Reproductive period and dementia: A 44-year longitudinal population study of Swedish women

Jenna Najar¹,² | Svante Östling¹,² | Margda Waern¹,³ | Anna Zettergren¹
Silke Kern¹,² | Hanna Wetterberg¹ | Tore Hällström¹ | Ingmar Skoog¹,²

¹ Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy/Centre for Ageing and Health (AGECAP), University of Gothenburg, Mölndal, Sweden
² Region Västra Götaland, Sahlgrenska University Hospital, Psychiatry Cognition and Old Age Psychiatry Clinic, Mölndal, Sweden
³ Region Västra Götaland, Sahlgrenska University Hospital, Psychosis Clinic, Gothenburg, Sweden

Correspondence
Jenna Najar, Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy/Centre for Ageing and Health (AGECAP), University of Gothenburg, Wallingsgatan 6, 431 41, Mölndal, Sweden.
Email: jenna.najar@gu.se

Abstract

Introduction: Longitudinal studies examining the effect of endogenous estrogens on dementia risk are needed to understand why women have higher dementia incidence than men after age 85.

Methods: A population-based sample of women with natural menopause (N = 1364) from Gothenburg, Sweden, was followed from 1968-2012. Information on endogenous estrogens (age at menarche and menopause, number of pregnancies, and months of breastfeeding) was obtained from interviews in 1968-1992. Dementia was diagnosed according to established criteria based on information from neuropsychiatric examinations and close informant interviews.

Results: We found that longer reproductive period was associated with increased risk of dementia (hazard ratio [HR] per year 1.06, 95% confidence interval [CI] 1.03-1.20) and Alzheimer’s disease (AD) (1.06, 1.02-1.11), particularly for those with dementia (1.10, 1.04-1.17) and AD (1.15, 1.06-1.26) onset after age 85.

Discussion: These results may explain why women have higher dementia incidence compared to men after age 85, the age with the highest number of dementia cases.

KEYWORDS
Alzheimer’s disease, dementia, estrogen, epidemiology, longitudinal study

1 BACKGROUND

The highest number of individuals with dementia is observed after age 80, an age group where women have the highest risk for dementia.¹,² Estrogen exposure is suggested as a possible explanation. Several observational studies have reported decreased dementia incidence among women taking exogenous estrogens.³⁻⁵ However, one study showed increased risk in women prescribed estrogen in late life.⁵ Results from randomized-controlled trials (RCTs) are mixed. The Women’s Health Initiative Memory Study reported that women assigned exogenous estrogens had an increased risk of dementia,⁶ while others reported no associations.⁷,⁸ The effect of long-term endogenous estrogen exposures on dementia risk and Alzheimer’s disease (AD) is less clear.⁹⁻¹¹ There are different forms of endogenous estrogens. The reproductive period (time from menarche to menopause) comprises exposure of mainly estradiol and estrone. Pregnancy entails higher levels of estradiol, estrone, and estriol, whereas estrogen levels drop during the postnatal phase, particularly among women who breastfeed. Furthermore, exposure to exogenous estrogens may occur during the reproductive phase through use of...
oral contraceptives, or later in life as hormonal replacement therapy (HRT).

1. Systematic review: The authors used PubMed to identify previous studies examining endogenous estrogens in relation to dementia. However, few studies have examined the longitudinal effect of endogenous estrogens on dementia incidence.

2. Interpretation: We found that longer reproductive period and a later menopause were associated with increased risk of dementia and Alzheimer’s disease (AD) among women with natural menopause followed over 44 years. The risk was higher for those with onset of dementia and AD after age 85. The associations remained after controlling for use of hormonal replacement treatment and oral contraceptives, apolipoprotein E (APOE) ε4 allele, and other potential confounders.

3. Future directions: Dementia incidence is higher among women compared to men after age 85, the age with the highest number of dementia cases. These findings have implications for understanding why women have higher dementia incidence than men after this age. However, studies are needed to evaluate underlying mechanisms of the associations.

Three longitudinal population studies have examined the effect of reproductive period on dementia risk. The Rotterdam Study, which included women with natural menopause, reported that those with longer reproductive period had higher risk of dementia and AD, especially among apolipoprotein E (APOE) ε4 carriers. In contrast, the Kaiser Permanente Study (KP) reported a higher risk of dementia in those with shorter reproductive span, while the 10/66 study found no association between reproductive period and dementia incidence. None of the studies included information on oral contraceptives, and the two latter did not assess HRT exposure. Although numerous studies have examined the effect of exogenous estrogens on dementia risk, few have examined the long-term effect of endogenous estrogens on dementia risk in longitudinal studies.

We examined the longitudinal effects of endogenous estrogen exposures, measured as reproductive period, age at menarche and menopause, number of pregnancies, and months of breastfeeding, on the risk of late-life dementia among women with natural menopause who were followed over 44 years. We also investigated whether results varied with age at dementia onset. In a subsample with genotyping data, we investigated if APOE ε4 allele modified the effect of endogenous estrogens on incident dementia.

2. METHODS

2.1. Study population

As part of the Gothenburg H70 Birth Cohort Studies, we examined incident dementia in the Prospective Population Study of Women (PPSW) from Gothenburg, Sweden. In 1968-1969, a total of 1462 women (participation rate 90.1%) born in 1908 (age 60), 1914 (age 54), 1918 (age 50), 1922 (age 46), and 1930 (age 38), participated in a health examination. The women were systematically selected from the Swedish Population Registry based on birth dates. Re-examinations occurred in 1974-1975, 1980-1981, 1992-1993, 2000-2001, 2005-2006, and 2009-2010. Additional women were enrolled in 1980-1981 (n = 47) and 1992-1993 (n = 34) (Figure 1). The University of Gothenburg Ethics Committee for Medical Research approved the study. All participants gave informed consent to participate according to the Declaration of Helsinki.

2.2. Endogenous estrogen exposures

Information on age at menarche and menopause (natural, premature, surgical), pregnancies, and months of breastfeeding were obtained from semi-structured interviews 1968-1969 (mean age 50.1 [SD 6.02]), 1974-1975 (mean age 53.0 [SD 3.09]), 1980-1981 (mean age 52.7 [SD 4.11]), and 1992-1993 (mean age 62.3 [SD 3.87]), covering the entire reproductive period of all birth cohorts (n = 1543). Age at menarche was defined as age at first menstruation (first given information was used), and menopause as 1 year without menstruation. The first given information on menopausal age was used to obtain information on age at menopause close to the actual event. Age at menarche and menopause were used as continuous variables. Reproductive period was defined as time from age at menarche to age at menopause (as a continuous variable or divided into quartiles). Fifty-nine women were excluded due to missing information on exposure variables, 92 due to premature or surgical menopause, and 28 due to dementia at baseline, leaving 1364 with natural menopause (Figure 1).

In 1968, the women reported number of children and miscarriages. Number of pregnancies in 1968 was defined as the sum of children and miscarriages. In 1974-1975 and 1980-1981, they were asked about the number of pregnancies since the last examination and months of breastfeeding. The last given information on numbers of pregnancies and months of breastfeeding was used to ensure coverage of all events. Number of pregnancies and months of breastfeeding were used as a continuous variables in all analyses.

2.3. Exogenous estrogens

Information on use of oral contraceptives was obtained at semi-structured interviews in 1968-1969, 1974-1975, 1980-1981, and 1992-1993, and estrogen treatment for menopausal symptoms (HRT) was obtained at semi-structured interviews in 1992. A composite variable of exogenous estrogens (use of oral contraceptives or HRT) was constructed because the duration of use for both HRT and oral contraceptives was skewed. Women reporting no lifetime use of exogenous estrogens were compared to those with previous or current use (ie, never users of either oral contraceptives or HRT vs former user or current user of exogenous estrogens).
FIGURE 1 Study flow chart. Flow chart of the participant included from the Prospective Population Study of Women and the Gothenburg H70 Birth Cohort Study from 1968-1992 in the analytic sample of the present study and the re-examinations in relation to dementia incidence. Response rates among survivors. In 1980, another 47 women born 1930 were included to the initial sample. In 1992 the PPSW and the Gothenburg H70 Birth Cohort Study were merged together, an additional 33 women born 1922, and 1 woman born 1930 were included to the initial sample. Twenty-seven women excluded due to premature menopause (3 at age 21-26, 3 at age 27-29, 22 at age 31-37). Sixty-four women were excluded due to surgical menopause. Those with hysterectomy and/or unilateral or bilateral oophorectomy prior to menopause were classified as ‘surgical menopause’ and excluded. Twenty-eight had missing information on dementia, and one woman had dementia prior menopause. All women were followed for dementia in the Swedish Inpatient Register until 2012.

2.4 Neuropsychiatric examination

Neuropsychiatric examinations were performed by psychiatrists in 1992-1993, and by experienced psychiatric nurses in 2000-2001, 2005-2006, and 2009-2010. The examinations were semi-structured and included comprehensive neuropsychiatric examinations and an extensive battery of neuropsychological tests. Close informant interviews were performed by psychiatric nurses in 1992-1993, 2000-2003, 2005-2006, and 2009-2010. The interviews were semi-structured and comprised questions about changes in behavior and intellectual function, psychiatric symptoms, and activities of daily living, and in cases of dementia, age at onset and disease course.

2.5 Diagnosis of dementia

The diagnosis of dementia at each examination was based on Diagnostic and Statistical Manual of Mental Disorders, Third Edition – Revised (DSM-III-R) criteria, using information from neuropsychiatric examinations and close informant interviews. Dementia diagnoses for individuals lost to follow-up were based on information obtained from the Swedish Inpatient Register until 2012.

AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). Vascular dementia (VaD) was diagnosed with criteria similar to those outlined by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN). Dementia with cerebrovascular disease (CVD) included individuals with dementia and stroke/transient ischemic attack (TIA) without consideration of the temporal relationship between dementia and stroke/TIA.

Age at dementia onset was based on information provided by close informants, the Swedish Inpatient Register, and the examinations. If no information could be obtained from these sources, the age at onset was determined as the mid-point between the last examination free from dementia and the first with a dementia diagnosis. Information on deaths during follow-up was obtained from the Swedish population register.

2.6 Assessments of covariates

Information on all covariates were obtained at each examination (1968-1969, 1974-1975, 1980-1981, 1992-1993), either through semi-structured interviews (education, physical activity, smoking, angina pectoris, stress) or through health examinations (hypertension, waste-hip ratio, diabetes mellitus, electrocardiography [ECG]) or by a combination of these (hypertension, diabetes mellitus, myocardial infarction). Education was dichotomized as compulsory (6 years for those born 1908-1922 and 7 years for those born 1930), or more. Participants were interviewed regarding levels of leisure physical activity using the Saltin-Grimby Physical Activity Level Scale. The women were assigned to four groups: group 1 was completely inactive, group 2 engaged in light physical activity for a minimum of 4 hours per week, group 3 had regular physical training for at least 2 hours per week, and group 4 had regular to intense physical training. Physical activity was dichotomized as inactive (group 1) versus active (groups 2-4). Hypertension was defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg, or taking antihypertensive medication. Smoking was divided into current/former smoker and...
non-smoker. Waist-hip ratio (WHR) was defined as the ratio between waist and hip circumference. Diabetes mellitus was defined as a diagnosis told by a doctor, being on antidiabetic drugs, or having one venous blood glucose value of ≥11.1 mmol/L. The diagnosis of ischemic heart disease was defined as having angina pectoris, myocardial infarction, and/or ECG changes. The diagnosis of myocardial infarction was based on information from interviews, medical records, and death certificates. Angina pectoris was diagnosed according to Rose criteria. ECG was performed on all participants during rest, and ischemic heart disease was diagnosed according to Minnesota codes 1.1-2, 4.1, 5.1-2 (in the absence of 3.1), 6.1, or 7.1. Women who reported frequent or constant stress symptoms, for example, tension, nervousness, and sleep disturbance (≥1 month) in relation to circumstances in everyday life, were considered to have psychological stress.

2.7 | APOE genotyping

In 2000-2001, all women who participated in the psychiatric examination (N = 962) were asked to consent to genetic analyses of their blood samples. Among these, 725 gave consent for genotyping and 603 of these had complete information on exposure variables. APOE genotyping was performed by polymerase chain reaction (PCR) followed by mini-sequencing.

2.8 | Statistical methods

Sociodemographic and health characteristics are presented as numbers, mean and median values, standard deviations (SDs), minimum (min) and maximum (max) values, and percentages. Differences in sociodemographic and health characteristics by quartiles of reproductive period were analyzed using analysis of variance (ANOVA) for differences in means, independent-sample Kruskal-Wallis test and the Mann-Whitney U test for medians, and chi-square test for proportions. Sociodemographic and health characteristics in relation to quartiles of reproductive period were analyzed using logistic regression models. Cox regression models were used to analyze the relation between each endogenous estrogen exposure (reproductive period, age at menarche and menopause, number of pregnancies, months of breastfeeding) and incident dementia disorders, presented as hazard ratios (HRs) and 95% confidence intervals (CIs) in three models. Model 1 included birth year as a covariate. Model 2 included birth year, each endogenous estrogen exposure, and exogenous estrogens. To select covariates in model 3, a primary analysis was performed, where each potential covariate was analyzed in relation to incident dementia disorders using birth year and each endogenous estrogen exposure as covariates in the model. Covariates not significantly related to dementia disorders were omitted (using P < .3 to include covariates that might affect the studied associations, even if they were not formally significantly associated with the factor). Time at risk was calculated from the examination year (1968-1969, 1974-1975, 1980-1981, or 1992-1993) when menopause age was first reported until (a) year of dementia onset; (b) date of death for those who died during follow-up; or (c) December 31, 2012 for survivors. The proportional hazard assumption was verified by Schoenfeld residuals for all models.

Furthermore, we examined endogenous estrogen exposures in relation to age at onset of dementia and AD stratified into four age groups (<65 years, 65-74 years, 75-84 years, ≥85 years).

We also performed a sensitivity analysis with the exclusion of those who developed dementia before 2000 (n = 144).

In a subsample, we examined the interaction of APOE e4 carrierness on the associations between endogenous estrogen exposures and incident dementia, and AD using models 1-3.

In a sensitivity analysis, we examined the relationship between reproductive period, age at menopause, and all-cause mortality to test if longer survival in those with longer reproductive period and later menopause could explain our results. The covariates used in model 3 were birth year, exogenous estrogens, physical activity, WHR, smoking status, hypertension, psychological stress, diabetes mellitus, ischemic heart disease, and dementia incidence. Time at risk was calculated from the baseline year to (a) year of death; and (b) December 31, 2012 for survivors.

IBM SPSS Statistics for Windows, v. 23 (IBM Corp., Armonk, NY, USA) was used for all analyses. R (version 3.6.1) was used to display the cumulative hazard by quartile of reproductive period shown in Figure 2.

3 | RESULTS

The mean length of reproductive period for women with natural menopause was 34.9 years (SD 4.5, range 20.5-46.0). The mean age at menopause for women with natural menopause was 48.7 years (SD 4.3, range 38.0-60.0). Table 1 shows sociodemographic factors and health characteristics by quartiles of reproductive period. Women in the higher quartiles of reproductive period had higher educational level and were less often smokers.

From 1968 to 2012 (mean follow-up 26.8 years; SD 10.2), 291 women (21.3%) developed dementia (146 AD, 116 dementia with CVD, 35 other dementias) during 36,579 person-years of follow-up. The mean age at first examination was 52.8 years (SD 6.1). The mean time from first examination to dementia onset was 26.5 years (SD 8.5). The mean age at dementia onset was 79.9 years (SD 7.8).

Longer reproductive period was associated with increased risk of dementia (HR per year 1.07; 95% CI 1.04-1.10) and AD (HR 1.07; 95% CI 1.03-1.12) in model 1. The greatest difference was observed between the 4th quartile and the 1st quartile of reproductive period for total dementia (HR 2.24; 95% CI 1.58-3.17) and AD (HR 2.84; 95% CI 1.72-4.70) (model 1). The associations remained similar in models 2 and 3 (Table 2). Furthermore, later menopause was associated with increased risk of dementia (HR 1.07; 95% CI 1.04-1.11) and AD (HR 1.08; 95% CI 1.04-1.13) in model 1, and remained similar in models 2 and 3 (Table 2). The results did not change after including blood pressure as a continuous variable.
FIGURE 2  Cumulative hazard of total dementia by quartiles of reproductive period (Q1-Q4). The y-axis depicts the cumulative hazard, and the x-axis depicts time at risk shown in years, using a Kaplan-Meier model. Quartiles of reproductive period are demonstrated in different colours (Q1-Q4), with shaded areas showing the 95% CIs.
TABLE 1  Sociodemographic and health characteristics by quartiles of reproductive years in women with natural menopause (N = 1364)

| Characteristics                               | Q1 ≤32.6 years (n = 333) | Q2 33.0–35.7 years (n = 347) | Q3 36.0–37.4 years (n = 320) | Q4 ≥38.0 years (n = 364) | P-value |
|-----------------------------------------------|--------------------------|------------------------------|------------------------------|--------------------------|---------|
| Age at baseline, year Median (min, max)       | 47.4 (38.0, 70.0)        | 51.9 (46.0, 66.0)            | 54.0 (50.0, 74.0)            | 57.5 (50.0, 78.0)        | <.001   |
| Reproductive period, year Mean (SD)           | 28.7 (3.0)               | 34.2 (0.8)                   | 36.5 (0.5)                   | 39.7 (1.8)               | <.001   |
| Age at menarche, year Mean (SD)               | 14.2 (1.5)               | 14.1 (1.3)                   | 13.7 (1.1)                   | 13.4 (1.3)               | <.001   |
| Age at menopause, year Mean (SD)              | 42.9 (3.3)               | 48.3 (1.4)                   | 50.2 (1.2)                   | 53.2 (2.0)               | <.001   |
| Pregnancies, number of Median (min, max)      | 2.0 (0.0, 8.0)           | 2.0 (0.0, 8.0)               | 2.0 (0.0, 9.0)               | 2.0 (0.0, 11.0)          | .095    |
| Breastfeeding, months Median (min, max)       | 7.0 (0.0, 60.0)          | 6.0 (0.0, 56.0)              | 7.0 (0.0, 84.0)              | 8.0 (0.0, 48.0)          | .015    |
| Oral contraceptives, used or user % (cases/total number) | 8.1 (27/333)           | 11.2 (39/347)                | 9.7 (31/320)                 | 12.4 (45/364)            | .282    |
| HRT, used or user % (cases/total number)      | 5.1 (17/333)             | 3.5 (12/347)                 | 4.4 (14/320)                 | 6.6 (24/364)             | .262    |
| Exogenous estrogen, used or user % (cases/total number) | 11.1 (37/333)           | 13.3 (46/347)                | 13.4 (43/320)                | 17.6 (64/364)            | .092    |
| Education*, > compulsory % (cases/total number) | 23.9 (79/331)            | 29.2 (101/346)               | 32.0 (102/319)               | 36.0 (131/364)           | .005    |
| Physical activity*, active % (cases/total number) | 79.8 (260/326)          | 79.7 (274/344)               | 82.3 (260/316)               | 84.9 (303/357)           | .234    |
| Smoking, current or previous % (cases/total number) | 54.1 (180/333)          | 53.0 (184/347)               | 49.1 (157/320)               | 37.1 (135/364)           | <.001   |
| Waist-Hip-Ratio*, >0.74 % (cases/total number) | 55.9 (184/329)          | 55.5 (192/346)               | 58.9 (188/319)               | 55.5 (202/364)           | .777    |
| Hypertension, % (cases/total number)          | 20.7 (69/333)            | 20.7 (72/347)                | 20.0 (64/320)                | 22.0 (80/364)            | .935    |
| Diabetes Mellitus, % (cases/total number)     | 1.2 (4/333)              | 0.6 (2/347)                  | 0.6 (2/320)                  | 0.6 (2/364)              | .720    |
| Ischemic heart disease % (cases/total number) | 23.1 (77/333)            | 19.3 (67/347)                | 20.3 (65/320)                | 19.8 (72/364)            | .612    |
| Psychological stress*, frequent or constant stress % (cases/total number) | 39.0 (129/331)          | 35.5 (110/346)               | 34.5 (110/319)               | 36.8 (134/364)           | .663    |
| APOE status‡ (at least one ε4 allele) % (cases/total number) | 28.4 (33/116)           | 26.1 (37/142)                | 31.8 (49/154)                | 31.4 (60/191)            | .662    |

1 n = 1360.
2 n = 1343.
3 n = 1348.
4 n = 1360.
5 Subsample of 603 women with information on endogenous estrogen exposures and APOE status.

Longer reproductive period and later menopause were associated with onset of dementia and AD after age 75 years, with the strongest associations observed after age 85 years in both models (Table 3).

We found no association between age at menarche, number of pregnancies, months of breastfeeding, and use of exogenous estrogens, and dementia incidence, and no relationship between endogenous estrogen exposures and dementia with CVD (Table S1). The results did
TABLE 2  The relationship between endogenous estrogen exposures and incident dementia and AD during the total observation period

|                          | Total dementia |               | Alzheimer’s disease |               |
|--------------------------|----------------|--------------|---------------------|--------------|
|                          | Model 2 HR (95%CI) | Model 3 HR (95%CI) | Model 2 HR (95%CI) | Model 3 HR (95%CI) |
| Reproductive period (years)<sup>b</sup> | 1.07 (1.03-1.10)<sup>a</sup> | 1.06 (1.03-1.20)<sup>a</sup> | 1.07 (1.02-1.12)<sup>a</sup> | 1.06 (1.02-1.11)<sup>a</sup> |
| Q1: <32.6 years | Reference | Reference | Reference | Reference |
| Q2: 33-35.7 years | 1.50 (1.05-2.15)<sup>a</sup> | 1.51 (1.05-2.16)<sup>a</sup> | 1.77 (1.05-3.00)<sup>a</sup> | 1.81 (1.07-3.07)<sup>a</sup> |
| Q3: 36-37.4 years | 1.40 (1.00-1.96)<sup>a</sup> | 1.69 (1.17-2.44)<sup>a</sup> | 1.96 (1.15-3.35)<sup>a</sup> | 1.91 (1.11-3.28)<sup>a</sup> |
| Q4: ≥38.0 years | 1.84 (1.32-2.55)<sup>a</sup> | 2.17 (1.51-3.11)<sup>a</sup> | 2.85 (1.69-4.80)<sup>a</sup> | 2.78 (1.65-4.71)<sup>a</sup> |
| Breastfeeding (months)<sup>b</sup> | 1.00 (0.98-1.01)<sup>a</sup> | 1.00 (0.98-1.01)<sup>a</sup> | 0.99 (0.97-1.02)<sup>a</sup> | 0.99 (0.97-1.02)<sup>a</sup> |
| Pregnancies (number)<sup>b</sup> | 0.97 (0.88-1.08)<sup>c</sup> | 0.97 (0.87-1.07)<sup>c</sup> | 0.98 (0.85-1.13)<sup>c</sup> | 0.96 (0.84-1.14)<sup>c</sup> |
| Age at menarche<sup>b</sup> | 0.99 (0.90-1.08)<sup>c</sup> | 0.99 (0.91-1.09)<sup>c</sup> | 1.00 (0.88-1.14)<sup>c</sup> | 1.01 (0.89-1.15)<sup>c</sup> |
| Age at menopause<sup>b</sup> | 1.07 (1.04-1.11)<sup>c</sup> | 1.07 (1.04-1.10)<sup>c</sup> | 1.07 (1.03-1.13)<sup>c</sup> | 1.07 (1.02-1.12)<sup>c</sup> |

<sup>a</sup>Included in the analysis are reproductive period, number of pregnancies, months of breastfeeding, birth year, and exogenous estrogen (n = 1364).
<sup>b</sup>Continuous variable.
<sup>c</sup>Included in the analysis are age at menarche, age at menopause, number of pregnancies, months of breastfeeding, birth year, and exogenous estrogen (n = 1330).
<sup>d</sup>Included in the analysis are age at menarche, age at menopause, number of pregnancies, months of breastfeeding, birth year, and exogenous estrogen (n = 1364).
<sup>e</sup>Included in the analysis are age at menarche, age at menopause, number of pregnancies, months of breastfeeding, birth year, psychological stress, and hypertension (n = 1330).

We then performed a sensitivity analysis excluding those who developed dementia before 2000. This analysis included 147 women who developed dementia during 36,062 person-years of follow-up from 2000-2012. Longer reproductive period (model 3, HR 1.2; 95% CI 1.12-1.23) and later menopause (model 3, HR 1.2; 95% CI 1.11-1.23) remained associated with dementia incidence. In the subsample of women with genotyping data, APOE ε4 allele was associated with dementia in models 1-3 (model 3, HR 1.5; 95% CI 1.12-1.23). The association between length of reproductive period, age at menopause, and incident dementia and AD did not change after including APOE ε4 allele and reproductive period (P = .997), or age at menopause (P = .139) in relation to incident dementia. The number of participants who died during follow-up was 973 (71.2%) and median age at death was 79.14 years (range 43.0-98.0 years). Longer reproductive period (model 3, HR 1.04; 95% CI 1.03-1.06) and later menopause (Model 3, HR 1.05; 95% CI 1.03-1.07) were associated with higher mortality.

4 | DISCUSSION

In a population-based sample of women followed over 44 years, we found that longer reproductive period and later menopause were related to increased risk of dementia and AD among women with natural menopause. This increased risk was strongest among those with onset after age 85 years, an age where dementia risk is highest in women and where most dementia cases occur. We did not find associations between endogenous estrogen exposures and dementia with CVD. Dementia risk was not associated with age at menarche, number of pregnancies, months of breastfeeding, or exogenous estrogens.

Our finding that women with longer reproductive period and later menopause had an increased risk of dementia and AD is in line with findings from the Rotterdam Study, while KP had opposite results, and the 10/66 study reported no associations. The Rotterdam Study found an association with incident dementia especially among APOE ε4 carriers, which we could not corroborate. Several differences between the studies might explain the results. First, studies where later menopause was associated with dementia risk had higher mean menopausal age; 48.7 years in our study, 49.6 years in the Rotterdam Study, while KP had opposite results. In addition, there were some differences regarding factors, which were adjusted for in the analysis.
### TABLE 3
The relationship between endogenous estrogen exposures and incident dementia and AD in four different ages of onset

| Age at onset | Total dementia | Alzheimer’s disease |
|--------------|----------------|---------------------|
|              | Model 2 HR (95% CI) | Model 3 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) |
| Reproductive period (years)

| Age at onset | Reproductive period (years) | Q1: < 32.6 years | Q2: 33-35.7 years | Q3: 36-37.4 years | Q4: ≥38.0 years
|--------------|----------------|---------------|----------------|----------------|----------------|
| Age at onset | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| < 65 years | 0.95 (0.85-1.08) | 0.94 (0.83-1.07) | 1.03 (0.86-1.23) | 1.17 (0.57-2.42) |
| Reproductive period (years) | Reference | Reference | Reference | Reference | Reference |
| < 65 years | 0.68 (0.15-3.08) | 0.59 (0.13-3.96) | 1.03 (0.86-1.23) | 0.98 (0.13-7.62) |
| Q2: 33-35.7 years | 0.75 (0.17-3.40) | 0.59 (0.13-3.79) | 1.67 (0.27-10.20) | 1.25 (0.19-8.33) |
| Q3: 36-37.4 years | 0.66 (0.15-3.00) | 0.57 (0.12-2.63) | 1.10 (0.15-7.93) | 0.98 (0.13-7.62) |
| Q4: ≥38.0 years | 1.01 (0.94-1.07) | 1.01 (0.94-1.07) | 1.01 (0.94-1.10) | 1.01 (0.93-1.10) |
| Breastfeeding (months) | 0.98 (0.64-1.50) | 0.88 (0.58-1.33) | 0.85 (0.57-1.67) | 0.87 (0.53-1.44) |
| Age at menarche | 0.91 (0.60-1.39) | 0.98 (0.64-1.50) | 0.83 (0.47-1.47) | 0.82 (0.46-1.48) |
| Age at menopause | 0.94 (0.83-1.07) | 0.94 (0.83-1.06) | 1.01 (0.85-1.21) | 0.99 (0.80-2.01) |

(Continues)
the analyses. This is probably not a major reason for discrepancies. However, KP had similar results as us in univariate analyses. Fifth, our study and the Rotterdam Study excluded women with oophorectomy (unilateral or bilateral), who have a more sudden fall in estrogen levels than women with natural menopause, while these were included in KP and 10/66. Sixth, KP used electronic health records to identify dementia, while the other studies used personal health examinations. Our finding that reproductive period and later menopause was associated mainly with onset of dementia after age 85 suggests a possible explanation for women having a higher incidence and prevalence of dementia than men after that age.2,25 The theory of the healthy cell proposes that estrogen is neuroprotective for healthy cells, but neurotoxic in diseased cell populations.26 Women with later menopause have higher estrogen levels later in life when dementia-related pathologies accumulate.27 Estrogen may thus become neurotoxic in older ages. Support for this theory comes from the “timing hypothesis,” proposing that HRT has beneficial effects on dementia risk if administrated within 5 years of menopause28 and negative effects if administrated later.2,28 This could explain why age at menarche, number of pregnancies, and months of breastfeeding were not associated with incident dementia, as pregnancies and lactation occur earlier in life. Women with later menopause might have late pregnancies. However, according to Statistics Sweden, very few births occurred after age 45 years in this population.29 In contrast, two cross-sectional studies reported higher odds ratios of dementia with number of pregnancies.30,31 Furthermore, exogenous estrogens did not affect incident dementia in our study, contrary to previous studies reporting that exogenous estrogens reduce6 or increase32 dementia risk.

Strengths of the study are the representative, systematically selected population-based sample of women, the long observation period, and the possibility of examining the interacting roles of different endogenous and exogenous estrogen exposures on dementia risk. In addition, psychiatrists or psychiatric nurses performed the neuropsychiatric examinations and multiple sources of information were used to detect and diagnose dementia. Some limitations should be considered. First, our exposure variables were based on retrospective information, which might lead to recall bias. The results did not change when those who developed dementia before 2000 were excluded, suggesting that our results are not due to misclassification because of preclinical dementia. Second, not all participants had data on all exposures and covariates. It is possible that our sample was healthier than the general population. However, a healthier sample would drive the results toward the null hypothesis rather than accentuate any associations. Third, different forms of endogenous estrogens may influence dementia risk differently, and the effect on dementia risk might be mediated by aging processes in the hypothalamic-pituitary unit. We are, however, not able to address these questions in our study. Fourth, we lacked information on type and level of exogenous estrogens, combinations with progesterone, and age when these drugs were taken. The latter is important, as the timing effect might be essential in predicting dementia risk. This could explain the lack of association between exogenous estrogen and dementia incidence in our study. Fifth, in studies with long follow-ups, competing risk of death may affect the results. The use of risk-time in the Cox regressions partly adjusts for this. Further, longer reproductive period and later menopause were related with increased mortality, which most likely attenuated the associations. Sixth, cumulative attrition is a problem in long-term follow-up studies. Although this was partly alleviated by using registry to detect dementia in those lost to follow-up, these sources underestimate the number of dementia cases. However, almost all people in Sweden receive hospital treatment within the public health care system and the Swedish Inpatient Register covers the entire country. Seventh, the sample comprises Caucasian women living in Sweden, limiting the possibility of generalizing to other populations. We found that women with longer reproductive period and later menopause had increased risk of dementia and AD, especially with onset after age 85. This may explain the higher incidence and prevalence of dementia among women compared to men in that age group. Furthermore, these results could contribute with additional knowledge to identify people at increased risk of dementia, which is important in the implementation of preventative strategies.

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**TABLE 3** (Continued)

|                          | Total dementia |                          |                          |
|--------------------------|----------------|--------------------------|--------------------------|
|                          | Model 2 HR (95% CI) | Model 3 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) |
| Age at menarche | 0.94 (0.80-1.10) | 0.91 (0.77-1.07) | 0.96 (0.77-1.19) | 0.96 (0.77-1.20) |
| Age at menopause | 1.10 (1.04-1.17) | 1.10 (1.03-1.18) | 1.16 (1.06-1.27) | 1.17 (1.07-1.29) |

1 Included are: reproductive period, number of pregnancies, months of breastfeeding, birth year, and exogenous estrogen.
2 Included are: reproductive period, number of pregnancies, months of breastfeeding, birth year, exogenous estrogen, physical activity, WHR, hypertension, ischemic heart disease, and psychological stress.
3 Continuous variable.
4 Included are: age at menarche, age at menopause, number of pregnancies, months of breastfeeding, birth year, and exogenous estrogen.
5 Included are: age at menarche, age at menopause, number of pregnancies, months of breastfeeding, birth year, psychological stress, and hypertension.
The authors declare no competing interests.

**CONFLICT OF INTEREST**

The authors declare no competing interests.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.