의학박사 학위논문

여성의 월경력 및 산과적 요인과 신경퇴행성 질환 발생 간의 관련성

The relationship between reproductive factors and incidence of neurodegenerative disease in women

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이 논문을 의학박사 학위 논문으로 제출함

2020년 6월

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국문 요약

연구 배경

최근 노인 인구가 증가함에 따라 치매 및 파킨슨병을 포함한 신경퇴행성 질환이 중요한 건강 문제로 부각되고 있다. 이러한 신경퇴행성 질환의 발생에는 성별에 따른 차이가 존재하는 것으로 보이며, 아직 정확한 기전은 알려져 있지 않으나 에스트로겐이 중요한 역할을 하는 것으로 보고되고 있다. 따라서 본 연구를 통하여 여성의 월경력 및 산과적 요인과 신경퇴행성 질환 발생 간의 관련성에 대해 조사하고자 하였다.

연구 방법

본 연구는 국민건강보험공단 자료를 이용하였다. 2009 년부터 2014 년까지 일반건강검진과 국가암검진을 모두 받은 40 세 이상의 폐경 후 여성을 대상으로 하였으며, 치매의 병력이 없는 4,696,633 명과 파킨슨병의 병력이 없는 4,729,546 명의 자료를 분석하였다. 암 검진에서 시행하는 여성력 관련 문진 자료를 이용하여, 초경 나이, 폐경 나이, 출산, 모유 수유, 여성호르몬제 및 피임약 사용 등의 월경력과 산과적 요인을 조사하였다. 신경퇴행성 질환(치매, 파킨슨병)은 제 10 차 국제질병분류에 따른 청구 자료로 정의하였다. 다중콕스회귀분석을 시행하여 여성의 월경력 및 산과적 요인에 따른 치매 및 파킨슨병 발생 위험을 평가하였다.

연구 결과

본 연구 결과 5.74 년의 추적 관찰기간 동안, 총 212,227 건 (4.5%)의 치매가 발생하였으며, 알츠하이머 치매가 162,901 건 (3.5%), 혈관성 치매가 24,029 건 (0.5%)이었다. 초경 연령이 13-14 세인 여성에 비하여, 초경 연령이 17 세 이상으로 늦은 여성에서 치매 발생의 위험비(95% 신뢰구간)가 1.15(1.13-1.16)으로 높은 반면, 폐경 연령이 40 세

미만인 여성에 비하여 폐경 연령이 55 세 이상으로 늦은 여성은 치매 위험비가 0.79(0.77-0.81)으로 낮았다. 즉, 가임 기간이 30 년 미만으로 짧은 여성에 비하여 40 년 이상으로 긴 여성에서 치매 위험비는 0.81(0.79-0.82)로 낮았다. 자녀가 없거나 모유 수유력이 없는 여성과 비교하여 자녀가 1 명 (위험비 0.89, 95% 신뢰구간 0.85-0.94) 이거나 모유 수유 기간이 6 개월 미만인 경우 (위험비 0.92, 95% 신뢰구간 0.88-0.95) 치매 위험비가 다소 감소하였으나, 자녀가 2 명 이상 (위험비 1.04, 95% 신뢰구간 0.99-1.08)이거나 모유 수유기간이 12 개월 이상인 경우 (위험비 1.14, 95% 신뢰구간 1.11-1.17) 치매 위험비가 증가하는 양상을 보였다. 여성 호르몬제 또는 피임약을 사용한 여성은 치매 위험이 각각 14% (위험비 0.86, 95% 신뢰구간 0.84-0.88)와 9% (위험비 0.91, 95% 신뢰구간 0.88-0.92) 감소하였다.

한편, 5.84 년의 추적 관찰기간 동안, 총 20,816 건의 파킨슨병이 발생하였다. 초경 연령이 13-14 세인 여성에 비하여, 초경 연령이 17 세 이상으로 늦은 여성에서 파킨슨병의 위험비가 1.10(1.05-1.16)으로 높았다. 반면, 폐경 연령이 늦어질수록, 파킨슨병의 위험은 유의하게 감소하는 추세를 보였다 (P for trend 0.019). 즉, 가임 기간이 30 년 미만인 여성과 비교하여, 가임 기간이 40 년 이상으로 긴 여성에서 파킨슨병 위험비가 0.91(0.85-0.96)으로 감소하였다. 여성호르몬제를 5 년 이상 복용한 경우 파킨슨병 위험이 17% 증가(위험비 1.17, 95% 신뢰구간 1.07-1.27)하였으며, 피임약을 1 년 이상 복용한 경우 파킨슨병 발생 위험이 7% 증(위험비 1.07, 95% 신뢰구간 1.01-1.13)하였다.

결론

여성의 월경력 및 산과적 요인은 신경퇴행성 질환 발생 위험과 독립적인 관련성을 보였다. 늦은 초경, 이른 폐경 등으로 체내 에스트로겐 노출이 적은 것은 치매와 파킨슨병의 발생 위험을 높이는 것으로 나타났다. 따라서 여성에서 치매와 파킨슨병 발생

위험과 관련하여 다양한 월경력과 산과적 요인의 평가 및 관리가 중요하다. 특히 난소절제술 등으로 체내 에스트로겐 노출이 적을 것으로 예상되는 여성의 경우 신경퇴행성 질환 발생에 주의하고, 예방 및 적절한 관리를 위한 개입이 필요할 것으로 판단된다.

중심단어

신경퇴행성 질환, 치매, 파킨슨병, 초경, 폐경, 가임 기간, 출산, 모유수유, 여성호르몬요법, 피임약

CONTENTS

1. Overview

Neurodegenerative diseases are hereditary or sporadic conditions that result in the progressive loss of the structure and function of neurons as well as neuronal death.[1)] Among the many risk factors for neurodegeneration, aging is a major risk factor of neurodegenerative disease. With increasing global population and average lifespan, the prevalence of neurodegenerative diseases is on the rise, worldwide.

The most common neurodegenerative diseases, Alzheimer's disease (AD) and Parkinson's disease (PD), are predominantly observed in elderly individuals, and the risk of these disease increases with age **(Table 1)**.[2)] Many age-related neurodegenerative diseases are characterized by accumulation of disease-specific misfolded proteins in the central nervous system.[3)] These include β-amyloid peptides and tau/phosphorylated tau proteins in AD and α-synuclein in PD.[3)] Molecular studies have revealed that brain tissue from older individuals contains abnormal deposits of aggregated proteins such as hyperphosphorylated tau (p-tau), amyloid-β (Aβ) and α-synuclein.[4)]

Table 1 Age-related neurodegenerative disease

Disease	Alzheimer's disease	Parkinson's disease
Prevalence	5.7 million in the USA in 2018	2–3% of the global population aged > 65 years in 2017
Major symptoms	Impairment of learning Memory and speech difficulties	Muscle rigidity Tremors Alterations in speech and gait
Risk factors	Age Family history Genetics History of head trauma Female gender Vascular risk factors Environmental factors	Environmental factors Genetics Male gender Ethnicity Age Psychiatric symptoms
Neuropathological hallmarks	Amyloid β plaques Neurofibrillary tangles Neuronal loss Neuroinflammation	α-Synuclein-containing Lewy bodies Loss of dopaminergic neurons Grey matter atrophy

Note. Adapted from Hou, Yujun, et al. "Ageing as a risk factor for neurodegenerative disease." *Nature Reviews Neurology* 15.10 (2019): 565-581.

Despite aging globally affects both men and women, various studies have reported that sex differences exist (**Figure 1)**.[4)] For example, AD and other dementias disproportionately affect women. It has long been known that female sex is the major risk factor for developing late-onset AD, the most common form of dementia. Notably, two-thirds of AD patients are women, regardless of age and ethnicity.[5-7)] Especially, postmenopausal women contribute to over 60% of all those affected.[8)] There are also sex differences in the time course of disease

progression.[9] In general, women show faster cognitive decline after disease onset than men,[10,11] as well as a higher severity for clinical dementia.[12-14]

On the other hand, previous epidemiological studies have shown that both incidence and prevalence of PD are 1.5–2 times higher in men than in women.[15-17] Furthermore, onset in women was slightly later than in men by a mean of 2.2 years.[18] After progression into the clinical phase of the disease, women had better Unified Parkinson's Disease Rating Scale (UPDRS) motor scores compared with men at a disease duration of more than 5 years.[19] Furthermore, men reported several parkinsonian symptoms more frequently than women when asked at a disease duration of 9 years.[19]

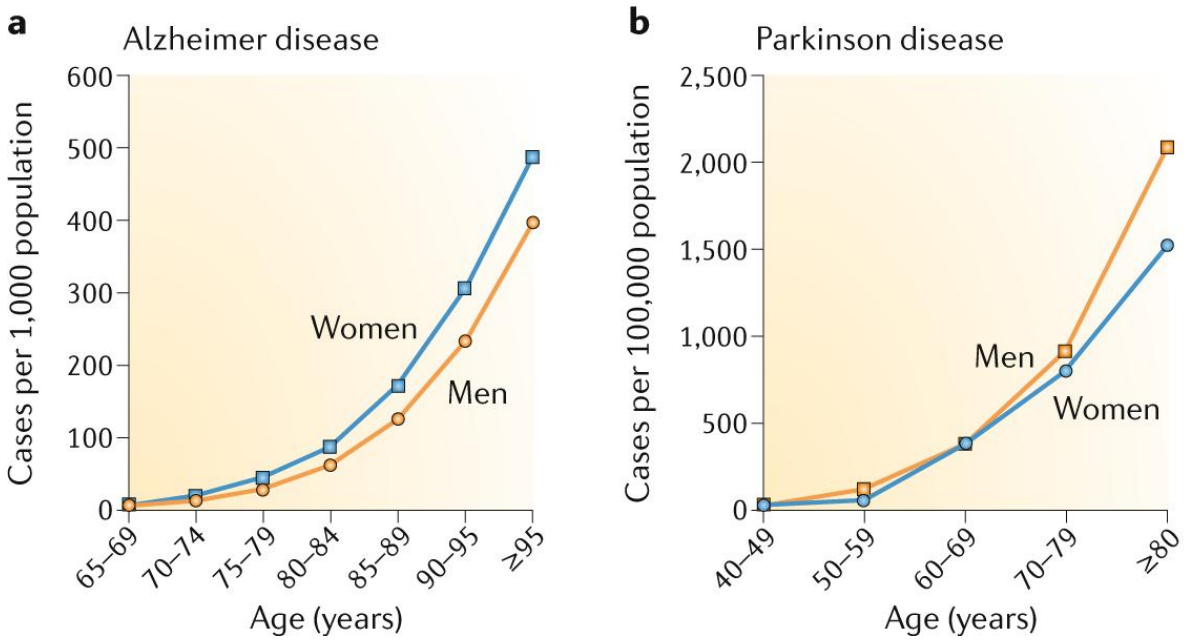

Figure 1 Neurodegenerative disease prevalence by age and sex

Note. Adapted from Hou, Yujun, et al. "Ageing as a risk factor for neurodegenerative disease." *Nature Reviews Neurology* 15.10 (2019): 565-581.

As mentioned above, one factor that is believed to play an important role in the sex differences observed in brain aging and neurodegeneration is sex hormone levels, estrogen. The neuroprotective effect of estrogen has been stressed by several investigations. Epidemiological studies suggest that the reduced concentration of sex steroid hormones after menopause may be responsible for the higher prevalence and greater severity of AD in women than men.[20,21] It has also been suggested that late symptom onset of PD in women may be related to such neuroprotective effect.[22,23] Moreover, in support of the neuroprotective effect of sex steroids, hormone replacement therapy (HRT) has been shown to have beneficial effects on neurodegenerative diseases such as AD[20] and PD[21], although others have failed to show clear evidence of benefit.[24,25]

As further discussed below section, previous studies were limited in the following aspects: 1) reproductive factors that could affect sex hormone levels have not been comprehensively evaluated; 2) potential confounders such as comorbidities were not fully adjusted; 3) relatively small population and number of cases; 4) cross-sectional or case-control design; and 5) difficulties in applying the study findings to the general public owing to specific populations studied (i.e., Down's syndrome). Indeed, the epidemiologic information regarding the neurodegenerative diseases of Asian women and its determinants is scarce, whereas a wide variation in reproductive factors exists across female racial or ethnic group.

Therefore, we designed a retrospective cohort study using a large population-based database to investigate the associations between various female reproductive factors and the incidence of neurodegenerative disease. We comprehensively included female reproductive factors. The focus is on the two most prevalent neurodegenerative diseases, dementia and PD.

2. Female reproductive factors and the risk of dementia

2.1. Introduction

Worldwide, according to dementia fact sheet from World Health Organization 2019, nearly 50 million people have dementia, and there are nearly 10 million new cases every year, representing a public health priority. Epidemiological studies have revealed a higher risk of developing dementia in post-menopausal women than in men of the same age group.[26] After menopause, brain atrophy in women accelerates at a faster rate than in men.[27] It has been postulated that this gender difference is due to the marked reduction of estrogens levels that occurs following the menopause.[28]

There is growing evidence that estrogens may have direct and indirect impacts on memory, affect, and motor coordination in women and also appear to have a neuroprotective effect with respect to dementia.[29-31] Previous studies have identified associations between increased lifetime endogenous estrogen exposure (EEE) and decreased risks of poor cognitive function[27,32-36] and dementia.[28,37-40] In addition, premature menopause has been reported to be associated with an increased risk of cognitive impairment and dementia, with a linear trend for increasing risk with younger age at menopause.[27] It has been also reported that surgical menopause caused by bilateral ovariectomy is associated with early-onset dementia.[39] However, such studies have tended to focus on a limited number of female reproductive factors, principally premature menopause[27,36] or age at menopause.[33,40] Even in the studies that have examined a larger number of reproductive factors (age at menarche, menopause,[37] and parity[28,34,35]), additional reproductive factors that could affect hormone levels, such as fertility duration or breast feeding history, have not been thoroughly evaluated.

Data regarding oral contraceptive (OC) use in women with dementia are very limited, and reported associations between estrogen-containing hormone therapy and cognitive function have been contradictory. While several observational studies have reported positive

association between hormone replacement therapy (HRT) and cognitive function[41-43], others have failed to show clear evidence of benefit[24,25] or have reported associations with mild cognitive impairment.[44,45]

Very few dementia studies have taken into account all of the above reproductive factors comprehensively, potentially resulting in improper adjustment for confounders. Additional limitations of many of the previous studies include cross-sectional designs[28,33,34,37], relatively small study populations and numbers of cases (e.g., 227 cases of incident dementia among 8,195 women[43]), and/or difficulties in applying the study findings to the general public owing to specific populations studied, such as those with Down's syndrome.[40]

We designed a retrospective cohort study using a large population-based database to investigate the associations between female reproductive factors and the incidence of dementia.

2.2 Methods

2.2.1. Data source and study setting

The National Health Insurance Service (NHIS) is the single insurer in Korea and provides mandatory universal comprehensive medical care to 97% of the Korean population and an additional medical aid program to the 3% of the population in the lowest income bracket. The NHIS also recommends free biennial cardiovascular health screening for all Koreans aged 40 and above and all employees regardless of age and annual screening for workers in jobs requiring physical labor. The NHIS databank contains databases compiling patient data pertaining to qualification (e.g., age, sex, income, region, and type of eligibility), claims (general information on specification, consultation statements, diagnosis statements defined by the International Classification of Disease 10th revision (ICD-10), and prescription statements), health check-ups (self-questionnaire on past medical history and health behavior [e.g., smoking, drinking, and physical activity], anthropometric measurements [e.g., body mass index and blood pressure], and laboratory test results [e.g., fasting glucose and lipid levels]), and mortality.[46,47)]

As part of the Korean National Cancer Control Plan, the National Cancer Screening Program (NCSP) was introduced in 1999.[48)] Currently, the NCSP includes screening for stomach, liver, colorectal, breast, and cervical cancers for all individuals exceeding the cancer-specific target age (**Supplementary 1**).[48)] All Korean women over the age of 20 are instructed to be screened for cervical cancer biennially, and those over 40 are to be screened for breast cancer biennially.[48)]

2.2.2. Study population

Among 10,539,723 female subjects (age ≥ 40 years) who underwent both cardiovascular and breast/cervical cancer screening from 1 January 2009 to 31 December 2014, we identified 4,775,398 eligible postmenopausal women. We first excluded individuals who reported having a hysterectomy procedure in general (n = 17,667), as most did not know whether they had a simultaneous oophorectomy. Individuals who had a diagnosis of dementia before the health screening date (n = 49,593), using ICD-10 codes for dementia (F00, F01, F02, F03, G23.1, G30, G31), were identified from the Korean NHIS medical service claims data. Individuals who died within one year after the health screening date were also excluded (n = 7,261). We excluded 4,244 individuals with missing data on at least one variable. A total of 4,696,633 individuals was included in the final analyses (**Figure 2**).

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB File No. SMC 2018-05-013). The review board waived requirement for written informed consent because of publicly open and anonymous data used for analysis and retrospective features.

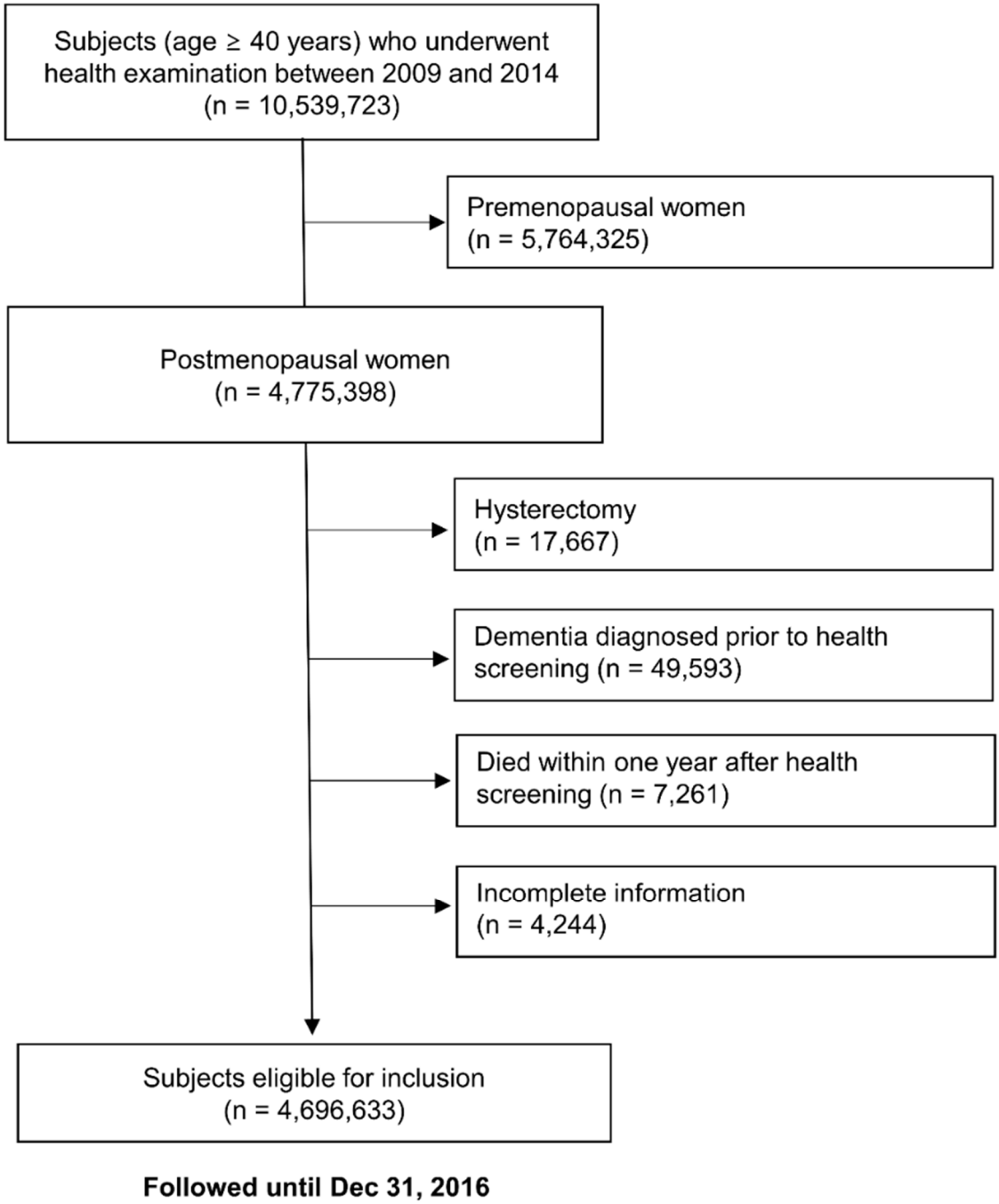

Figure 2 Flow chart of study population

2.2.3. Reproductive factors

According to NCSP guidelines, the study subjects completed a questionnaire addressing their age at menarche, age at menopause, and parity. The detailed questionnaires can be found in **Supplementary 2**. Information regarding total lifetime breast feeding history, HRT history, and use of oral contraceptives (OC) was also collected. Age at menarche was categorized as ≤ 12 years, 13-14 years, 15-16 years, and ≥ 17 years, to be consistent with the distribution of age at menarche among Korean women. Age at menopause was categorized as < 40 years, 40-44 years, 45-49 years, 50-54 years, and ≥ 55 years. The duration of fertility was calculated as the interval between the age at menarche and the age at menopause. Parity was categorized 0, 1, or ≥ 2 children. Total lifetime breast feeding history was categorized as never, < 6 months, 6-12 months or ≥ 12 total months. The duration of HRT was categorized as never, < 2 years, 2-5 years, ≥ 5 years, or unknown. The duration of OC was categorized as never, < 1 years, ≥ 1 years, or unknown.

2.2.4. Study outcomes and follow-up

The endpoints of the study were newly-diagnosed dementia, which was defined if acetylcholinesterase inhibitors (donepezil hydrochloride, rivastigmine, galantamine) or N-methyl-D-aspartate (NMDA) receptor antagonist (memantine) were prescribed at least two times, and the patient data included codes for AD (ICD-10 F00 or G30), vascular dementia (VaD, ICD-10 F01), or other dementia (ICD-10 F02, F03, or G31). The exact diagnostic codes for dementias are described in **Supplementary 3**. To file expense claims for acetylcholinesterase inhibitor or NMDA receptor antagonist prescriptions for dementia treatment, Korean physicians need to document evidence of cognitive dysfunction according

to the National Health Insurance Reimbursement criteria: a Mini-Mental State Examination (MMSE) ≤ 26 and either a Clinical Dementia Rating (CDR) ≥ 1 or a Global Deterioration Scale (GDS) ≥ 3.[49,50] The cohort was followed from baseline to the date of incident dementia or until the end of the study period (December 31, 2016), whichever came first. The median follow-up duration was 5.74 years (interquartile range 3.65-6.85 years).

2.2.5. Covariates

Detailed information of individuals' demographics and lifestyle was obtained through standardized self-reporting questionnaires. Income level was based on monthly insurance premium because insurance contribution is determined based on income level and not on health risk in Korea. Smoking status was classified into never, ex-, and current smoker. Based on daily alcohol consumption, data on drinking was classified into none (0 g/day), mild (< 30 g/day), and heavy (≥ 30 g/day). Regular exercise was defined as performing ≥ 30 minutes of moderate physical activity at least 5 times per week or ≥ 20 minutes of strenuous physical activity at least 3 times per week.

The health examination provided by NHIS includes anthropometric and laboratory measurements. Body mass index (BMI, kg/m^2) was calculated as the subject's weight in kilograms divided by the square of the subject's height in meters, and classified into 5 categories according to Asia-Pacific criteria of the World Health Organization; underweight (< 18.5 kg/m^2), normal (18.5–23 kg/m^2), overweight (23–25 kg/m^2), obese (25–30 kg/m^2), and severely obese (≥ 30 kg/m^2).[51] Systolic and diastolic blood pressure (BP) were measured in a seated position after at least 5 minutes rest. Blood samples for measurement of serum fasting glucose and lipid levels were drawn after an overnight fast. Hospitals where these health examinations were performed were certified by the NHIS and subjected to regular quality

control.

Baseline comorbidities (hypertension, diabetes mellitus, dyslipidemia, and cancer) were identified based on the combination of past medical history and ICD-10 and prescription codes. The exact diagnostic codes for comorbidities are described in **Supplementary 3**. Comorbidities were defined based on claims data before the screening date and health examination results.[52,53] Hypertension was defined based on the presence of at least 1 claim per year under ICD-10 codes I10–13 or I15 and at least 1 claim per year for the prescription of antihypertensive agents or systolic/diastolic BP ≥ 140/90 mmHg. Diabetes mellitus was defined based on the presence of at least 1 claim per year under ICD-10 codes E11–14 and at least 1 claim per year for the prescription of antidiabetic medication or fasting glucose level ≥ 126 mg/dL. Dyslipidemia was defined based on the presence of at least 1 claim per year under ICD-10 code E78 and at least 1 claim per year for the prescription of a lipid-lowering agent or total cholesterol ≥ 240 mg/dL.[54] Cancer was defined as patient registration in the NHIS with ICD-10 code C and V193, specific insurance codes that were issued by the NHIS of Korea.

2.2.6. Statistical analyses

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as number and percentage. The incidence rates of dementia were calculated by dividing the number of incident cases by 1,000 person-years. The cumulative incidence of outcomes according to reproductive factors was calculated using Kaplan–Meier curves, and the log-rank test was performed to analyze differences among the groups. Hazard ratios (HR) and 95% confidence interval (95% CI) values for dementia were analyzed using the Cox proportional hazards model for various reproductive factors. The multivariate-adjusted proportional hazards model was applied: (1) Model 1 was not adjusted; (2) Model 2 was full

model with age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HRT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes mellitus, dyslipidemia, and cancer; and (3) Model 3 included duration of fertility instead of the age at menarche and menopause variables in Model 2. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a P-value < 0.05 was considered statistically significant.

2.3. Results

2.3.1. Baseline characteristics of the study population

The characteristics of the study participants are presented in **Table 2**. The mean age of the total population in this study was 61.2 years (standard deviation 8.6 years). Most of study population were never smoker (95.8%) and non-drinkers (86.5%). Of the subjects, 40.5% performed regular physical activity. The proportion of obesity and severe obesity were 31.5% and 4.5%, respectively. Among comorbidities, 42.2% had hypertension, 13.7% had diabetes mellitus, 36.4% had dyslipidemia, and 8.1% had cancer.

Regarding reproductive factors, the overall mean ages at menarche and menopause were estimated to be 16.3 and 50.2 years, respectively. Of these women, 90.1% had greater than 2 parity, 65.9% had breast fed for more than 12 months, 81.6% were never HRT users, and 80.6% were never OC users.

Table 2 Baseline characteristics of study subjects

Variables	Total (n = 4,696,633)
Age (years)	61.2 ± 8.6
Income (quartile)	
Q1	1,321,500 (28.1)
Q2	1,045,709 (22.3)
Q3	1,098,570 (23.4)
Q4	1,230,854 (26.2)
Smoking status	
Never	4,500,803 (95.8)
Ex-smoker < 10 pack-year	42,821 (0.9)
Ex-smoker ≥ 10 pack-year	10,794 (0.2)
Current smoker < 10 pack-year	93,436 (2.0)
Current smoker ≥ 10 pack-year	48,779 (1.0)
Alcohol consumption	
None	4,061,505 (86.5)
Mild	612,698 (13.1)
Heavy	22,430 (0.5)
Regular exercise	1,901,185 (40.5)
Systolic blood pressure (mmHg)	125.2 ± 16.0
Diastolic blood pressure (mmHg)	76.7 ± 10.0
Fasting glucose (mg/dL)	100.4 ± 23.8
Total cholesterol (mg/dL)	206.8 ± 38.8
Body mass index (kg/m^2)	
< 18.5	107,579 (2.3)
18.5-23	1,672,453 (35.6)
23-25	1,226,936 (26.1)
25-30	1,479,129 (31.5)
≥ 30	210,536 (4.5)
Comorbidities	
Hypertension	1,979,488 (42.2)
Diabetes mellitus	645,127 (13.7)
Dyslipidemia	1,710,839 (36.4)
Cancer	379,878 (8.1)

Data are expressed as mean ± standard deviation or n (%).

Table 2 Continued

Variables	Total (n = 4,696,633)
Age at menarche (years)	16.3 ± 1.9
≤ 12	63,275 (1.4)
13-14	680,953 (14.5)
15-16	1,879,203 (40.0)
≥ 17	2,073,202 (44.1)
Age at menopause (years)	50.2 ± 4.0
< 40	76,635 (1.6)
40-44	248,056 (5.3)
45-49	1,218,122 (25.9)
50-54	2,601,970 (55.4)
≥ 55	551,850 (11.8)
Duration of fertility (years)	33.9 ± 4.4
< 30	584,182 (12.4)
30-34	1,831,593 (39.0)
35-39	1,916,595 (40.8)
≥ 40	364,263 (7.8)
Parity	
Nulliparity	103,671 (2.2)
1	363,216 (7.7)
≥ 2	4,229,746 (90.1)
Duration of breast feeding (months)	
Never	383,752 (8.2)
< 6	379,887 (8.1)
6-12	838,259 (17.9)
≥ 12	3,094,735 (65.9)
Duration of hormone replacement therapy (years)	
Never	3,830,524 (81.6)
< 2	408,848 (8.7)
2-5	158,343 (3.4)
≥ 5	126,416 (2.7)
Unknown	172,502 (3.7)
Duration of oral contraceptive use (years)	
Never	3,783,154 (80.6)
< 1	413,359 (8.8)
≥ 1	272,361 (5.8)
Unknown	227,759 (4.9)

Data are expressed as mean ± standard deviation or n (%).

2.3.2. Incidence of dementia according reproductive factors

During the median follow-up of 5.74 years, there were 212,227 new cases of all-cause dementia (4.5%), 162,901 cases of AD (3.5%), and 24,029 cases of VaD (0.5%). The cumulative incidence of all these outcomes up to 8 years according to reproductive factors is shown in Kaplan-Meier curves **(Figure 3A, 3B, and 3C)**. The incidence of all-cause dementia increased significantly with later age of menarche, earlier age of menopause, and shorter duration of fertility. The usage of HRT was associated with a decreased risk of developing all-cause dementia (log-rank test, $P < 0.001$). Similar patterns were noted for both AD and VaD.

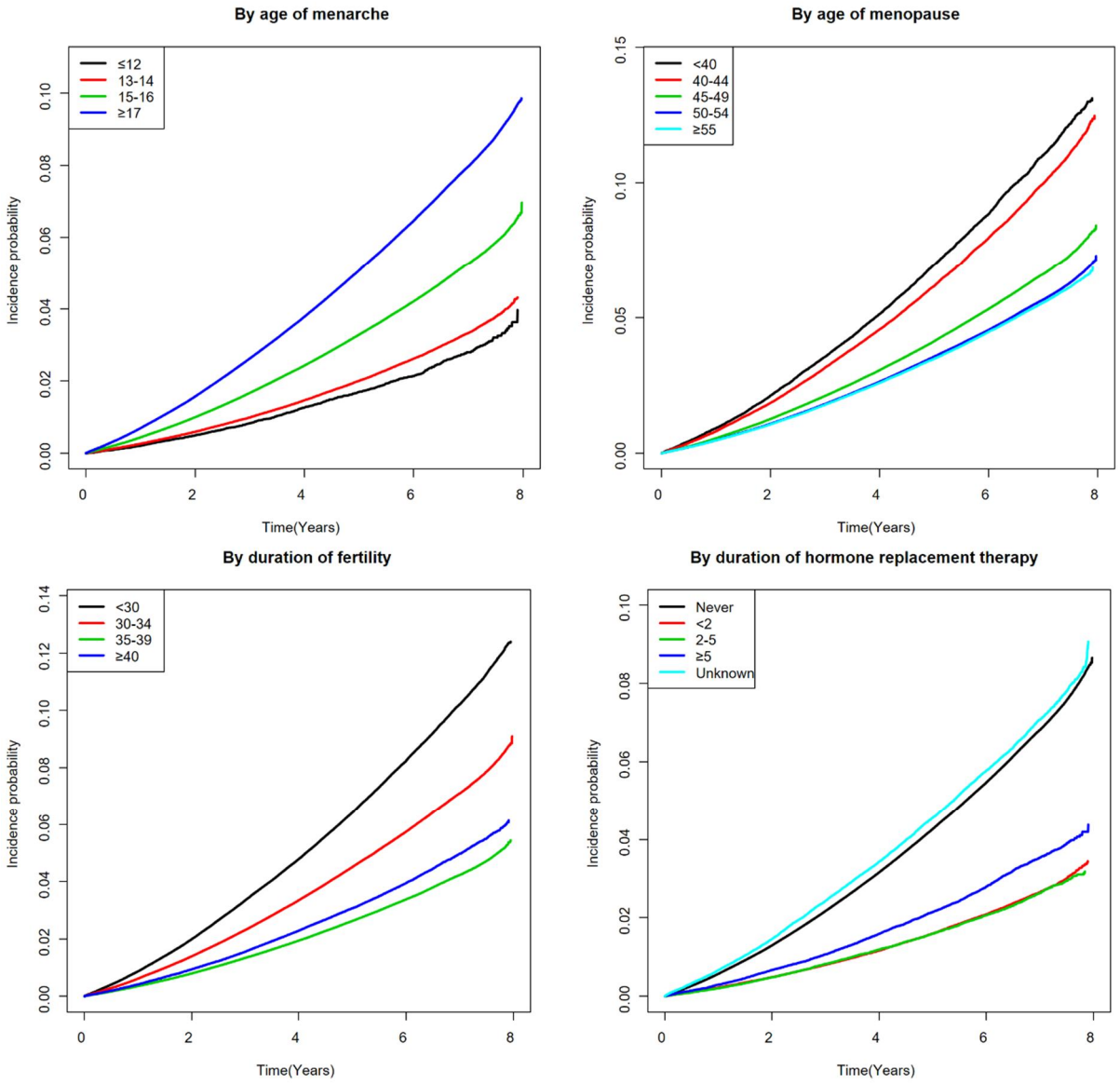

Figure 3A Cumulative incidence* of all-cause dementia according to reproductive factors

*The cumulative incidence of outcomes according to reproductive factors was calculated using Kaplan–Meier curves, and the log-rank test was performed to analyze differences among the groups.

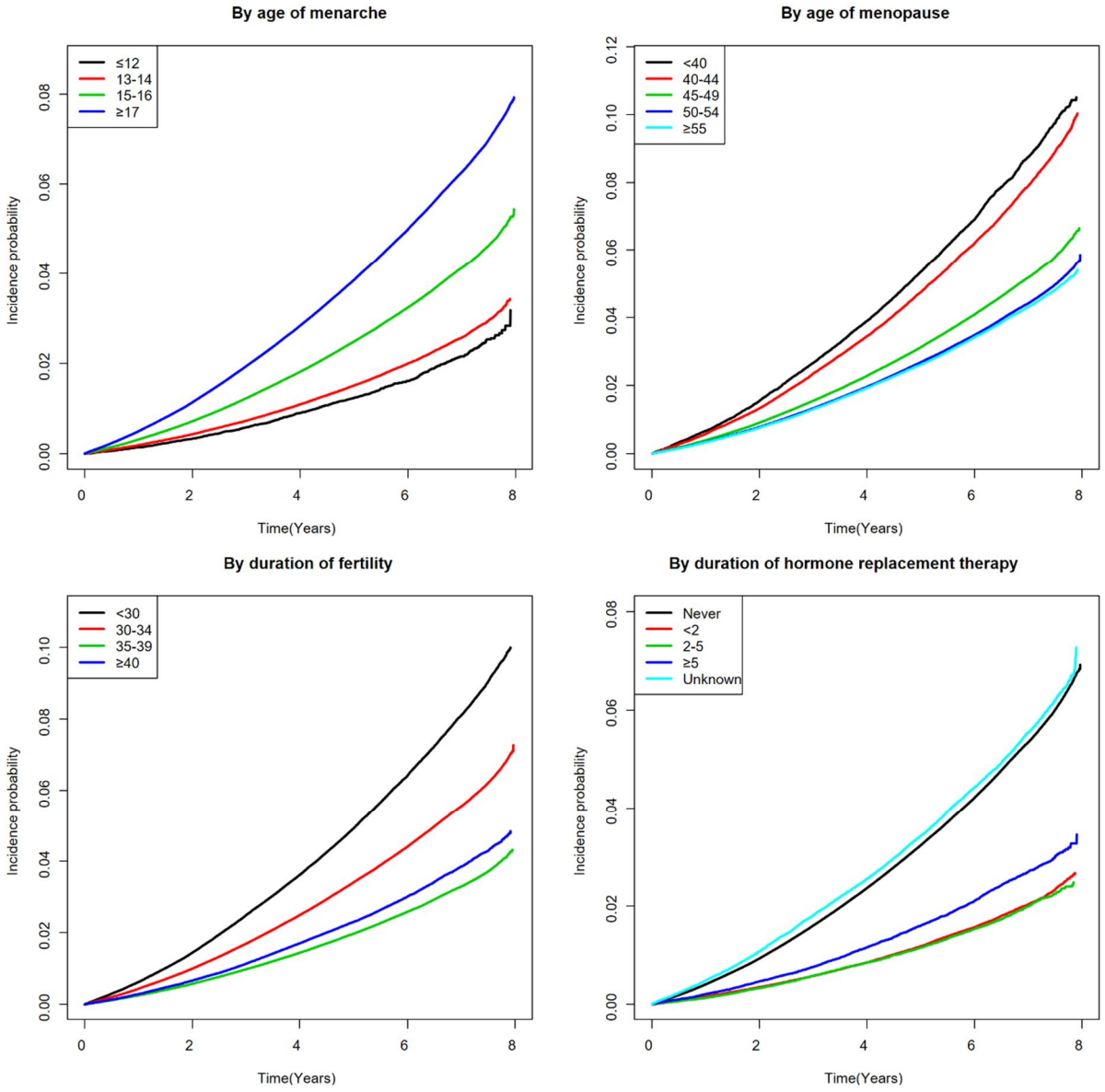

Figure 3B Cumulative incidence* of Alzheimer's disease according to reproductive factors

*The cumulative incidence of outcomes according to reproductive factors was calculated using Kaplan–Meier curves, and the log-rank test was performed to analyze differences among the groups.

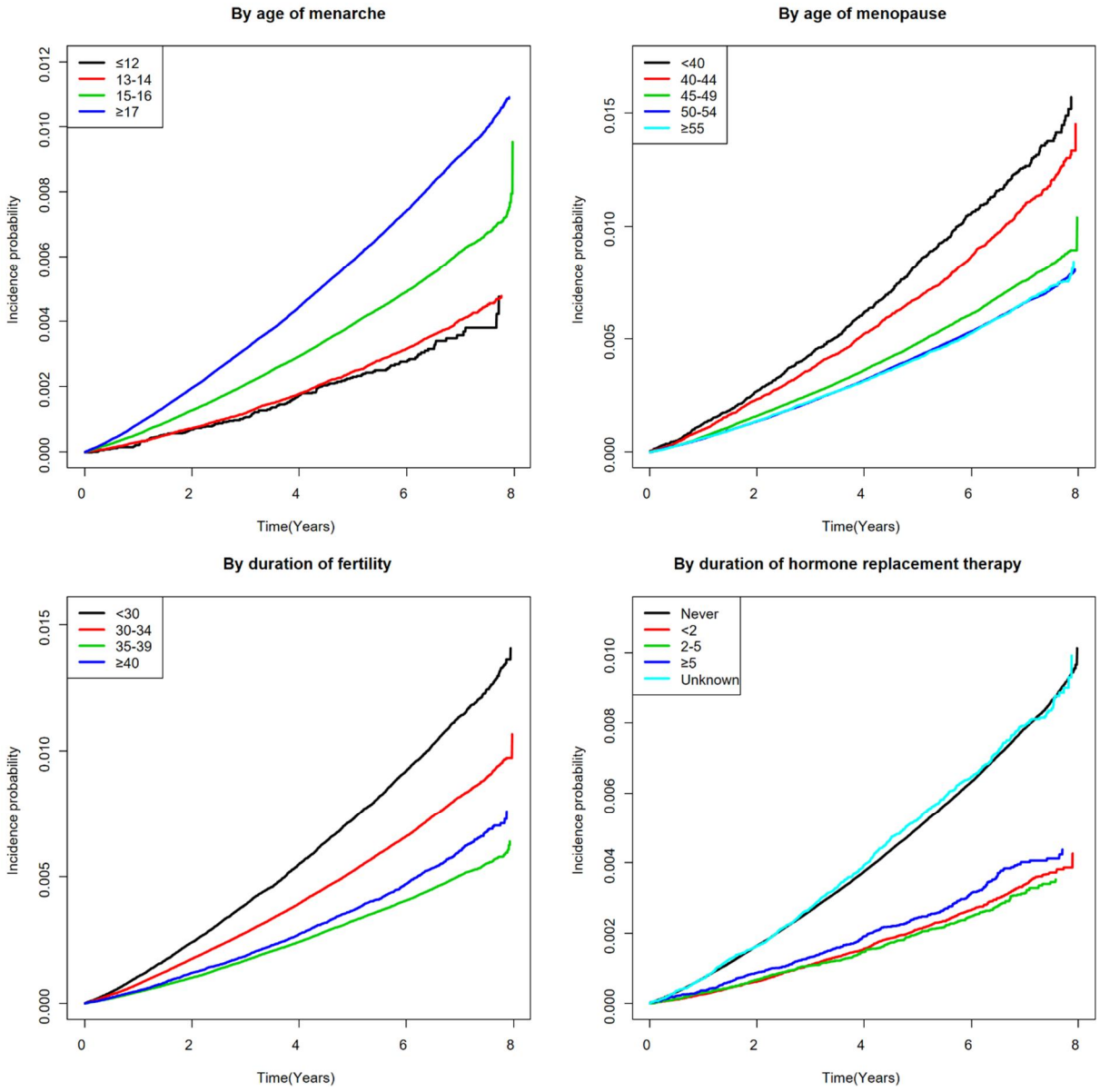

Figure 3C Cumulative incidence* of vascular dementia according to reproductive factors

*The cumulative incidence of outcomes according to reproductive factors was calculated using Kaplan–Meier curves, and the log-rank test was performed to analyze differences among the groups.

2.3.3. Menstrual history

Compared with women who experienced menarche at the age of 13-14 years, women who experienced menarche before the age of 12 years had an approximately 7% greater risk of all-cause dementia (adjusted HR [aHR] 1.07, 95% CI 1.01-1.14), and those who experienced menarche after the age of 17 years had an approximately 15% greater risk of all-cause dementia (aHR 1.15, 95% CI 1.13-1.16; **Table 3**). There was a significant trend of inverse association between age at menopause and risk of all-cause dementia, AD, and VaD (P for trend <0.0001) **(Table 3, 4, and 5)**. Compared to women who experienced menopause before the age of 40, those who underwent menopause after the age of 55 had an especially significant association with lower risk for dementia: all-cause dementia (aHR 0.79, 95% CI 0.77-0.81), AD (aHR 0.79, 95% CI 0.77-0.82), and VaD (aHR 0.76, 95% CI 0.70-0.83). Furthermore, in Model 3, a longer duration of fertility was consistently associated with a lower risk of dementia: all-cause dementia (aHR 0.81, 95% CI 0.79-0.82), AD (aHR 0.81, 95% CI 0.79-0.83), and VaD (aHR 0.81, 95% CI 0.76-0.86).

2.3.4. Parity and breast feeding

The 1 parity group was found to have a lower risk of all-cause dementia (aHR 0.89, 95% CI 0.85-0.94) than the nulliparity group in all models, although a small increase in dementia risk for the ≥ 2 parity group was of only borderline significance (aHR 1.04, 95% CI 0.99-1.08). While subjects in the breast feeding < 6 months group had an approximately 8% lower risk of all-cause dementia (aHR 0.92, 95% CI 0.88-0.95) compared with the never-breast feeding group, subjects in the breast feeding 6-12-months group had a 4% greater of all-cause dementia (aHR 1.04, 95% CI 1.01-1.07) and the ≥ 12 months group had a 14% greater risk

(aHR 1.14, 95% CI 1.11-1.17). Similar patterns were observed in both AD and VaD.

2.3.5. Hormone replacement therapy and oral contraceptive use

When compared with the never-HRT group, any HRT user groups had approximately 15% lower risks of all-cause dementia (aHR 0.86, 95% CI 0.84-0.88 for the HRT < 2 years group; aHR 0.81, 95% CI 0.78-0.84 for the 2 years ≤ HRT < 5 years group; and aHR 0.87, 95% CI 0.84-0.90 for the HRT ≥ 5 years group). Similarly, when compared with OC nonusers, any OC users had approximately 10% lower risks of all-cause dementia (aHR 0.91; 95% CI 0.88-0.92 for OC use < 1 year; and aHR 0.90, 95% CI 0.88-0.92, for OC use ≥ 1 year). Similar patterns were also noted in both AD and VaD.

Table 3 Hazard ratios and 95% confidence intervals of all-cause dementia by reproductive factors

Reproductive factors	Subjects (N)	Events (n)	Follow-up duration (PYs)	IR (per 1,000 PYs)	Model 1	Model 2	Model 3
All-cause dementia	**4,696,633**	**212,227**	**24,780,569.2**	**8.6**			
Age at menarche (years)							
≤ 12	63,275	1,134	311,174.0	3.6	**0.84 (0.79-0.89)**	**1.07 (1.01-1.14)**	
13-14	680,953	15,339	3,473,304.5	4.4	1 (ref.)	1 (ref.)	
15-16	1,879,203	70,707	9,834,834.2	7.2	**1.61 (1.59-1.64)**	**1.07 (1.05-1.09)**	
≥ 17	2,073,202	125,047	11,161,256.5	11.2	**2.49 (2.45-2.53)**	**1.15 (1.13-1.16)**	
Age at menopause (years)							
< 40	76,635	6,308	406,261.4	15.5	1 (ref.)	1 (ref.)	
40-44	248,056	18,440	1,322,749.7	13.9	**0.90 (0.87-0.92)**	**0.96 (0.93-0.98)**	
45-49	1,218,122	59,452	6,506,774.6	9.1	**0.59 (0.57-0.60)**	**0.89 (0.86-0.91)**	
50-54	2,601,970	106,193	13,665,541.7	7.8	**0.50 (0.49-0.52)**	**0.85 (0.83-0.87)**	
≥ 55	551,850	21,834	2,879,242.0	7.6	**0.49 (0.48-0.51)**	**0.79 (0.77-0.81)**	
Duration of fertility (years)							
< 30	584,182	45,408	3,140,629.8	14.5	1 (ref.)		1 (ref.)
30-34	1,831,593	97,165	9,806,305.6	9.9	**0.69 (0.68-0.70)**		**0.93 (0.92-0.94)**
35-39	1,916,595	57,242	9,975,643.9	5.7	**0.40 (0.40-0.41)**		**0.81 (0.80-0.82)**
≥ 40	364,263	12,412	1,857,989.9	6.7	**0.47 (0.46, 0.48)**		**0.81 (0.79-0.82)**
Parity							
Nulliparity	103,671	2,670	582,818.7	4.6	1 (ref.)	1 (ref.)	1 (ref.)
1	363,216	6,146	1,817,313.6	3.4	**0.77 (0.73-0.80)**	**0.89 (0.85-0.94)**	**0.89 (0.85-0.94)**
≥ 2	4,229,746	203,411	22,380,436.9	9.1	**2.01 (1.94-2.09)**	1.04 (0.99-1.08)	1.04 (0.99-1.08)
Duration of breast feeding (months)							
Never	383,752	6,825	1,953,876.5	3.5	1 (ref.)	1 (ref.)	1(ref.)
< 6	379,887	5,279	1,888,786.2	2.8	**0.81 (0.78-0.84)**	**0.92 (0.88-0.95)**	**0.92 (0.88-0.95)**
6-12	838,259	23,046	4,392,910.2	5.2	**1.49 (1.45-1.53)**	**1.04 (1.01-1.07)**	**1.04 (1.01-1.07)**
≥ 12	3,094,735	177,077	16,544,996.3	10.7	**3.01 (2.93-3.08)**	**1.14 (1.11-1.17)**	**1.14 (1.11-1.17)**

Table 3 Continued

Reproductive factors	Subjects (N)	Events (n)	Follow-up duration (PYs)	IR (per 1,000 PYs)	Model 1	Model 2	Model 3
Duration of HRT (years)							
Never	3,830,524	189,459	20,166,294.7	9.4	1 (ref.)	1 (ref.)	1 (ref.)
< 2	408,848	7,885	2,200,577.8	3.6	**0.38 (0.37-0.39)**	**0.86 (0.84-0.88)**	**0.86 (0.84-0.88)**
2-5	158,343	3,030	856,684.6	3.5	**0.37 (0.36-0.39)**	**0.81 (0.78-0.84)**	**0.81 (0.78-0.84)**
≥ 5	126,416	3,236	679,725.7	4.8	**0.50 (0.49-0.52)**	**0.87 (0.84-0.90)**	**0.87 (0.84-0.90)**
Unknown	172,502	8,617	877,286.6	9.8	**1.06 (1.03-1.08)**	**1.06 (1.04-1.09)**	**1.07 (1.04-1.09)**
Duration of oral contraceptive use (years)							
Never	3,783,154	177,150	19,903,947.8	8.9	1 (ref.)	1 (ref.)	1 (ref.)
< 1	413,359	13,064	2,213,236.1	5.9	**0.66 (0.65-0.67)**	**0.90 (0.89-0.92)**	**0.91 (0.89-0.92)**
≥ 1	272,361	10,249	1,464,782.8	7.0	**0.78 (0.77-0.80)**	**0.90 (0.88-0.92)**	**0.90 (0.89-0.92)**
Unknown	227,759	11,764	1,198,602.6	9.8	**1.10 (1.08-1.12)**	**1.07 (1.05-1.10)**	**1.07 (1.05-1.09)**

PY, person-years; IR, incidence rate; HRT, hormone replacement therapy

Model 1: non-adjusted

Model 2: the full model includes age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HRT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes mellitus, dyslipidemia, and cancer.

Model 3: the full model includes duration of fertility instead of age at menarche and menopause in Model 2.

Table 4 Hazard ratios and 95% confidence intervals of Alzheimer's disease by reproductive factors

Reproductive factors	Subjects (N)	Events (n)	Follow-up duration (PYs)	IR (per 1,000 PYs)	Model 1	Model 2	Model 3
Alzheimer's disease	**4,696,633**	**162,901**	**24,780,569.2**	**6.6**			
Age at menarche (years)							
≤ 12	63,275	848	311,174.0	2.7	**0.82 (0.77-0.88)**	1.06 (0.99-1.14)	
13-14	680,953	11,663	3,473,304.5	3.4	1 (ref.)	1 (ref.)	
15-16	1,879,203	54,154	9,834,834.2	5.5	**1.62 (1.59-1.66)**	**1.06 (1.04-1.09)**	
≥ 17	2,073,202	96,236	11,161,256.5	8.6	**2.51 (2.46-2.56)**	**1.14 (1.12-1.16)**	
Age at menopause (years)							
< 40	76,635	4,893	406,261.4	12.0	1 (ref.)	1 (ref.)	
40-44	248,056	14,330	1,322,749.7	10.8	**0.90 (0.87-0.93)**	**0.96 (0.93-0.99)**	
45-49	1,218,122	45,753	6,506,774.6	7.0	**0.58 (0.57-0.60)**	**0.88 (0.86-0.91)**	
50-54	2,601,970	81,274	13,665,541.7	5.9	**0.50 (0.48-0.51)**	**0.85 (0.82-0.87)**	
≥ 55	551,850	16,651	2,879,242.0	5.8	**0.48 (0.47-0.50)**	**0.79 (0.77-0.82)**	
Duration of fertility (years)							
< 30	584,182	35,210	3,140,629.8	11.2	1 (ref.)		1 (ref.)
30-34	1,831,593	74,555	9,806,305.6	7.6	**0.68 (0.67-0.69)**		**0.93 (0.92-0.94)**
35-39	1,916,595	43,690	9,975,643.9	4.4	**0.40 (0.39-0.40)**		**0.81 (0.80-0.82)**
≥ 40	364,263	9,446	1,857,989.9	5.1	**0.46 (0.45-0.47)**		**0.81 (0.79-0.83)**
Parity							
Nulliparity	103,671	2,032	582,818.7	3.5	1 (ref.)	1 (ref.)	1 (ref.)
1	363,216	4,666	1,817,313.6	2.6	**0.77 (0.73-0.81)**	**0.91 (0.86-0.96)**	**0.91 (0.86-0.96)**
≥ 2	4,229,746	156,203	22,380,436.9	7.0	2.03 (1.95-2.12)	1.05 (1.00-1.10)	1.05 (1.00-1.10)
Duration of breast feeding (months)							
Never	383,752	5,233	1,953,876.5	2.7	1 (ref.)	1 (ref.)	1 (ref.)
< 6	379,887	3,955	1,888,786.2	2.1	**0.79 (0.76-0.82)**	**0.89 (0.86-0.93)**	**0.89 (0.86-0.93)**
6-12	838,259	17,566	4,392,910.2	4.0	**1.47 (1.43-1.52)**	1.02 (0.98-1.05)	1.02 (0.98-1.05)
≥ 12	3,094,735	136,147	16,544,996.3	8.2	**3.00 (2.92-3.09)**	**1.11 (1.08-1.15)**	**1.11 (1.08-1.15)**

Table 4 Continued

Reproductive factors	Subjects (N)	Events (n)	Follow-up duration (PYs)	IR (per 1,000 PYs)	Model 1	Model 2	Model 3
Duration of HRT (years)							
Never	3,830,524	145,665	20,166,294.7	7.2	1 (ref.)	1 (ref.)	1 (ref.)
< 2	408,848	5,948	2,200,577.8	2.7	**0.37 (0.36-0.38)**	**0.87 (0.84-0.89)**	**0.87 (0.84-0.89)**
2-5	158,343	2,261	856,684.5	2.6	**0.36 (0.35-0.38)**	**0.81 (0.77-0.84)**	**0.81 (0.77-0.84)**
≥ 5	126,416	2,439	679,725.7	3.6	**0.49 (0.47-0.51)**	**0.87 (0.84-0.91)**	**0.87 (0.84-0.91)**
Unknown	172,502	6,588	877,286.6	7.5	**1.05 (1.02-1.08)**	**1.07 (1.04-1.09)**	**1.07 (1.04-1.09)**
Duration of oral contraceptive use (years)							
Never	3,783,154	136,246	19,903,947.8	6.8	1 (ref.)	1 (ref.)	1 (ref.)
< 1	413,359	9,925	2,213,236.1	4.5	**0.65 (0.64-0.67)**	**0.91 (0.89-0.92)**	**0.91 (0.89-0.93)**
≥ 1	272,361	7,768	1,464,782.8	5.3	**0.77 (0.75-0.79)**	**0.90 (0.88-0.92)**	**0.90 (0.88-0.92)**
Unknown	227,759	8,962	1,198,602.6	7.5	**1.09 (1.07-1.12)**	**1.06 (1.04-1.09)**	**1.06 (1.04-1.09)**

PY, person-years; IR, incidence rate; HRT, hormone replacement therapy

Model 1: non-adjusted

Model 2: the full model includes age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HRT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes mellitus, dyslipidemia, and cancer

Model 3: the full model includes duration of fertility instead of age at menarche and menopause in Model 2

Table 5 Hazard ratios and 95% confidence intervals of vascular dementia by reproductive factors

Reproductive factors	Subjects (N)	Events (n)	Follow-up duration (PYs)	IR (per 1,000 PYs)	Model 1	Model 2	Model 3
Vascular dementia	**4,696,633**	**24,029**	**24,780,569.2**	**1.0**			
Age at menarche (years)							
≤ 12	63,275	146	311,174.0	0.5	0.90 (0.76-1.07)	1.14 (0.96-1.34)	
13-14	680,953	1,825	3,473,304.5	0.5	1 (ref.)	1 (ref.)	
15-16	1,879,203	8,123	9,834,834.2	0.8	**1.56 (1.48-1.64)**	**1.08 (1.03-1.13)**	
≥ 17	2,073,202	13,935	11,161,256.5	1.2	**2.34 (2.23-2.46)**	**1.16 (1.10-1.22)**	
Age at menopause (years)							
< 40	76,635	706	406,261.4	1.7	1 (ref.)	1 (ref.)	
40-44	248,056	1,949	1,322,749.7	1.5	**0.85 (0.78-0.92)**	**0.91 (0.83-0.99)**	
45-49	1,218,122	6,666	6,506,774.6	1.0	**0.59 (0.55-0.64)**	**0.87 (0.80-0.94)**	
50-54	2,601,970	12,158	13,665,541.7	0.9	**0.51 (0.48-0.55)**	**0.83 (0.77-0.90)**	
≥ 55	551,850	2,550	28,79,242.0	0.9	**0.51 (0.47-0.56)**	**0.76 (0.70-0.83)**	
Duration of fertility (years)							
< 30	584,182	4,874	3,140,629.8	1.6	1(ref.)		1 (ref.)
30-34	1,831,593	10,909	9,806,305.6	1.1	**0.72 (0.69-0.74)**		**0.95 (0.92-0.98)**
35-39	1,916,595	6,773	9,975,643.9	0.7	**0.44 (0.43-0.46)**		**0.82 (0.79-0.85)**
≥ 40	364,263	1,473	1,857,989.9	0.8	**0.52 (0.49-0.55)**		**0.81 (0.76-0.86)**
Parity							
Nulliparity	103,671	293	582,818.7	0.5	1 (ref.)	1 (ref.)	1 (ref.)
1	363,216	721	1,817,313.6	0.4	**0.81 (0.71-0.93)**	0.91 (0.79-1.05)	0.91 (0.79-1.05)
≥ 2	4,229,746	23,015	22,380,436.9	1.0	**2.07 (1.84-2.32)**	1.09 (0.96-1.24)	1.09 (0.96-1.24)
Duration of breast feeding (months)							
Never	383,752	780	1,953,876.5	0.4	1 (ref.)	1 (ref.)	1 (ref.)
< 6	379,887	631	1,888,786.2	0.3	**0.84 (0.76-0.93)**	0.94 (0.85-1.05)	0.94 (0.85-1.05)
6-12	838,259	2,676	4,392,910.2	0.6	**1.51 (1.40-1.64)**	**1.10 (1.00-1.19)**	**1.10 (1.00-1.20)**
≥ 12	3,094,735	19,942	16,544,996.3	1.2	**2.98 (2.77-3.20)**	**1.22 (1.13-1.33)**	**1.23 (1.13-1.33)**

Table 5 Continued

Reproductive factors	Subjects (N)	Events (n)	Follow-up duration (PYs)	IR (per 1,000 PYs)	Model 1	Model 2	Model 3
Duration of HRT (years)							
Never	3,830,524	21,376	20,166,294.7	1.1	1 (ref.)	1 (ref.)	1 (ref.)
< 2	408,848	992	2,200,577.8	0.5	**0.42 (0.40-0.45)**	**0.86 (0.81-0.92)**	**0.86 (0.81-0.92)**
2-5	158,343	362	856,684.5	0.4	**0.40 (0.36-0.44)**	**0.77 (0.70-0.86)**	**0.77 (0.70-0.86)**
≥ 5	126,416	359	679,725.7	0.5	**0.50 (0.45-0.55)**	**0.78 (0.71-0.87)**	**0.78 (0.71-0.87)**
Unknown	172,502	940	877,286.6	1.1	1.02 (0.96-1.09)	1.05 (0.98-1.12)	1.05 (0.97-1.12)
Duration of oral contraceptive use (years)							
Never	3,783,154	19,977	19,903,947.8	1.0	1 (ref.)	1 (ref.)	1 (ref.)
< 1	413,359	1,545	2,213,236.1	0.7	**0.69 (0.65-0.73)**	**0.88 (0.84-0.93)**	**0.89 (0.84-0.93)**
≥ 1	272,361	1,235	1,464,782.8	0.8	**0.84 (0.79-0.89)**	**0.90 (0.85-0.95)**	**0.90 (0.85-0.96)**
Unknown	227,759	1,272	1,198,602.6	1.1	1.06 (1.00-1.12)	1.03 (0.97-1.10)	1.03 (0.97-1.10)

PY, person-years; IR, incidence rate; HRT, hormone replacement therapy

Model 1: non-adjusted

Model 2: the full model includes age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HRT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes mellitus, dyslipidemia, and cancer

Model 3: the full model includes duration of fertility instead of age at menarche and menopause in Model 2

2.4. Discussion

In this large-scale and long-term follow-up study, we confirmed that female reproductive factors were independently associated with the incidence of all-cause dementia, AD, and VaD. Later menarche, earlier menopause, and shorter duration of fertility were each independently associated with increased risk of dementia in postmenopausal women. In contrast, having one child and breast feeding for less than six months were associated with lower risks of dementia. Women who had two or more children and breast fed them for a total period of longer than six months were found to have a greater risk of dementia than nulliparous women or those with no history of breast feeding. Use of HRT or OC independently decreased the risk of dementia in postmenopausal women.

A woman's endogenous estrogen exposure occurs mainly during the reproductive phase bounded by menarche and menopause. Consistent with our findings, recent studies have showed that earlier menarche[34,37,42] and later menopause,[33-35] hence a longer reproductive period[34,42,55], were associated with the occurrence of dementia. In addition, the present study confirmed that dementia risk is reduced in women with a longer duration of fertility regardless of the covariate adjustment, and this effect was consistently detected when age at menarche or age at menopause was considered individually.

We showed a significant U-shaped association between parity and duration of breast feeding and the incidence of dementia. This finding is consistent with a cognitively protective role of estrogen. Provided that lower parity and shorter average duration of breast feeding per child represent greater estrogen exposure throughout life[35,55,56], the risk of dementia may increase with increasing parity and duration of breast feeding. Nonetheless, in the present study, nulliparity and no history of breast feeding were not associated with better cognitive outcomes, but rather with worse outcomes. These findings perhaps indicate a more complex interplay of

estrogen exposure with pregnancy. We did not collect data addressing the causes of nulliparity and were not able to address these causes in the analyses: nulliparity could result from either infertility or avoidance of pregnancy. Certain disorders, disabilities, and lifestyle habits, not considered in this present study, may cause unmarried status and are associated with infertility. For example, those who are more educated may have lower parity or use more HRT or OC. Where infertility is caused by genetic disorders, the risk of developing dementia due to a genetic disorder may be high.[57)]

As dementia is not an etiology but a syndrome, estrogen can have different effects according to etiology of dementia. Although exact mechanisms underlying the association between estrogen and AD are still very poorly understood, several possible explanations have been suggested. First, estrogen exerts potentially helpful effects on brain synapse structure and function in regions such as the prefrontal cortex and hippocampus.[58)] In ovariectomized rats, estrogen increases choline acetyltransferase activity in the basal forebrain and hippocampus regions of the brain that are acetylcholine-deficient in patients with AD.[59)] Additionally, estrogen improves synapse formation on dendritic spines in the hippocampus of oophorectomized rats.[60,61)] Furthermore, estrogen reduces the deposition amyloid-β peptide (Aβ), which is implicated in the pathogenesis of AD, in the brain.[62,63)]

In terms of VaD, a state of estrogen depletion promotes secondary changes in metabolic parameters, thus resulting in a higher prevalence of strokes, which may lead to VaD.[59-61)] While the effects of estrogen on cerebrovascular and cardiovascular health remain inconclusive, the molecular actions of estrogen in the cerebral vasculature have been demonstrated and include (1) vascular tone regulation (estrogen decreases myogenic tone of the cerebrovasculature), (2) anti-inflammatory effects that include suppression of pro-inflammatory cytokines, reduction in free radical production, and decrease in blood brain permeability and edema, and (3) an increase in mitochondrial bioenergetics.[64)] Indeed, estrogen also promotes formation of new

blood vessels and improves functional recovery following ischemic insult in a process known as angiogenesis.[64]

The present study also demonstrated that use of HRT or OC was associated with a lower risk of dementia. The result of studies investigating the cognitive effects of exogenous estrogen (which have typically addressed HRT use) have been contradictory. In the Women's Health Initiative Memory Study (WHIMS), HRT did not improve cognitive function and increased dementia risk for postmenopausal women over the age of 65.[65] Subsequent criticisms of this study have pointed out that the participants were, on average, 72 years old, and were not therefore truly representative on the usual clinical population, whereas women often seek HRT treatment around the time of menopause.[42] More recently, two randomized controlled trials addressed some of the weaknesses of the WHIMS study. The KEEPS trial found that neither type of hormone benefited cognitive function[66], although in women who carried the APOE4 gene, bioidentical hormones were associated with lower levels of beta-amyloid plaques in the brain[67]. The ELITE trial also found no evidence of cognitive benefit or harm.[68] These studies had only four to five years of follow-up, which is likely not sufficient to assess dementia risks. On the other hand, a recent observational study that followed 8,195 women aged 47-56 years for 20 years found that women who used HRT for more than 10 years had a lower risk of dementia.[43] Cumulatively, these data support the critical period hypothesis of the neuroprotective effect of estrogen, called a "window of opportunity." The hypothesis claims that estrogen must be administered soon after ovarian estrogen depletion to be neuro- and vaso-protective and exert positive effects on brain circuitry.[64] The findings of our study further support the theory that HRT may be a potential preventive therapy for dementia in women.

The clinical implications of our study are that women with shorter fertility duration, resulting from combined estrogen-altering reproductive events, such as early natural or surgical menopause, should be made aware of potential risks for accelerated cognitive decline. Based

on the available evidence, HRT appears to provide cognitive benefits, although the use of HRT may be associated with small increases in the risks of heart attack, stroke, deep vein thrombosis, and breast cancer.[69] In addition, a recent study proposed that an appropriate estrogen-containing drug regimen used in combination with cholinergic-enhancing drugs may be a viable therapeutic strategy for use in postmenopausal women with early evidence of mild cognitive decline.[70]

There are several limitations of our study. First, discrepancies between the diagnoses made by individuals in medical practice and those recorded in claims data may have led to inaccurate analyses. However, under the Korean National Health Insurance System, the specificity of the data is usually high because of the requirements to fulfill strict insurance criteria. The sensitivity of the data is also considered high because dementia could be detected with only clinically meaningful symptoms owing to accessibility to healthcare system. Second, our data might not be generalizable to other countries. In Korea, regular cardiovascular and cancer screening is widely available, and this could reduce the risk of dementia by early detection and controlling of modifiable risk factors of dementia. Third, because this study was based on data that were not originally collected to study dementia, we did not have all the pertinent information relevant to a dementia study. For example, we did not have genetic data, such as APOE4 carrier status, and we were not able to assess education and literacy levels, which might affect cognitive function. However, to the best of our knowledge, it is not likely that APOE acts as hidden confounder to explain early menopause and dementia.[71] Furthermore, as level of education is the most important determinant of income,[72] the effect of education on dementia could be minimized by controlling for income. Fourth, we were unable to obtain sufficient information about female hormone use, such as age at use, delay after menopause, or dose. Further detailed information about female hormone use and user potential risk factors for dementia is required to clarify this possible association between exogenous female hormone

use and risk of dementia. Lastly, this was a retrospective study, and the findings should be interpreted accordingly. To minimize the possible effects of reverse causality, we excluded subjects diagnosed with dementia prior to the health screening date.

In conclusion, in this nationwide population-based cohort study, we demonstrated that female reproductive factors are independent predictors for developing dementia and its subtypes in postmenopausal women. An association was also noted between lower lifetime endogenous estrogen exposure and increased dementia incidence. Future studies are needed to elucidate the precise mechanism of association between female reproductive factors and the incidence of dementia.

3. Female reproductive factors and the risk of Parkinson's disease

3.1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, affecting 1% of the population over 60 years of age.[73] Notably, sex differences of the disease exist among PD patients. Women usually have a lower incidence of PD at all ages than men.[74-76] Females with PD have several different epidemiological characteristics, as well as motor and non-motor symptom distribution compared with male PD patients including age of onset, risk factors, motor complications, and various non-motor domains.[77]

Hormones, especially estrogen, could be an explanation for the pathogenesis of PD and considered a risk factor for PD. Although the exact role of estrogen in PD is unknown, results from animal studies indicate that estrogen exerts neuroprotective activities against neurotoxins,[78] with anti-inflammatory, anti-apoptotic, and anti-oxidative effects.[21] In addition, estrogen was found to modulate nigrostriatal dopaminergic activity.[79,80]

To date, the relationship between estrogen status and risk or progression of PD has been reported in several studies; however, the results are conflicting. In particular, early age at menopause was reported in a few studies to increased risk of PD,[23,81-83] but did not do so in another study.[84] Although results of some studies showed that use of exogenous estrogen after menopause was associated with decreased risk of PD,[81,85] clear evidence of benefit was not found in other studies[84,86] or increased risk was reported.[83]

In addition, previous studies had several limitations. The researchers did not fully investigate reproductive factors such as age at menarche,[23,81,83-87] duration of fertility,[23,81,84,86,87] parity,[23,81,83,86,87] and breast feeding.[23,81-87] Most of the research only focused on menopause[23,81,83,86,87] or estrogen use.[81,83-87] Potential confounding factors, such as comorbidities including cardiovascular risk factors, were not fully adjusted.[23,81-87] Furthermore, limitations existed, including case-control design[81-83,85-87] as well as small study population

and number of cases.[23,84,87] For example, the largest study regarding the association between exogenous hormone use and risk of PD only included 410 incident PD cases among 119,166 women.[87]

Therefore, in the present retrospective cohort study using a large population-based database (DB), the associations between female reproductive factors and PD development were investigated. In addition, several reproductive factors associated with natural variability of estrogen level were comprehensively examined to verify potential effects on the occurrence of PD.

3.2. Methods

3.2.1. Data source and study setting

The National Health Insurance Service (NHIS) is a single-payer system that provides mandatory universal comprehensive medical care to 97% of the Korean population and medical aid to 3% of the population in the lowest income bracket. The NHIS also recommends free biennial cardiovascular health screening to all Koreans 40 years of age and older and all employees regardless of age, as well as annual screenings for workers in physical labor jobs. Hence, the NHIS retains an extensive health information DB that consists of a qualification DB (e.g., age, sex, income, region, and type of eligibility), a claim DB (general information on specification, consultation statements, diagnosis statements defined by the International Classification of Disease10th revision (ICD-10), and prescription statements), a health check-up DB, and death information.[46,47)]

In addition, as part of the National Cancer Control Plan, the National Cancer Screening Program (NCSP) was introduced in 1999 (**Supplementary 1**).[48)] Currently, the NCSP includes screening for stomach, liver, colorectal, breast, and cervical cancers for all individuals based on age.[48)] All Korean women are instructed to be biennially screened for breast and cervical cancers.[48)]

3.2.2. Study population

Among 6,414,645 female subjects (age ≥ 40 years) who underwent both cardiovascular and breast/cervical cancer screening from January 1, 2009 to December 31, 2014, 4,775,398 eligible postmenopausal women were initially identified. Subjects were excluded for the

following reasons: (1) they reported having a hysterectomy (n = 17,667) because most did not know whether they had oophorectomy simultaneously; (2) they had a history of PD before the health screening date (n = 16,293); (3) they died within 1 year after the health screening date (n = 7,623); or (4) they had any missing information (n = 4,269). Finally, a total of 4,729,546 individuals was included in the analysis (**Figure 4**).

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB File No. SMC 2018-05-013). The review board waived written informed consent because the data are public and anonymized under confidentiality guidelines.

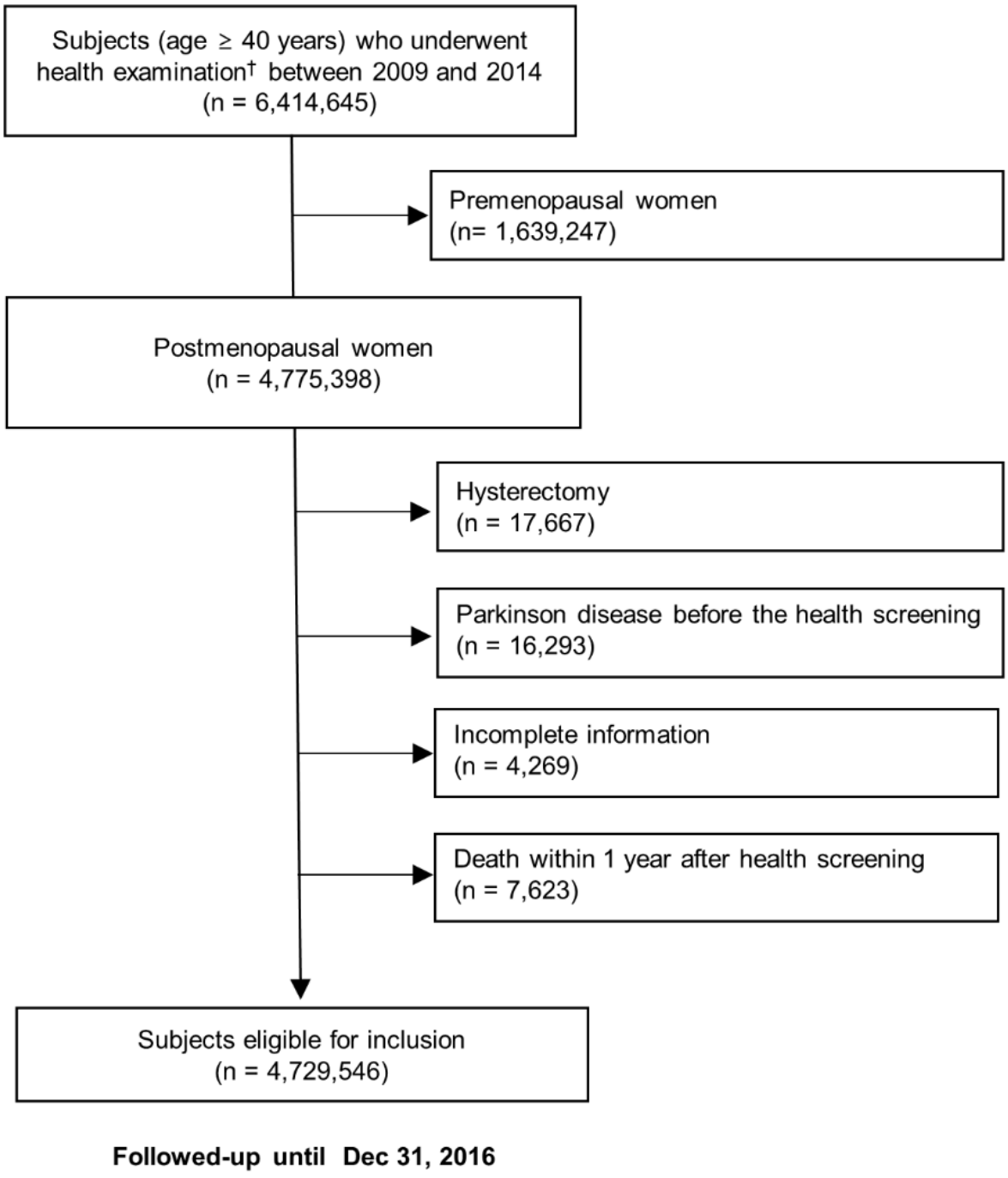

Figure 4 Flow chart of study population

3.2.3. Exposure: Reproductive factors

According to NCSP guidelines, information on the age at menarche, age at menopause, number of parities, total lifetime breast feeding history, hormone replacement therapy (HRT) history, and use of oral contraceptives (OCs) was obtained using a self-administered questionnaire. The detailed questionnaires can be found in **Supplementary 2**. Data on age at menarche were categorized as ≤ 12 years, 13-14 years, 15-16 years, and ≥ 17 years based on distribution of age at menarche in the Korean population. The age at menopause was categorized as < 40 years, 40-44 years, 45-49 years, 50-54 years, and ≥ 55 years. The duration of fertility was calculated as the interval between age at menarche and age at menopause. Parity was categorized as 0, 1, or ≥ 2 children. Total lifetime breast-feeding history was categorized as never, < 6 months, 6-12 months, and ≥ 12 months. Duration of HRT was categorized as never, < 2 years, 2-5 years, ≥ 5 years, and unknown. Duration of OC use was categorized as never, < 1 year, ≥ 1 year, and unknown.

3.2.4. Study outcome: PD case ascertainment

The primary endpoint was newly diagnosed PD during the follow-up period. PD was defined based on ICD-10 code for PD (G20) and the registration code for PD (V124) in the program implemented by NHIS to enhance the health coverage for rare intractable diseases including PD since 2006.[88] To receive copayment reduction for PD-related medical care, physicians must confirm whether patients' clinical conditions are correctly diagnosed as PD. The exact diagnostic codes for PD are described in **Supplementary 3**. The cohort was followed from baseline to date of incident PD or until the end of the study period (December 31, 2016), whichever came first. The median follow-up duration was 5.84 years (interquartile range 3.75-

6.91 years).

3.2.5. Covariates

Detailed information of individuals' demographics and lifestyle was obtained through standardized self-reporting questionnaires. Income level was based on monthly insurance premium because insurance contribution is determined based on income level and not on health risk in Korea. Smoking status was classified into non-, ex-, and current smoker. Individuals who consumed 30 g of alcohol per day were defined as heavy alcohol consumers. Regular exercise was defined as performing > 30 minutes of moderate physical activity at least 5 times per week or > 20 minutes of strenuous physical activity at least 3 times per week.

The health examination provided by NHIS includes anthropometric and laboratory measurements. Body mass index (BMI, kg/m^2) was calculated as the subject's weight in kilograms divided by the square of the subject's height in meters, and classified into 5 categories according to Asia-Pacific criteria of the World Health Organization; underweight (< 18.5 kg/m^2), normal (18.5–23 kg/m^2), overweight (23–25 kg/m^2), obese (25–30 kg/m^2), and severely obese (≥ 30 kg/m^2).[51] Systolic and diastolic blood pressure (BP) were measured in a seated position after at least 5 minutes rest. Blood samples for measurement of serum fasting glucose and lipid levels were drawn after an overnight fast. Hospitals where these health examinations were performed were certified by the NHIS and subjected to regular quality control.

Baseline comorbidities (hypertension, diabetes mellitus, dyslipidemia, and cancer) were identified based on the combination of past medical history and ICD-10 and prescription codes. The exact diagnostic codes for comorbidities are described in **Supplementary 3**. Comorbidities were defined based on claims data before the screening date and health

examination results.[52,53] Hypertension was defined based on the presence of at least 1 claim per year under ICD-10 codes I10–13 or I15 and at least 1 claim per year for the prescription of antihypertensive agents or systolic/diastolic BP ≥ 140/90 mmHg. Diabetes mellitus was defined based on the presence of at least 1 claim per year under ICD-10 codes E11–14 and at least 1 claim per year for the prescription of antidiabetic medication or fasting glucose level ≥ 126 mg/dL. Dyslipidemia was defined based on the presence of at least 1 claim per year under ICD-10 code E78 and at least 1 claim per year for the prescription of a lipid-lowering agent or total cholesterol ≥ 240 mg/dL.[54] Cancer was defined as patient registration in the NHIS with ICD-10 code C and V193, specific insurance codes that were issued by the NHIS of Korea.

3.2.6. Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as number and percentage. The incidence rate of PD was expressed as number of events per 1,000 person-years. Cox proportional hazards regression analysis was conducted to evaluate the associations of various reproductive factors with incidence of PD. Model 1 was non-adjusted, whereas Model 2 was full model which included age, age at menarche, age at menopause, number of parities, duration of breast feeding, duration of HRT, duration of OC use, alcohol consumption, smoking, regular exercise, income, BMI, hypertension, diabetes mellitus, dyslipidemia, and cancer. Model 3 included duration of fertility instead of age at menarche and menopause in Model 2. The cumulative incidence probability of PD according to reproductive factors was calculated using Kaplan-Meier curves and the log-rank test. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a P-value < 0.05 was considered to indicate statistical significance.

3.3. Results

3.3.1. Baseline characteristics of the study subjects

Table 6 shows the baseline characteristics of the study population. The mean age of the total population in this study was 61.3 years (SD, 8.7 years). Most of study population were never smoker (95.8%) and non-drinkers (86.6%). Of the subjects, 40.4% performed regular physical activity. The proportion of obesity and severe obesity were 31.5% and 4.5%, respectively. Among comorbidities, 42.3% had hypertension, 13.8% had diabetes mellitus, 36.5% had dyslipidemia, and 8.1% had cancer.

The estimated overall mean ages at menarche and menopause were 16.3 years (SD, 1.9 years) and 50.2 years (SD, 4.0 years), respectively. Among the study subjects, 90.1% had 2 or more parities, 66.0% experienced breast feeding for ≥ 12 months, 81.6% were never HRT users, and 80.6% were never OC users.

Table 6 Baseline characteristics of the study subjects

Variables	Total (n = 4,729,546)
Age (years)	61.3 ± 8.7
Income (quartile)	
Q1 (lowest)	1,330,186 (28.1)
Q2	1,051,422 (22.2)
Q3	1,106,036 (23.4)
Q4 (highest)	1,241,902 (26.3)
Smoking status	
Never	4,532,366 (95.8)
Ex-smoker < 10 pack-years	43,182 (0.9)
Ex-smoker ≥ 10 pack-years	10,953 (0.2)
Current smoker < 10 pack-years	93,851 (2.0)
Current smoker ≥ 10 pack-years	49,194 (1.0)
Alcohol consumption	
None	4,092,863 (86.6)
Mild	614,194 (13.0)
Heavy	22,489 (0.5)
Regular exercise	1,909,304 (40.4)
Systolic blood pressure (mmHg)	125.2 ± 16.0
Diastolic blood pressure (mmHg)	76.7 ± 10.0
Fasting glucose (mg/dL)	100.4 ± 23.8
Total cholesterol (mg/dL)	206.7 ± 38.8
Body mass index (kg/m^2)	
< 18.5	109,375 (2.3)
18.5 – 23	1,685,282 (35.6)
23 – 25	1,234,542 (26.1)
25 – 30	1,488,480 (31.5)
≥ 30	211,867 (4.5)
Comorbidities	
Hypertension	2,001,096 (42.3)
Diabetes mellitus	653,605 (13.8)
Dyslipidemia	1,726,261 (36.5)
Cancer	382,703 (8.1)

Data are expressed as the mean ± standard deviation or n (%)

Table 6 Continued

Variables	Total (n = 4,729,546)
Age at menarche (years)	16.3 ± 1.9
≤ 12	63,503 (1.3)
13 – 14	683,326 (14.5)
15 – 16	1,890,488 (40.0)
≥ 17	2,092,229 (44.2)
Age at menopause (years)	50.2 ± 4.0
< 40	77441 (1.6)
40 – 44	250,520 (5.3)
45 – 49	1,226,592 (25.9)
50 – 54	2,619,731 (55.4)
≥ 55	555,262 (11.7)
Duration of fertility (years)	33.9 ± 4.4
< 30	590,489 (12.5)
30 – 34	1,847,085 (39.1)
35 – 39	1,925,526 (40.7)
≥ 40	366,446 (7.8)
Parity	
Nulliparity	104,022 (2.2)
1	364,106 (7.7)
≥ 2	4,261,418 (90.1)
Duration of breast feeding (months)	
Never	384,787 (8.1)
< 6	380,767 (8.1)
6 – 12	841,791 (17.8)
≥ 12	3,122,201 (66.0)
Duration of hormone replacement therapy (years)	
Never	3,859,365 (81.6)
< 2	409,929 (8.7)
2 – 5	158,706 (3.4)
≥ 5	126,828 (2.7)
Unknown	174,718 (3.7)
Duration of oral contraceptive use (years)	
Never	3,809,970 (80.6)
< 1	415,128 (8.8)
≥ 1	273,880 (5.8)
Unknown	230,568 (4.9)

Data are expressed as the mean ± standard deviation or n (%)

3.3.2. Incidence and risk of PD based on reproductive factors

The median follow-up duration was 5.84 years. There were 20,816 new cases of PD, and the incidence rate of PD was 0.8 per 1,000 person-years. The Kaplan-Meier curve in **Figure 6** presents the incidence probability of PD according to reproductive factors. PD incidence was correlated with later age of menarche, earlier age of menopause, shorter duration of fertility, and never user of HRT (log-rank test, $P < 0.001$).

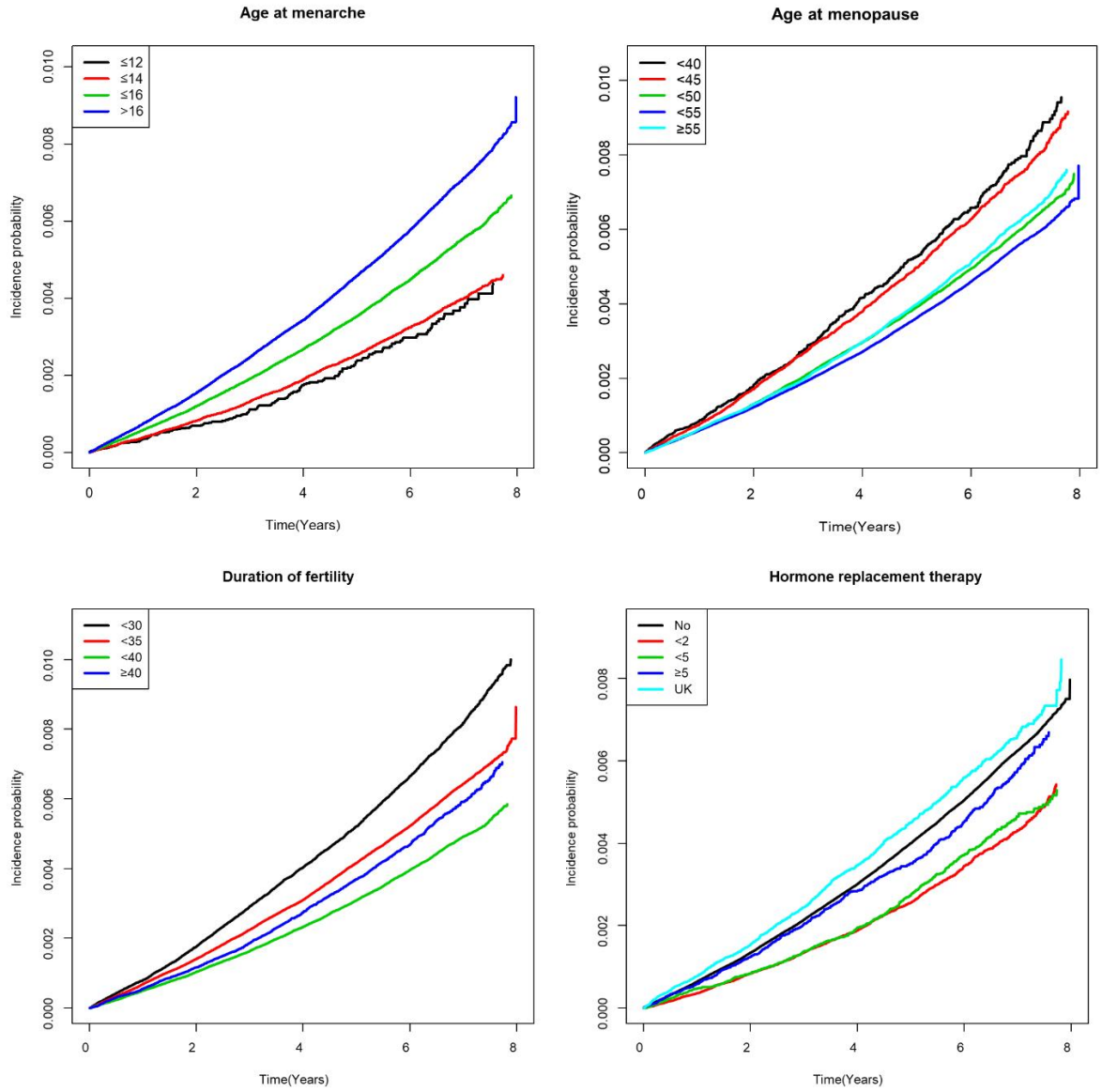

Figure 6 Cumulative incidence* of Parkinson's disease according to reproductive factors

*The cumulative incidence of outcomes according to reproductive factors was calculated using Kaplan–Meier curves, and the log-rank test was performed to analyze differences among the groups.

UK, unknown

3.3.3. Menstrual history

Compared with women who experienced menarche at the age of 13-14 years, women who experienced menarche after the age of 17 years had an approximately 10% higher risk of PD (adjusted hazard ratio [aHR] 1.10, 95% confidence interval [CI] 1.05-1.16). The risk for PD decreased as age at menopause increased (*P* for trend = 0.019). In Model 3, longer duration of fertility (≥ 40 years) was consistently associated with lower risk of PD (aHR 0.91, 95% CI 0.85 – 0.96) compared with short duration of fertility (< 30 years) **(Table 7)**.

3.3.4. Parity and breast feeding

In the crude model, a higher risk of PD was observed in women with ≥ 2 parities (HR 1.53, 95% CI 1.37 – 1.70) and breast feeding ≥ 12 months (HR 1.92, 95% CI 1.80-2.04) compared with nulliparity and never breast-feeding, respectively. However, this association did not persist in the fully adjusted model.

3.3.5. HRT and OC use

Compared with never HRT user as the reference, the highest risk of PD incidence was observed in HRT user ≥ 5 years in duration (aHR 1.17, 95% CI 1.07-1.27). Similarly, compared with OC nonuser, OC users ≥ 1 year in duration had approximately 7% higher risk of PD (aHR 1.07, 95% CI 1.01-1.13).

Table 7 Hazard ratios and 95% confidence intervals of Parkinson's disease based on reproductive factors

Reproductive factors	Subjects (n)	Events (n)	Follow-up duration (PYs)	IR (per 1,000 PYs)	Model 1	Model 2	Model 3
	4729546	**20816**	**25382221.9**	**0.8**			
Age at menarche (years)							
≤ 12	63,503	152	314,469.0	0.5	0.92 (0.78-1.08)	1.07 (0.91-1.27)	
13 – 14	683,326	1,875	3,515,037.0	0.5	1 (ref.)	1 (ref.)	
15 – 16	1,890,488	7,549	10,033,525.2	0.8	**1.40 (1.33-1.47)**	**1.09 (1.03-1.14)**	
≥ 17	2,092,229	11,240	11,519,190.7	1.0	**1.80 (1.71-1.89)**	**1.10 (1.05-1.16)**	
Age at menopause (years)*							
< 40	77,441	476	423,769.0	1.1	1 (ref.)	1 (ref.)	
40 – 44	250,520	1462	1,374,686.3	1.1	0.95 (0.85-1.05)	1.00 (0.90-1.11)	
45 – 49	1,226,592	5572	6,673,313.0	0.8	**0.74 (0.68-0.82)**	0.98 (0.89-1.08)	
50 – 54	2,619,731	10,784	13,969,915.6	0.8	**0.69 (0.63-0.76)**	0.95 (0.87-1.05)	
≥ 55	555,262	2,522	2,940,538.1	0.9	**0.77 (0.70-0.85)**	0.95 (0.86-1.05)	
Duration of fertility (years)							
< 30	590,489	3,708	3,269,851.6	1.1	1 (ref.)		1 (ref.)
30 – 34	1,847,085	8,903	10,086,417.1	0.9	**0.78 (0.75-0.81)**		**0.95 (0.92-0.99)**
35 – 39	1,925,526	6,711	10,132,274.9	0.7	**0.59 (0.57-0.62)**		**0.89 (0.86-0.93)**
≥ 40	366,446	1,494	1,893,678.3	0.8	**0.71 (0.67-0.75)**		**0.91 (0.85-0.96)**
Parity							
Nulliparity	104,022	334	590,103.0	0.6	1 (ref.)	1 (ref.)	1 (ref.)
1	364,106	839	1,832,978.9	0.5	**0.83 (0.73-0.94)**	0.98 (0.86-1.12)	0.98 (0.86-1.12)
≥ 2	4,261,418	19,643	22,959,140.0	0.9	**1.53 (1.37-1.70)**	1.05 (0.93-1.18)	1.05 (0.93-1.18)
Duration of breast feeding (months)							
Never	384,787	969	1,971,991.6	0.5	1 (ref.)	1 (ref.)	1 (ref.)
< 6	380,767	818	1,903,073.4	0.4	**0.88 (0.80-0.96)**	0.93 (0.85-1.03)	0.93 (0.85-1.03)
6 – 12	841,791	2,717	445,7031.0	0.6	**1.23 (1.14-1.32)**	0.98 (0.90-1.06)	0.98 (0.90-1.06)
≥ 12	3,122,201	16,312	17,050,125.9	1.0	**1.92 (1.80-2.04)**	1.02 (0.94-1.09)	1.02 (0.95-1.10)

**P* for trend 0.019 in Model 2

Table 7 Continued

Reproductive factors	Subjects (n)	Events (n)	Follow-up duration (PYs)	IR (per 1,000 PYs)	Model 1	Model 2	Model 3
Duration of HRT (years)							
Never	3,859,365	17,618	20,703,282.6	0.9	1 (ref.)	1 (ref.)	1 (ref.)
< 2	409,929	1,293	2,221,411.7	0.6	**0.68 (0.65-0.72)**	**1.07 (1.01-1.13)**	**1.07 (1.01-1.13)**
2 – 5	158,706	526	864,401.6	0.6	0.71 (0.65-0.78)	1.07 (0.98-1.17)	1.07 (0.98-1.17)
≥ 5	126,828	541	687,963.3	0.8	0.92 (0.85-1.00)	**1.17 (1.07-1.27)**	**1.17 (1.07-1.27)**
Unknown	174,718	838	905,162.6	0.9	**1.10 (1.02-1.18)**	1.07 (0.99-1.15)	1.07 (0.99-1.15)
Duration of OC use (years)							
Never	3,809,970	16,732	20,404,876.3	0.8	1 (ref.)	1 (ref.)	1 (ref.)
< 1 year	415,128	1,592	2,248,452.1	0.7	0.86 (0.82-0.91)	0.99 (0.94-1.04)	0.99 (0.94-1.04)
≥ 1 year	273,880	1,315	1,492,628.9	0.9	**1.07 (1.01-1.13)**	**1.07 (1.01-1.13)**	**1.07 (1.01-1.13)**
Unknown	230,568	1,177	1,236,264.5	1.0	**1.16 (1.09-1.23)**	**1.10 (1.03-1.17)**	**1.10 (1.03-1.17)**

PY, person-years; IR, incidence rate; HRT, hormone replacement therapy; OC, oral contraceptive
Model 1: non-adjusted
Model 2: full model includes age, age at menarche, age at menopause, parity, duration of breast feeding, duration of HRT, duration of OC use, alcohol consumption, smoking, regular exercise, income, body mass index, hypertension, diabetes mellitus, dyslipidemia, and cancer
Model 3: full model includes duration of fertility instead of age at menarche and menopause in Model 2

3.4. Discussion

In this large-scale population study, female reproductive factors were confirmed to be associated with incidence of PD. Women with early menarche, late menopause, and longer duration of fertility showed decreased risk of PD in postmenopausal women. Conversely, use of HRT or OC increased the risk of PD in postmenopausal women. The strength of the present study is that unprecedented large representative sample and outcome incidence (> 4.7 million with 20,816 incident PD cases) were used, which allowed sufficient statistical power for data analysis. In addition, comprehensive evaluation of reproductive variables of interest provides further support for association between female reproductive factors and PD risk.

Results from the present study confirmed that PD risk is reduced in women with a longer duration of fertility regardless of covariate adjustment, and this effect was consistently detected when age at menarche or age at menopause was individually considered. Because age at menarche and age at menopause reflect estrogen exposure, this result could be evidence for neuroprotective effects of estrogen. Similarly, in previous studies, lifetime estrogen level reduced by early menopause, fewer pregnancies, hysterectomy, or oophorectomy was reportedly associated with development of PD.[23,81-83] The results from the present study further support the proposal of a potential neuroprotective role of endogenous estrogen.

Although the mechanism by which estrogen protects dopaminergic neurons has not been clarified, several possible explanations have been suggested. First, estrogen has an anti-oxidant property determined by the presence of the hydroxyl group in the C3 position on the A ring of the steroid structure.[89] Although the mechanisms responsible for dopaminergic neuron degeneration in PD remain unknown, oxidative stress and depletion of endogenous anti-oxidants are believed to play a key role in nigrostriatal dopaminergic neuronal degeneration in

PD.[90] Second, estrogen has neurotrophic effects on dopamine neurons by interacting with brain-derived neurotrophic factor (BDNF),[91] which is involved in neuronal survival, promoting neuronal regeneration following injury, regulating transmitter systems, and attenuating neural-immune responses.[92] Estrogen's action overlaps with BDNF because estrogen receptors co-localize to cells that express BDNF and its receptor, and estrogen further regulates the expression of this neurotrophin system.[92] Finally, estrogen contributes to modulate glial neuroinflammatory reaction in protection of mesencephalic dopaminergic neurons by enhancing neuroprotective functions of astrocytes and microglia.[90] This mechanism represents an important compensatory response to begin healing, restore homeostasis, and stimulate the repair process.[90]

Conversely, regarding exogenous estrogen exposure, hormone use has been associated with either higher,[83,93] lower,[85,87] or null risk[81,82,84,86,94] of PD based on epidemiological data. In the present study, women who had HRT < 2 years or > 5 years showed increased PD risk by 7% and 17%, respectively. In addition, women who used OCs > 1 year had 7% higher risk of PD compared with those who never used OCs. In particular, based on previous study results, the association was dependent on not only duration of hormone therapy, but also type of menopause.[83] The risk of PD increased with longer duration of estrogen therapy in women with a history of hysterectomy compared with never users; however, the risk decreased with increasing duration of HRT in women with natural menopause.[83] In addition, analysis regarding type of HRT showed increased risk of PD in women using progestin-only[94] or estrogen plus progestin hormones.[65] The synthetic compound medroxyprogesterone acetate (MPA) is the major formulation of progestin used in HRT and OCs. MPA and the natural hormone progesterone exhibit important differences, particularly in relation to their effects on the brain. Progesterone is considered neuroprotective, whereas the synthetic progestin MPA antagonizes the neuroprotective effects of estrogen.[95] Furthermore, the timing of estrogen

replacement treatment was considered important and has been referred to as the "timing hypothesis."[96-98] Therefore, type and timing of HRT could affect evaluation of beneficial or harmful effects of estrogen on the risk of PD. Unfortunately, the association between exogenous hormone use and risk of PD could not be fully investigated in the present study because information on type of menopause, type of hormone formulation used, and age at hormone initiation was lacking.

The results showing no association between parity or breast feeding and risk of PD is consistent with findings in several studies.[83-85,94] In contrast, increased duration of pregnancies was associated with increased risk of PD in a case-controlled study.[82] Hypothetically, this could be explained by differences in estrogen metabolism and serum hormone binding protein (SHBG) in nulliparous women compared with parous women, which results in low bioavailability of estrogen in parous women.[82] However, in accordance with the results from the present study, serum sex hormones showed no differences related to parity associated with serum estrogen level or SHBG among pre- and postmenopausal women.[99-101]

The present study had several limitations. First, because the NHIS database relies on physician assignment of a diagnostic code for PD, misdiagnosis of PD may exist and could result in inaccurate analyses. Second, the type of menopause was not assessed. This limitation could be partially overcome by excluding individuals who reported any type of hysterectomy procedure. Third, because primary data did not include information regarding type or timing of hormone use, adequate investigation of the effects of postmenopausal hormone therapy on the risk of PD was not possible. Lastly, due to the retrospective design, causality could not be determined. To minimize the possible effects of reverse causality, subjects with prior diagnosis of PD before the health screening date were excluded. However, a possibility of reverse causality exists based on the long prodromal phase of PD.

In conclusion, in this nationwide population-based cohort study, female reproductive

factors were independent predictors for PD among postmenopausal women. An association was also observed between lower lifetime exposure to endogenous estrogen and increased PD incidence. Future studies are needed to elucidate the precise mechanism of the associations between female reproductive factors and the incidence of PD.

4. Conclusion

Evidence from a range of sources suggests that estrogen has neuroprotective effects that may reduce neurodegenerative disease. In this nationwide retrospective cohort study, we demonstrated that reproductive factors modify estrogen exposure in a way that is relevant to etiology of neurodegenerative disease, both dementia and PD. The strength of the present study includes 1) a large, population-based database linked to claims data, which enabled the investigation of relatively rare clinical outcomes such as PD and allowed sufficient statistical power for data analysis, and 2) comprehensive evaluation of reproductive factors.

This study clearly showed that female reproductive factors were independently associated with the incidence of all-cause dementia, Alzheimer's disease, and vascular dementia. Lower lifetime exposure to endogenous estrogen, which resulted from later menarche, earlier menopause, and shorter duration of fertility, was significantly associated with dementia risk in postmenopausal women. We showed a significant U-shaped association between parity and duration of breast feeding and the incidence of dementia. Use of HRT or OC independently decreased the risk of dementia in postmenopausal women.

In addition, female reproductive factors were independent predictors for PD among postmenopausal women. Postmenopausal women with lower endogenous estrogen exposure from early menarche, late menopause, and longer duration of fertility had a reduced risk of PD. Parity and breast feeding history did not affect PD risk in this cohort. In contrast, use of HRT or OC increased the risk of PD in postmenopausal women.

The differences in reproductive history between individuals should be considered when assessing individual women's particular neurodegenerative disease risk. While the mechanism for this association is unclear, there are several potential explanations and future studies should explore the details of the precise mechanism linking reproductive factors and neurodegenerative disease development.

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6. Supplementary

Supplementary 1 National Cancer Screening Program in Korea

Cancer	Target population	Frequency	Test or procedure	Co-payment[†] (US $)
Stomach	40 and over (adults)	Every 2 years	Endoscopy or upper gastrointestinal series	7
Liver	40 and over with high risk group[*]	Every 6 months	Abdominal ultrasonography + Serum Alpha-Fetoprotein test (Combined)	8
Colorectum	50 and over (adults)	Every 1 year[‡]	Fecal occult blood test[§]	0.5
Breast	40 and over (women)	Every 2 years	Mammography and clinical breast exam	3.5
Cervix	30 and over (women)	Every 2 years	Pap smear	0

[†] Co-payment is applied only for those with higher income (upper 50%) and accounted for 20% of total price. No co-payment is applicable to low-income population (lower 50%). There is no copayment for cervical cancer screening regardless of income level.

[*] 40 & over with HBsAg positive or anti-HCV positive or liver cirrhosis

[‡] Colorectal screening is actually provided every 2 years to most of the target population, with exception of low-income or manual laborer.

[§] Colonoscopy or barium enema follows, if fecal occult blood test is positive

Supplementary 2 The questionnaire included in breast and cervical cancer screening

※ 유방암 및 자궁경부암 관련 문항(여성분들만 응답해주세요.)

9. 월경을 언제 시작하셨습니까?
① 만 세 ② 초경이 없었음

10. 현재 월경의 상태는 어떠십니까?
① 아직 월경이 있음 ② 자궁적출술을 하였음
③ 폐경 되었음 (폐경연령 : 만 세)

11. 폐경 후 증상을 완화하기 위해서 호르몬 제제를 복용하고 계시거나 과거에 복용하신 적이 있습니까?
① 호르몬 제제를 복용한 적 없음 ② 2년 미만 복용
③ 2년 이상~5년 미만 복용 ④ 5년 이상 복용 ⑤ 모르겠음

12. 자녀를 몇 명 출산하셨습니까?
① 1명 ② 2명이상 ③ 출산한 적 없음

13. 모유 수유 여부 및 총 수유기간은?
① 6개월 미만 ② 6개월~1년 미만 ③ 1년 이상 ④ 수유한적 없음

14. 과거에 유방에 양성 종양으로 진단받은 적이 있습니까?
(양성 종양이란 악성종양인 암이 아닌 기타 물혹, 덩어리 등을 말합니다)
① 예 ② 아니오 ③ 모르겠음

15. 피임약을 복용하고 계시거나 과거에 복용하신 적이 있습니까?
① 피임약을 복용한 적 없음 ② 1년 미만 복용
③ 1년 이상 복용 ④ 모르겠음

Supplementary 3 Diagnostic ICD-10 codes used in this study.

Disease	ICD-10 codes	
Alzheimer's disease	F00	Dementia in Alzheimer disease
	G30	Alzheimer disease
Vascular dementia	F01	Vascular dementia
Other dementia	F02	Dementia in other diseases classified elsewhere
	F03	Unspecified dementia
	G31	Other degenerative diseases of nervous system, not elsewhere classified
Parkinson's disease †	G20	Parkinson disease
Hypertension	I10	Essential (primary) hypertension
	I11	Hypertensive heart disease
	I12	Hypertensive renal disease
	I13	Hypertensive heart and renal disease
	I15	Secondary hypertension
Diabetes mellitus	E11	Type 2 diabetes mellitus
	E12	Malnutrition-related diabetes mellitus
	E13	Other specified diabetes mellitus
	E14	Unspecified diabetes mellitus
Dyslipidemia	E78	Disorders of lipoprotein metabolism and other lipidaemias
Cancer ‡	C	Neoplasms

† In combination with the specialized claim code V124, which identifies patients with Parkinson's disease for reimbursement.

‡ In combination with the specialized claim code V193, which identifies patients with cancer for reimbursement.

Abstract

Background

Neurodegenerative diseases including dementia and Parkinson's disease (PD) are becoming increasingly prevalent, in part because the elderly population has increased in recent years. Sex differences in these diseases are well described. Estrogen is believed to play an important role in the sex differences observed in brain aging and neurodegeneration. We aimed to investigate whether female reproductive factors are associated with the incidence of dementia and PD.

Methods

We used the Korean National Health Insurance System database. Among women aged ≥ 40 years who underwent both cardiovascular and national cancer screening from 1 January 2009 to 31 December 2014, we respectively identified 4,696,633 postmenopausal women without dementia, and 4,729,546 postmenopausal women without PD. Information on reproductive factors were collected using self-administered questionnaire. Reproductive factors included age at menarche, age at menopause, parity, breast feeding, and use of hormone replacement therapy or oral contraceptives. During the follow-up period, the new incidence of dementia and PD was defined using claims data based on the International Classification of Disease 10th revision. Multivariable Cox proportional hazards regression was conducted to assess hazard ratios (HR) and 95% confidence intervals (CI) for dementia or PD, according to reproductive factors.

Results

During the median follow-up of 5.74 years, there were 212,227 new cases of all-cause dementia (4.5%), 162,901 cases of Alzheimer's disease (3.5%), and 24,029 cases of vascular dementia (0.5%). The adjusted HR (aHR) of dementia was 1.15 (95% CI 1.13-1.16) for menarcheal age ≥ 17 years compared with menarcheal age 13-14 years, 0.79 (0.77-0.81) for menopausal age ≥ 55 years compared with menopausal age < 40 years, and 0.81 (0.79-0.82) for fertility duration ≥ 40 years compared with fertility duration < 30 years. While having 1 parity (aHR 0.89, 95% CI 0.85-0.94) and breast feeding < 6 months (aHR 0.92, 95% CI 0.88-0.95) was associated with lower risk of dementia, having ≥ 2 parity (aHR 1.04, 95% CI 0.99-1.08) and breast feeding ≥ 12 months (aHR 1.14, 95% CI 1.11-1.17) were associated with higher risk of dementia than women without parity or breast feeding history. Use of hormone replacement therapy and oral contraceptives independently reduced the dementia risk by 14% (aHR 0.86, 95% CI 0.84-0.88) and 9% (aHR 0.91, 95% CI 0.88-0.92), respectively.

During the median follow-up of 5.84 years, 20,816 individuals were diagnosed with PD. An increased risk of PD incidence was observed in subjects with a later age at menarche (≥ 17 years) compared with reference subjects (13 years ≤ age at menarche ≤ 14 years) (aHR 1.10, 95% CI 1.05 – 1.16). As age at menopause increased, risk of PD decreased (P for trend 0.019). Consistently, decreased risk of PD incidence was observed (aHR 0.91, 95% CI 0.85-0.96) in subjects with longer duration of fertility (≥ 40 years of age) compared with shorter duration of fertility (< 30 years of age). Compared with never HRT user, the highest risk of PD incidence was observed in HRT user ≥ 5 years in duration (aHR 1.17, 95% CI 1.07-1.27). Similarly, compared with OC nonuser, OC users ≥ 1 year in duration had approximately 7% higher risk of PD (aHR 1.07, 95% CI 1.01-1.13).

Conclusion

Female reproductive factors are independent risk factors for neurodegenerative disease incidence. Lower endogenous estrogen exposure from late menarche and early menopause increased the risk of neurodegenerative diseases, both dementia and PD. Therefore, it is important to assess various reproductive factors in relation to the risk of dementia and PD in women. Especially, in women who are expected to have lower endogenous estrogen exposure due to oophorectomy, it is necessary to be careful about the occurrence of neurodegenerative diseases, and intervention for prevention and proper management is required.

Keywords

Neurodegenerative disease, Dementia, Parkinson's disease, Menarche, Menopause, Duration of fertility, Parity, Breast feeding, Hormone replacement therapy, Oral contraceptive