, 13 (0.4%) were lost to follow-up. The FIGURE shows crude age-specific incidence rates of dementia per 1000 person-years by quartile of reproductive period and type of menopause. Incidence rates among women younger than 70 years and older than 94 years are not presented because there were too few dementia cases in these women. Incidence rates were somewhat higher in women with a longer reproductive period compared with those with the shortest period until age 85 years, after which no pattern in incidence rates could be discerned (Figure). The incidence rates were significantly higher only for the highest vs lowest quartiles when adjusted for age only (TABLE 2). However, in Cox proportional hazards models adjusted for age, education, smoking status, alcohol intake, BMI, HRT use, number of children, and APOE genotype, risk of dementia was consistently higher in women with a longer reproductive period compared with women with a shorter reproductive period. Risk of dementia in women with 34 to 36 reproductive years was 1.56 (95% CI, 1.00-2.43) times higher than in women with less than 34 reproductive years; in women with 37 to 39 reproductive years, this risk was 1.64 (95% CI, 1.07-2.53) times higher, and in women with more than 39 reproductive years, it was 1.78 (95% CI, 1.12-2.84) times higher than in women with less than 34 reproductive years (Table 2). When reproductive period was entered as a continuous variable, the adjusted rate ratio (RR) per year increase in women with a natural menopause was 1.04 (95% CI, 1.01-1.08). For AD, the risks showed a similar but not statistically significant

pattern of higher risk with longer reproductive period (Table 2).

Women with artificial menopause did not have a significantly increased risk of dementia or AD compared with women with less than 34 reproductive years (Table 2). When we compared women with artificial menopause with all women with natural menopause (regardless of their reproductive period), again, their risk of dementia was not increased (adjusted RR, 0.81; 95% CI, 0.55-1.19). When we examined the relationship in women who reported never using oral contraceptives or HRT (167 incident dementia cases), the adjusted RRs associated with dementia for the second, third, and fourth quartiles of reproductive period relative to the lowest quartile were 1.76 (95% CI, 1.10-2.82), 1.74 (95% CI, 1.10-2.76), and 1.52 (95% CI, 0.90-2.58), respectively. Among women who never used oral contraceptives or HRT, women with artificial menopause did not have a significantly increased risk of dementia compared with women with less than 34 reproductive years (RR, 1.31; 95% CI, 0.77-2.21). To determine whether the relationship between reproductive period and risk of dementia may have been influenced by women who were diagnosed as having dementia after a relatively short period, we performed the analyses without the first 2 years of follow-up. In these analyses, the observed relationship remained unchanged. The adjusted RR associated with dementia for the highest quartile of reproductive period compared with the lowest quartile was 2.74 (95% CI, 1.50-4.99); these RRs for the second and third quartiles were 1.59 (95% CI, 0.84-3.01) and 2.06 (95% CI, 1.14-3.72), respectively.

TABLE 3 presents the relationship between reproductive period and AD across strata of APOE genotype. Number of reproductive years was not clearly associated with risk of AD and dementia in women without an APOE  $\epsilon 4$  allele. However, women with at least 1 APOE  $\epsilon 4$  allele had a higher risk of dementia and AD if they had had a longer reproductive period. For dementia, in the group with at least 1 APOE  $\epsilon 4$  allele, the adjusted RR



**Table 2.** Rate Ratios of the Relationship Between Reproductive Period or Artificial Menopause and Incident Dementia and Alzheimer Disease

	Dementia (n = 199)			Alzheimer Disease (n = 159)		
	No. of Cases	Age-Adjusted Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)*	No. of Cases	Age-Adjusted Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)*
Reproductive period, y						
<34	37	Referent	Referent	34	Referent	Referent
34-36	44	1.43 (0.92-2.22)	1.56 (1.00-2.43)	34	1.23 (0.76-1.98)	1.32 (0.81-2.14)
37-39	50	1.46 (0.95-2.25)	1.64 (1.07-2.53)	39	1.27 (0.80-2.02)	1.41 (0.88-2.25)
>39	36	1.64 (1.03-2.60)	1.78 (1.12-2.84)	28	1.40 (0.84-2.31)	1.51 (0.91-2.50)
Artificial menopause	32	1.09 (0.67-1.75)	1.17 (0.72-1.89)	24	0.91 (0.53-1.54)	0.95 (0.56-1.63)
Per y increase in reproductive period†	167	1.03 (1.00-1.07)	1.04 (1.01-1.08)	135	1.03 (0.99-1.07)	1.03 (1.00-1.07)

\*Data are adjusted for age, education, smoking status, alcohol intake, body mass index, use of hormone replacement therapy, number of children, and apolipoprotein E genotype. CI indicates confidence interval.

†Among women with natural menopause.

**Table 3.** Rate Ratios for AD Associated With Reproductive Period According to APOE Genotype\*

	No APOE ε4 Allele			At Least 1 APOE ε4 Allele		
	No. of AD Cases	Age-Adjusted Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†	No. of AD Cases	Age-Adjusted Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†
Reproductive period, y						
<34	20	Referent	Referent	10	Referent	Referent
34-36	19	1.17 (0.62-2.20)	1.19 (0.63-2.25)	11	1.78 (0.73-4.35)	1.62 (0.65-4.03)
37-39	19	1.02 (0.54-1.93)	1.13 (0.59-2.13)	13	1.67 (0.72-3.89)	1.74 (0.74-4.09)
>39	9	0.87 (0.39-1.91)	0.87 (0.39-1.91)	17	3.16 (1.42-7.05)	3.42 (1.51-7.75)
Artificial menopause	16	0.99 (0.51-1.94)	1.03 (0.53-2.03)	8	1.16 (0.45-2.99)	0.92 (0.34-2.47)
Per y increase in reproductive period‡	67	1.00 (0.95-1.05)	1.00 (0.95-1.06)	51	1.08 (1.01-1.15)	1.09 (1.02-1.16)

\*AD indicates Alzheimer disease; APOE, apolipoprotein E gene; and CI, confidence interval. Seventeen AD cases had missing data on APOE genotype.

†Data are adjusted for age, education, smoking status, alcohol intake, body mass index, use of hormone replacement therapy, and number of children.

‡Among women with natural menopause.

in the highest quartile compared with the lowest quartile was 4.20 (95% CI, 1.97-8.92), in the third quartile it was 1.93 (95% CI, 0.87-4.31), and in the second quartile it was 2.43 (95% CI, 1.10-5.36), whereas in the group with no APOE ε4 alleles, these RRs were 1.10 (95% CI, 0.54-2.26), 1.29 (95% CI, 0.71-2.34), and 1.29 (95% CI, 0.71-2.36), respectively. The interaction term testing statistical interaction was significant for dementia ( $P=.02$ ) but not for AD ( $P=.07$ ). When reproductive period was entered as a continuous variable, the adjusted RR per year of increase in women with natural menopause was 1.08 (95% CI, 1.02-1.15) for dementia and 1.09 (95% CI, 1.02-1.16) for AD in the group with at least 1 APOE ε4 allele, whereas in the group without an APOE ε4 allele, this RR was 1.02 (95% CI, 0.97-1.07) for dementia and 1.00 (95% CI, 0.95-1.06) for AD. The  $P$  values for tests of statistical interaction for dementia and AD were .07 and .02, respectively.

**Table 4.** Adjusted Rate Ratios for Association of Ages at Menarche and Natural Menopause With Incident Dementia and Alzheimer Disease

	Dementia (n = 199)		Alzheimer Disease (n = 159)	
	No. of Cases	Rate Ratio (95% CI)*	No. of Cases	Rate Ratio (95% CI)*
Age at menarche, y				
>14	61	Referent	52	Referent
14	37	0.89 (0.57-1.29)	28	0.76 (0.48-1.21)
13	40	1.00 (0.67-1.50)	30	0.89 (0.56-1.40)
≤12	61	1.18 (0.82-1.70)	49	1.15 (0.77-1.72)
Age at menopause, y				
<48	32	Referent	30	Referent
48-49	23	1.24 (0.72-2.15)	16	0.90 (0.48-1.68)
50-52	75	1.95 (1.28-2.96)	60	1.64 (1.05-2.56)
>52	37	1.78 (1.11-2.88)	29	1.47 (0.88-2.46)

\*Data are adjusted for age, education, smoking status, alcohol intake, body mass index, hormone replacement therapy, number of children, and apolipoprotein E genotype. Data adjusted for age only did not differ significantly (available on request from author). CI indicates confidence interval.

TABLE 4 presents the RRs for the association of age at menarche and age at natural menopause with incident dementia and AD. Age at menarche was not significantly associated with risk of dementia and AD, whereas age at natural

menopause reflected the results of the analyses using reproductive period.

## COMMENT

In this population-based study, a longer reproductive period was associated with

a higher risk of dementia in women with natural menopause, after adjustment for multiple confounding variables. This risk was found in women with at least 1 *APOE*  $\epsilon 4$  allele, whereas women without *APOE*  $\epsilon 4$  alleles did not have an association between reproductive period and dementia. Insofar as reproductive period is a marker of long-term exposure to endogenous estrogen, these findings do not support the hypothesis that high estrogen levels reduce risk of dementia.

Several methodological issues should be considered. First, misclassification may have occurred as a result of errors in recall with respect to age at menarche and menopause. In particular, age at menopause may be difficult to remember because it is not an event that occurs at 1 point in time. We tried to avoid recall bias as much as possible by using consistent reports at baseline and the first follow-up measurement (for women who were still available at the first follow-up interview). Still, it is possible that, in particular, women in the highest age range and those who were diagnosed as having dementia after a relatively short period had difficulty remembering their age at menopause. However, when we excluded all women who were diagnosed as having dementia within 2 years of follow-up, the point estimates were higher than the risk estimates based on the entire follow-up period. Thus, possible misclassification resulted in a weakening of the association. Second, we had no data on number of pregnancies that did not end in a live birth, lactation, or regularity of menstrual cycles, nor do we know to what extent use of other hormones (eg, progesterone) may have influenced the observed relationship. Finally, due to the small number of cases, we could not examine the relationship between reproductive period and vascular dementia.

This study is, to our knowledge, the first to examine the long-term effects of reproductive period on risk of developing dementia and AD. The strengths of this study are its size, its prospective design, and its population-based character. Furthermore, we were able to obtain complete follow-up with

respect to dementia diagnoses. In this respect, selection bias cannot explain the results. However, selection could have occurred prior to study entry. Women with a very early natural menopause may have a higher risk of coronary heart disease<sup>2</sup> and death.<sup>34-36</sup> As a result, women with an early menopause who survived and entered the cohort may have been healthier than women with a later menopause and, thus, at lower risk of dementia. Women with a shorter reproductive period (and, thus, a younger age at menopause) were, on average, older at baseline than women with a longer reproductive period. Although this could indicate longer survival as a result of better health status, their higher age at baseline would have made them at higher risk of dementia. Alternatively, this age difference may reflect a cohort effect in that women in a younger birth cohort tend to have a later age at menopause and an earlier age at menarche. Finally, we did not observe a significant relationship between reproductive period and survival in the women who did enter our cohort. Thus, it is unlikely that selective survival could explain the findings of this study.

Although a number of studies have found protective effects of exogenous estrogen on risk of dementia<sup>11-16</sup> and cognitive functions,<sup>37-40</sup> others have not found a relationship,<sup>41,42</sup> and some have even suggested that estrogen may have negative effects.<sup>20,21,43-45</sup> Recently, a large, randomized, controlled clinical trial of women with mild-to-moderate AD did not find a slower rate of disease progression in women treated with estrogen compared with placebo.<sup>43</sup> On 1 outcome measure (the Clinical Dementia Rating Scale), the estrogen group worsened even more rapidly than the placebo group. In another randomized controlled clinical trial of patients with AD, the estrogen replacement therapy group showed somewhat greater decline on the Alzheimer's Disease Assessment Scale—Cognitive compared with the control group.<sup>44</sup> More recently, the Cardiovascular Health Study reported that women who used estro-

gen replacement therapy had greater ventricular enlargement and larger bi-frontal distance than nonusers, suggesting more cerebral atrophy.<sup>45</sup> With respect to endogenous estrogen, some studies have observed that high levels of estradiol and estrone were associated with lower scores on 1 of several cognitive tasks.<sup>21,20</sup>

It is possible that factors associated with reproductive period other than endogenous estrogens increase risk of dementia. Although we used reproductive period as an indirect indicator of exposure to endogenous estrogens, many other factors are involved throughout the reproductive period that may influence estrogen levels, including number of pregnancies (with or without live births), lactation, regularity of menstrual cycles, and use of oral contraceptives. Although we took some of these factors into account in the analyses, we did not have information on other factors. This may have limited the validity of reproductive period as an indicator of long-term exposure to endogenous estrogens. It is also possible that another unknown factor interacts with hormonal influences or that reproductive period is an indicator of another risk factor for dementia. The increased risk with longer reproductive period was most significant in overall dementia (relative to AD). It may be possible that vascular factors interact with hormonal factors in increasing risk of dementia. Unfortunately, there were too few cases of vascular dementia to explore this possibility.

The risk of dementia associated with reproductive period was higher in women with at least 1 *APOE*  $\epsilon 4$  allele, while no association was observed in women without an *APOE*  $\epsilon 4$  allele. Estrogen and *APOE* may interact at several levels. Estrogen modulates the expression of *APOE* in mice.<sup>46</sup> Women with an *APOE*  $\epsilon 4$  allele may have a higher incidence of AD than men with an *APOE*  $\epsilon 4$  allele.<sup>47,48</sup> A recent study found that estrogen replacement therapy was less effective in women with an *APOE*  $\epsilon 4$  allele.<sup>49</sup> An increased risk of dementia in women with both

a longer reproductive period and an APOE  $\epsilon 4$  allele has not been reported before, however.

In conclusion, this population-based study does not support the hypothesis that a longer reproductive period in women, as an indicator of long-term exposure to endogenous estrogen, reduces risk of dementia and AD. Further research is needed on the possible differential effects of endoge-

nous vs exogenous estrogen and the short- vs long-term effects of estrogen on risk of dementia.

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