



Menarche age, menopause age and other reproductive factors in association with post-menopausal onset depression: Results from Health Examinees Study (HEXA)

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ABSTRACT

Background: Although there are plausible mechanisms of female hormones in depression, epidemiological evidence has shown conflicting results.

Objective: This study aimed to evaluate the associations between female hormonal events and post-menopausal depression and further investigate the relative association between the age of menarche, the age of menopause and depression.

Methods: Among 111,589 women who took part in the Health Examinees (HEXA) Study, a total of 60,114 postmenopausal participants were included in the final analysis. Each participant provided information on depression and questions related to reproductive history. The outcome variable was self-reported by the history of depression diagnosed by physicians and the Center for Epidemiologic Studies Depression Scale (CES-D) score. With the multivariate logistic regression, odds ratios were calculated. Possible interactions between depression prevalence and the ages of menarche and menopause were assessed.

Results: A total of 2.2% (1342/60,114) women were diagnosed with depression after menopause, and 5.9% (500/8472) showed depressive symptoms. As the age of menopause and duration of reproductive years increased, the odds ratio of depression decreased (P -trend < 0.001). As the age of menarche increased, the likelihood of physician-diagnosed depression also increased (P -trend 0.048). As the number of both spontaneous and induced abortions increased, the odds ratio of depression increased (P -trend < 0.001).

Limitation: it is possible that women show inaccuracies in recalling their hormonal events and reporting other past mental disorders as depression.

Conclusion: Both the ages of the initiation and the termination of menstruation were associated with the increased odds ratio of post-menopausal depression. However, the age of menopause seems to be more important.

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1. Introduction

Based on the results of the Global Burden of Disease Study 2010, major depressive disorders contributed approximately 8.1% of years lived with disability (YLD), which became one of the four leading reasons for disease burden worldwide (Vos et al., 2012). Around 16.2% of the U.S. adults were found to have major depression in their lifetime in the National Comorbidity Survey Replication (NCS-R) done in 2001–2002 (Kessler et al., 2003), and

approximately 20.1% people stated that they had depressive symptoms on the Patient Health Questionnaire with 9 items (PHQ-9) in the National Health and Nutrition Examination Survey (NHANES) (Shim et al., 2011). It is known that women show higher prevalence of depression than men, and the female-to-male ratio of depression is approximately 2:1 (Bebbington, 1998; Kessler, 2003). In Korea, the results appear to follow this trend (Cho and Lee, 2005). Several studies suggest that this difference in trend by sex initiates at puberty and remains until the end of menstruation in women (Ge et al., 2001; Soares and Zitek, 2008).

Some studies hypothesized that puberty itself increases the risk for depression, as it is related to the change in the level of sex hormones (Angold et al., 1999; Cyranowski et al., 2000; Opoliner et al., 2014; Steiner et al., 2003). Additionally, women with socio-emotional

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complexities, such as girls with early menarche, tend to be more sensitive to stressors around them, which may cause differences (Ge et al., 1996; Joinson et al., 2011). As a consequence, some studies assumed that early menarche may occupy an important role in developing depression and have described a positive association between early menarche and later depression (Joinson et al., 2011). However, the results are not consistent. Many studies have reported that there is no significant association between early menarche and depressive symptoms in later adulthood (Boden et al., 2011; Opoliner et al., 2014). However, there are findings contrary to the results of the previous studies, in which a significant association between delayed menarche and later depression has been found (Herva et al., 2004).

Compared with numerous findings regarding age of menarche and depression, relatively few studies have focused on the association between menopausal age and depression. However, the results seem to be more consistent in association between the age of menopause and depression. A study conducted in a nationwide sample of Koreans reported a significant decreasing trend in prevalence of depression as the age of menopause increased (Jung et al., 2015). Similarly, the results from a study conducted in France showed that earlier menopause increased the risk of later depression with a linear trend (Ryan et al., 2008). Menopause brings hormonal transitions as well as menarche, and it is known that people with depression in the post-menopausal period show decreased serotonin and estradiol concentrations that change the neurotransmitter activity in the central nervous system (CNS) in women (Andrade et al., 2005).

Additionally, as multiple studies were conducted in regard to other reproductive events of women and depression, the results are still conflicting. Contrary to the evidence of pregnancy being harmful to major depression (Cohen et al., 2006), many studies have reported no associations between these two factors, including the result from Korea (Jung et al., 2015). Similarly, a meta-analysis of 26 studies suggested that there is a protective effect of hormone replacement therapy (HRT) against depression (Zweifel and O'Brien, 1997). However, the opposite result was found in a recent study conducted in a nationwide sample in Korea (Jung et al., 2015).

We aim to evaluate the association between various female-hormonal life events and the prevalence of post-menopausal depression in a large population and, further, to investigate the relative associations between the ages of menarche and menopause and depression.

2. Materials and methods

2.1. Study population

The participants of the study were from the Health Examinees (HEXA) Study. A main purpose of the HEXA study was to investigate the epidemiologic characteristics of major chronic diseases in a Korean population (Health Examinees Study, 2015). In 35 major hospitals and local health examination centers, subjects were recruited with strict selection criteria to fulfill representativeness. Although the HEXA study was designed as a community based prospective cohort study with its large-scale, only the baseline data were available in the point of analysis. A total of 170,078 participants from 2004 to 2012 who were aged 35 to 74 years old participated in the study at baseline. With standardized interviews with trained staff, women were requested to respond to the questionnaire for information on general factors including socio-demographic items, past medical history, family medical history, drug use and lifestyle factors. Reproductive and hormone related factors were additionally asked only in women. Additional information from the HEXA study is provided elsewhere (Health

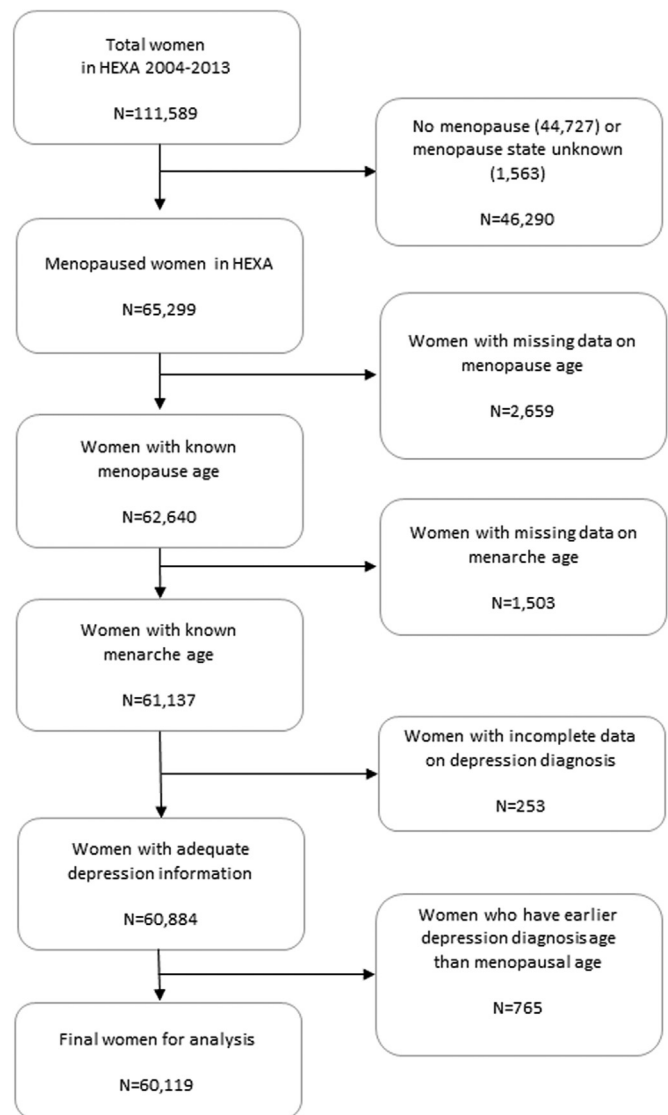


Fig. 1. Selection for the participants for the analysis.

Examinees Study, 2015).

The total number of women at baseline was 111,589. Among them, we excluded 44,727 women who were not menopausal and 1563 women with unknown menopausal status. In women with menopause, we excluded women with no information on age of menopause ($n=2659$). Women without valid age of menarche were also excluded ($n=1503$). To confirm later depression status, we excluded women with incomplete data on depression diagnosis ($n=253$) and those who have an earlier depression diagnosis age than menopause age ($n=765$). The final total of women used in the analysis was 60,114 (Fig. 1).

2.2. Measurement

In measuring depression status, we applied two measures: (1) past history of depression diagnosed by a physician and (2) Center for Epidemiologic Studies Depression (CES-D), a psychometric instrument which was translated and modified to a Korean version Cho and Kim (1993). If a participant reported a past depression diagnosis confirmed by physicians, she was also interviewed about the exact age at which she was diagnosed with depression. Although the past history of depression was recorded in all participants across the entire study period, CES-D scales

were used only with the subjects who participated in the study in 2009. In the validation study of the CES-D Korean version, the optimal cutoff point was suggested to be 21 for the community epidemiological research in Korea (Cho and Kim, 1993), whereas a cutoff point of 16 is commonly used in Western society (Radloff, 1977). We applied a CES-D score of 21 and over to indicate depressive symptoms.

The total reproductive years were calculated as the duration between the age at menarche and the age at menopause. In women who experienced more than one pregnancy, duration between menarche and first pregnancy was computed. As menopause was categorized as natural or artificial, abortion was also classified as spontaneous or artificial. Using the number of spontaneous abortions and artificial abortions, the total number of abortions was calculated. Factors in regard to menarche, menopause, pregnancy, abortion, childbirth and breastfeeding were grouped as endogenous hormonal factors. For exogenous hormonal factors, information on oral contraceptive and hormone replacement therapy usage and duration was applied.

Within interviews, information on age at baseline, education attainment years, household income, marital status, alcohol consumption, and usual exercise frequency was obtained.

2.3. Statistical analysis

To compare the general characteristics between the groups with and without depression, we conducted χ^2 tests. All continuous variables were categorized into 4 groups, except household income, number of spontaneous abortions and total childbirths due to their distribution. The age of menarche and age of menopause was also categorized into 4 groups, following the distribution in the sample. The median age of menarche (15.5 years) and menopause (50.5) were similar to known age of menarche (Cho et al., 2010) and age of menopause (Ministry of Health and Welfare, 1996) among Korean population considering the birth year of the participants. We conducted a likelihood ratio test to select the most appropriate covariate for the model. Possible confounders such as age, education, marital status, alcohol consumption, exercise and comorbidity were tested, and factors including age, education and marital status were selected as covariates in the final model. We performed multivariate logistic regression to evaluate the association between each female reproductive factor and past depression diagnosed by a physician. Similarly, a logistic regression was conducted for depressive symptoms categorized by CES-D score which represents the current (baseline) depression status of the participants. By applying the order of categories, tests for trend were conducted. A sensitivity analysis was performed by excluding those patients who had already had a depression diagnosis in the past.

To examine the relative magnitude of association between menarche and menopause with depression, a total of 16 cells were compared with the 4 categories of age of menarche and menopause. The youngest category was set as the reference group. The trend tests were performed within the same row or column. Comparison of age of menarche and menopause with reproductive years was performed in the same way.

All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). A *P*-value less than 0.05 was set as the level of significance.

2.4. Ethics

In HEXA, the written consents were provided by all participants at the baseline survey. As HEXA data are publicly open for use, the Institutional Review Board of the Seoul National University Hospital, Seoul, Korea approved it for statistical analysis (IRB No.

E-1503-103-657).

3. Results

3.1. Characteristics of the study subjects

Among 60,119 women with menopause, 1342 women (2.2%) were reported by physicians to have been diagnosed with depression. The mean age of women with depression was 58.8 years, whereas women without depression had a mean age of 57.4 years. Among the 8472 menopausal women in the 2009 survey, 500 women (5.9%) showed depressive symptoms (CES-D score ≥ 21). The mean ages of women with and without depressive symptoms were 57.1 years and 57.3 years, respectively. Among the participants who underwent CES-D tests, those who reported to have a previous depression diagnosis by a physician had a mean CES-D score of 13.3, whereas participants without depression had a mean score of 5.07, and there was a significant difference across the two groups ($P < 0.001$).

Women who were diagnosed with depression comprised a larger proportion in the lower education group (9.5% vs. 6.9% in education attainment < 6 years). A large proportion of women without depression were married without separation or divorce (82.7% w. 78.2%). Women with a depression history tended to rate their health as “very bad” (6.6% vs. 1.4%), and approximately 10.8% of women with depression reported to have 2 or more comorbid diseases compared with 3.8% of women without depression (Table 1).

3.2. Association of hormonal events and depression diagnosed by physician

In Table 2, the results of the multivariable analysis are shown. In a crude analysis, women with later menarche tended to show an increased likelihood of depression contrary to the women who experienced their menarche at age 14 or under (*P*-trend 0.003). In the adjusted model, this trend was also significant, but only women who had their menarche at age 16 showed a significantly increased likelihood of depression diagnosis (OR 1.23, 95% CI 1.04–1.44, in full model).

Compared with women who underwent their menopause at age 47 or younger, gradually decreased likelihoods of depression were observed as age of menopause increased (*P*-trend < 0.001 in crude and in full model). When women had menopause at age 53 or older, the odds ratio for depression was 0.45 (95% CI 0.38–0.53) compared with women with menopause at age 47 or younger in the fully adjusted model. Similarly, compared with the women with 31 reproductive years or less, the odds ratio decreased gradually as the total reproductive years extended. Women with 38 years or more between menarche and menopause showed an OR of 0.43 (95% CI 0.36–0.51) in the fully adjusted model. In women who experienced menopause by artificial procedures such as oophorectomy, the likelihood of depression diagnosis increased with an OR of 1.61 (95% CI 1.41–1.83) in the model with full adjustment compared with natural menopause.

Women who ever experienced pregnancy showed a reduced likelihood of depression (OR 0.72, 95% CI 0.48–1.08); however, the results were only marginally significant. In a crude model, women with a longer duration between menarche and first pregnancy showed a significantly decreased likelihood compared with 6 years or less duration (for women with ≥ 12 years of duration, OR 0.76, 95% CI 0.64–0.89, *P*-trend < 0.001). This trend was also significant in the fully adjusted model, with marginal significance in strata with longest duration (OR 0.84, 95% CI 0.70–0.99).

As the number of total abortions, including both spontaneous

Table 1
Characteristics of post-menopausal women who ever had menstruation stratified by depression using the Health Examinees Study (HEXA) 2004–2012.

	Never diagnosed depression (n=58,777, 97.8%)	Post-menopausal onset depression (n=1342, 2.2%)	p-value
General factors	N (%)	N (%)	
Age (years)			< 0.001
≤ 52	13,557 (23.1)	229 (17.1)	
53–56	14,549 (24.8)	272 (20.3)	
57–61	14,852 (25.3)	357 (26.6)	
> 61	15,819 (26.9)	484 (36.1)	
Education attainment (years) ^a			< 0.001
< 6	4062 (6.9)	127 (9.5)	
6–8	14,108 (24.0)	382 (28.5)	
9–11	13,009 (22.1)	321 (23.9)	
≥ 12	26,760 (45.5)	505 (37.6)	
Familial income (per month)			< 0.001
< \$1000	9737 (20.1)	316 (28.2)	
\$1000–\$1999	12,541 (25.9)	324 (28.9)	
\$2000–\$3999	18,292 (37.7)	347 (31.0)	
\$4000–\$5999	5299 (10.9)	93 (8.3)	
≥ \$6000	2610 (5.4)	40 (3.6)	
Marital Status			< 0.001
Never married	722 (1.2)	12 (0.9)	
Married–living apart	9222 (15.7)	276 (20.6)	
Married or cohabited–living together	48,597 (82.7)	1049 (78.2)	
Alcohol consumption			< 0.001
Never drinker	43,094 (73.3)	967 (72.1)	
Past drinker	1136 (1.9)	48 (3.6)	
Current drinker	14,312 (24.4)	323 (24.1)	
Usual exercise frequency			0.023
No	28,249 (48.1)	618 (46.1)	
1–2/week	6339 (10.8)	144 (10.7)	
3–4/week	11,108 (18.9)	282 (21.0)	
5–6/week	6211 (10.6)	127 (9.5)	
Everyday	5529 (9.4)	150 (11.2)	
Self-rated health			< 0.001
Very good	914 (1.6)	7 (0.5)	
Good	17,803 (30.3)	203 (15.1)	
Fair	26,506 (45.1)	475 (35.4)	
Bad	12,295 (20.9)	558 (41.6)	
Very bad	808 (1.4)	89 (6.6)	
Number of comorbidities ^a			< 0.001
None	44,158 (75.2)	809 (60.5)	
1	12,319 (21.0)	384 (28.7)	
2+	2213 (3.8)	145 (10.8)	

2. Each income amount in quartile is different by age strata.

3. Number of comorbidities were calculated from diseases such as myocardial infarct, cerebrovascular disease, diabetes mellitus, peptic ulcer disease, liver disease and any form of cancers.

^a Sum of numbers can miss the total number in group due to missing values.

and artificial abortions, increased, the likelihood of depression also grew. If women had 3 or more abortions, the likelihood of depression increased with an OR of 1.62 (95% CI 1.39–1.90) in the fully adjusted model (data not shown). This trend was similarly found when analyzing both spontaneous abortions and artificial abortions separately (both *P*-trend < 0.001). In women who experienced two or more spontaneous abortions, the OR increased by 1.77 (95% CI 1.46–2.15). In regard to artificial abortion, the likelihood of depression increased by approximately 62% (95% CI 1.40–1.88) in woman who had 3 or more artificial abortions. The results regarding the first birth age or the last birth age showed no significance (results not shown). Compared with women who had either zero or one breastfed children, the likelihood of depression decreased by an OR of 0.81 (95% CI 0.65–1.00) if women had 4 or

more breastfed children. However, there were no significant trends in the duration of breastfeeding and depression (results not shown).

In regard to oral contraceptive usage, the OR increased significantly in former users compared with those who never used contraceptives (OR 1.15, 95% CI 1.02–1.31). However, there was no significant results in comparing groups by age at initiation of oral contraceptive or the duration of oral contraceptive usage (results not shown). In HRT after menopause, the likelihood of depression increased significantly both in the former user group (OR 1.87, 95% CI 1.65–2.12) and current user group (2.36, 95% CI 1.97–2.84). In HRT users, women who took HRT for 41 months or more showed increased likelihood of depression (OR 1.28, 95% CI 1.00–1.65) compared to women who had HRT approximately 4 months or less.

3.3. Association of hormonal events and depressive symptoms evaluated with CES-D

In Table 3, the association between each reproductive factor and depressive symptoms measured by CES-D is shown. There were no significant differences in the fully adjusted model for age at menarche. Regarding age of menopause, women who had menopause at age 51–52 showed a significant decreased OR (OR 0.63, 95% CI 0.47–0.83 in fully adjusted model). The results were similar with reproductive years. In women who had 38 years or more of reproductive years, the OR was 0.74 (95%, 0.55–0.99).

Other results were similar to Table 2, and the interval between menarche and the first pregnancy showed a more significant trend (*P*-trend 0.005 in the full model). The likelihoods of depression decreased as the interval between menarche and the first pregnancy increased. In women who had an interval of 12 years or longer, the likelihood of depression decreased to an OR of 0.68 (95% CI 0.51–0.90). Additionally, as the likelihood of depression was higher in current HRT users (OR 2.36, 95% CI 1.97–2.84) compared with former users (OR 1.87, 95% CI 1.65–2.12) as defined by a physician's diagnosis (Table 2), the likelihood of depression in current HRT users was lower and insignificant (OR 1.14, 95% CI 0.78–1.65) compared with the likelihood in former users (OR 1.46, 95% CI 1.16–1.82) according to the CES-D results.

In the sensitivity analysis, the results were very similar if we excluded the participants who had a prior history of depression diagnosis (data not shown).

3.4. Association of joint probability of menarche and menopause

Table 4 showed the association of depression and joint probability with menarche and menopause. In every group with different age of menarche, the likelihood of depression significantly decreased as the age of menopause increased (all, *P*-trend < 0.001). When groups were restricted to the same menopause age, there was no significant decreasing trend observed as the age of menarche changed, except for the groups who had menopause at age 53 or older. The results were similar when comparing the age of menarche and reproductive years.

4. Discussion

In this study, a longer interval between menarche and menopause showed a decreased likelihood with post-menopausal depression defined by both a previous diagnosis by a physician and a psychometrical approach using the CES-D. Later menarche and earlier menopause were both associated with post-menopausal depression. According to the results of the CES-D, the likelihood of depression significantly decreased as the interval between

Table 2

Association between each reproductive factors and post-menopausal onset depression by self-reported physician's diagnosis in Health Examinees Study (HEXA) 2004–2012.

Variables	No. of control	No. of depression	Odds ratio age adjusted (95% CI)	Odds ratio ^a multivariable adjusted (95% CI)
Endogenous hormonal factors				
Menarche age (years)				
≤ 14	16,438	308	1.00 (Ref)	1.00 (Ref)
15	12,488	263	1.08 (0.91–1.27)	1.06 (0.90–1.25)
16	11,812	307	1.28 (1.09–1.50)	1.23 (1.04–1.44)
≥ 17	18,039	464	1.22 (1.05–1.41)	1.14 (0.98–1.33)
		<i>P</i> -trend	0.003	0.048
Menopause age (years)				
≤ 47	16,320	492	1.00 (Ref)	1.00 (Ref)
48–50	17,567	421	0.75 (0.66–0.86)	0.76 (0.66–0.86)
51–52	11,529	207	0.55 (0.46–0.65)	0.55 (0.47–0.65)
≥ 53	13,361	222	0.45 (0.38–0.53)	0.45 (0.38–0.53)
		<i>P</i> -trend	< 0.001	< 0.001
Reproductive years (years)				
≤ 31	16,321	519	1.00 (Ref)	1.00 (Ref)
32–34	14,351	348	0.75 (0.65–0.86)	0.75 (0.66–0.86)
35–37	16,587	302	0.55 (0.48–0.64)	0.56 (0.48–0.65)
≥ 38	11,518	173	0.41 (0.35–0.49)	0.43 (0.36–0.51)
		<i>P</i> -trend	< 0.001	< 0.001
Type of menopause				
Natural	45,507	964	1.00 (Ref)	1.00 (Ref)
Artificial	10,708	319	1.59 (1.39–1.81)	1.61 (1.41–1.83)
Pregnancy				
Never	1350	33	1.00 (Ref)	1.00 (Ref)
Ever	57,417	1309	0.88 (0.62–1.25)	0.72 (0.48–1.08)
Duration between menarche and first pregnancy among ever pregnant women (years)				
0–6	12,262	345	1.00 (Ref)	1.00 (Ref)
7–9	16,496	386	0.87 (0.75–1.01)	0.91 (0.78–1.06)
10–11	11,636	253	0.84 (0.71–0.99)	0.91 (0.76–1.08)
≥ 12	16,108	305	0.76 (0.64–0.89)	0.84 (0.70–0.99)
		<i>P</i> -trend	< 0.001	0.054
Number of spontaneous abortion ^b among ever pregnant women				
0	44,291	945	1.00 (Ref)	1.00 (Ref)
1	8799	213	1.13 (0.97–1.31)	1.13 (0.97–1.31)
≥ 2	3226	121	1.77 (1.46–2.15)	1.77 (1.46–2.15)
		<i>P</i> -trend	< 0.001	< 0.001
Number of artificial abortion among ever pregnant women				
0	18,782	357	1.00 (Ref)	1.00 (Ref)
1	13,270	291	1.18 (1.00–1.37)	1.19 (1.02–1.40)
2	11,850	238	1.07 (0.91–1.27)	1.10 (0.93–1.29)
≥ 3	11,771	374	1.61 (1.39–1.86)	1.62 (1.40–1.88)
		<i>P</i> -trend	< 0.001	< 0.001
Number of total childbirth including abortions among ever parous women				
1	4534	104	1.00 (Ref)	1.00 (Ref)
2	26,903	553	0.89 (0.72–1.10)	0.90 (0.73–1.12)
≥ 3	25,271	638	0.89 (0.71–1.10)	0.85 (0.68–1.06)
		<i>P</i> -trend	0.448	0.139
Number of total breastfed children among ever parous women				
0–1	11,711	247	1.00 (Ref)	1.00 (Ref)
2	22,873	483	0.98 (0.84–1.14)	0.96 (0.82–1.12)
3	14,196	355	0.99 (0.84–1.17)	0.93 (0.79–1.11)
≥ 4	7764	201	0.91 (0.74–1.11)	0.81 (0.65–1.00)
		<i>P</i> -trend	0.437	0.062
Exogenous hormonal factors				
Oral contraceptive usage				
Never user	46,102	1,006	1.00 (Ref)	1.00 (Ref)
Former user	12,176	328	1.18 (1.04–1.34)	1.15 (1.02–1.31)
Current user	109	4	1.60 (0.59–4.34)	1.59 (0.59–4.34)
Hormone usage ^c				
Never user	41,986	772	1.00 (Ref)	1.00 (Ref)
Former user	10,776	376	1.83 (1.62–2.08)	1.87 (1.65–2.12)
Current user	3635	144	2.33 (1.94–2.79)	2.36 (1.97–2.84)
Duration of hormone replacement therapy (months) among ever users ^c				
≤ 4	3533	121	1.00 (Ref)	1.00 (Ref)
5–15	3429	106	0.90 (0.69–1.18)	0.93 (0.82–1.22)
16–40	3435	117	0.99 (0.76–1.28)	1.03 (0.80–1.34)
≥ 41	3364	143	1.21 (0.94–1.55)	1.28 (1.00–1.65)
		<i>P</i> -trend	0.097	0.035

^a Adjusted with age, education and marital status.^b Miscarriage before the 20th week of pregnancy. Delivering a baby born with no signs of life at or after 20 weeks' gestation.^c Only the data from HEXA 2005–2012 was used due to lack of information.

Table 3
Association between each reproductive factors and women with depressive symptom (CES-D score ≥ 21) among women who completed CES-D in Health Examinees Study (HEXA) 2009.

Variables	No. of control	No. of depression	Odds ratio age adjusted (95% CI)	Odds ratio ^a multivariable adjusted (95% CI)
Endogenous hormonal factors				
Menarche age (years)				
≤ 14	2187	126	1.00 (Ref)	1.00 (Ref)
15	1642	81	0.86 (0.65–1.15)	0.85 (0.63–1.13)
16	1585	98	1.10 (0.83–1.44)	1.05 (0.79–1.38)
≥ 17	2558	195	1.36 (1.07–1.72)	1.21 (0.95–1.55)
		<i>P</i> -trend	0.003	0.054
Menopause age (years)				
≤ 47	2110	163	1.00 (Ref)	1.00 (Ref)
48–50	2489	159	0.83 (0.66–1.04)	0.83 (0.66–1.05)
51–52	1618	76	0.62 (0.46–0.82)	0.63 (0.47–0.83)
≥ 53	1755	102	0.77 (0.59–1.01)	0.79 (0.60–1.04)
		<i>P</i> -trend	0.011	0.020
Reproductive years (years)				
≤ 31	2158	159	1.00 (Ref)	1.00 (Ref)
32–34	2035	154	1.04 (0.82–1.30)	1.05 (0.83–1.32)
35–37	2311	114	0.68 (0.53–0.87)	0.72 (0.56–0.93)
≥ 38	1468	73	0.69 (0.51–0.92)	0.74 (0.55–0.99)
		<i>P</i> -trend	< 0.001	0.004
Duration between menarche and first pregnancy among ever pregnant women (years)				
0–6	1799	43	1.00 (Ref)	1.00 (Ref)
7–9	2388	52	0.63 (0.50–0.80)	0.71 (0.56–0.92)
10–11	1590	29	0.50 (0.37–0.67)	0.59 (0.43–0.80)
≥ 12	2231	37	0.56 (0.44–0.73)	0.68 (0.51–0.90)
		<i>P</i> -trend	< 0.001	0.005
Number of spontaneous abortion ^b among ever pregnant women				
0	6243	353	1.00 (Ref)	1.00 (Ref)
1	1100	76	1.22 (0.94–1.57)	1.23 (0.95–1.59)
≥ 2	333	37	1.96 (1.37–2.80)	2.01 (1.40–2.87)
		<i>P</i> -trend	< 0.001	< 0.001
Number of artificial abortion among ever pregnant women				
0	2454	156	1.00 (Ref)	1.00 (Ref)
1	1922	99	0.82 (0.63–1.06)	0.85 (0.66–1.10)
2	1673	90	0.85 (0.65–1.11)	0.89 (0.68–1.17)
≥ 3	1556	118	1.19 (0.93–1.52)	1.24 (0.96–1.59)
		<i>P</i> -trend	0.287	0.161
Exogenous hormonal factors				
Oral contraceptive usage				
Never user	6320	380	1.00 (Ref)	1.00 (Ref)
Former user	1612	116	1.20 (0.97–1.49)	1.18 (0.95–1.47)
Current user	22	3	2.28 (0.68–7.66)	2.21 (0.65–7.51)
Hormone usage ^c				
Never user	6038	352	1.00 (Ref)	1.00 (Ref)
Former user	1412	112	1.39 (1.11–1.73)	1.46 (1.16–1.82)
Current user	498	33	1.13 (0.78–1.64)	1.14 (0.78–1.65)
Duration of hormone replacement therapy (months) among ever users ^c				
≤ 4	421	30	1.00 (Ref)	1.00 (Ref)
5–15	460	31	0.95 (0.57–1.60)	0.96 (0.57–1.62)
16–40	477	36	1.08 (0.65–1.79)	1.14 (0.68–1.89)
≥ 41	490	43	1.26 (0.77–2.06)	1.33 (0.81–2.20)
		<i>P</i> -trend	0.289	0.190

^a Adjusted with age, education and marital status.

^b Miscarriage before the 20th week of pregnancy. Delivering a baby born with no signs of life at or after 20 weeks' gestation.

^c Only the data from HEXA 2005–2012 was used due to lack of information.

Table 4
Association of depression and joint probability of menarche, menopause and reproductive years

Menarche age (years)	Menopause age (years)								<i>P</i> -trend
	Case N	≤ 46 OR ^a (95% CI)	Case N	47–49 OR ^a (95% CI)	Case N	50–52 OR ^a (95% CI)	Case N	≥ 53 OR ^a (95% CI)	
≤ 14	132	1.00 (Ref)	85	0.66 (0.50–0.87)	44	0.52 (0.67–0.73)	47	0.51 (0.36–0.72)	< 0.001
15	95	1.03 (0.79–1.35)	94	0.88 (0.67–1.15)	31	0.73 (0.29–0.64)	43	0.49 (0.35–0.70)	< 0.001
16	106	1.20 (0.92–1.56)	96	0.94 (0.72–1.23)	55	0.72 (0.52–1.00)	50	0.51 (0.36–0.71)	< 0.001
≥ 17	159	1.14 (0.89–1.45)	146	0.84 (0.66–1.08)	77	0.69 (0.52–0.93)	82	0.48 (0.36–0.64)	< 0.001
<i>P</i> -trend		0.784		0.853		0.433		0.007	<i>P</i> -int 0.525

^a Adjusted with age, education and marital status.

menarche and first pregnancy increased. There were significant associations between depression and an increasing number of both total and spontaneous abortions. In HRT, former users showed significantly increased ORs compared to those who never used HRT.

The mean age of menarche in this study was 15.6 years, and this finding was similar to a previous study with nationally representative data conducted in Korea (Jung et al., 2015). Although the mean menarche age in this study seems older than the current Caucasian population, it is consistent with a previous survey in which approximately 70% of women who were born between 1950 and 1959 experienced menarche after age 15 (Park et al., 2006).

The older age of menarche was significantly associated with increased post-menopausal depression diagnosed by physicians. This finding is inconsistent with other previous reports suggesting that women who had earlier menarche show a high risk of depressive symptoms (Joinson et al., 2011; Trepanier et al., 2013). However, there was a difference in defining 'early menarche', as these prior studies defined 10–11 years as early menarche (Joinson et al., 2011). In our study, the reference group was women who had menarche at the age of 14 or younger, whereas studies conducted in Canada and U.K. set the ages 12–13 as the normal menarche age (Joinson et al., 2011; Trepanier et al., 2013). A study conducted in Finland reported to have an increased OR of depression in women who had menarche at age 16 or older compared with women who had menarche at age 12–15 (Herva et al., 2004). Similarly, a study conducted in the U.S. found an association between later menarche and increased depressive symptoms after adjusting for age and other factors (Bisaga et al., 2002).

Compared with menarche, the trend of decreasing ORs with an increasing age of menopause was more prominent. These results are coherent with other prior results including studies conducted in a nationwide sample of the Korean population (Jung et al., 2015). In Europe and the U.S., the results of studies show the same relationship (Harlow et al., 2003; Ryan et al., 2008). The association between depression and number reproductive years, the interval between menarche and menopause, is very similar to the relationship between depression and the age of menopause. A calculation of reproductive years was frequently used to measure the lifetime exposure to estrogen (Low et al., 2005). A younger age of menarche and older age of menopause are associated with a greater total exposure of estrogen. According to the results of the joint analysis, the age of menopause seems to be a more important factor in the association with post-menopausal depression, and the age of menarche becomes a significant factor only for women who experienced late menopause.

As the total number of abortions increased, the likelihood of depression also increased. This trend was prominent in spontaneous abortions in both depression measurements. However, in regard to artificial abortions, a significant trend was observed only in physician-diagnosed depression. Most studies reported that no associations were observed between induced abortions and depression (Boersma et al., 2014), and some systematic reviews proposed that the results are mostly neutral according to the association between induced abortion and depression (Charles et al., 2008). Most of these studies used psychometrics such as the CES-D and Brief Symptom Inventory-short form to define depression. However, as our results showed a significant association between an increasing number of artificial abortions and depression, the most recent meta-analysis on this issue asserts that women with induced abortion showed an elevated risk of depression (Coleman, 2011).

In exogenous hormone usage, hormone replacement after menopause was associated with post-menopausal onset depression. However, the Women's Health Initiative Study of Cognitive Aging (WHISCA) which evaluated whether exogenous hormone

use influence cognitive functions and affect among 1416 post-menopausal women showed that participants in hormone therapy arm who received combination of estrogen and progesterone showed no significant change in positive or negative affect and depressive symptoms (Resnick et al., 2006). In contrary, a study suggest the protective effect of HRT on depression development (Schmidt et al., 2000) and a pilot study in Korea demonstrated a decreased likelihood of depression in HRT users (Lim et al., 2006). However, there was a significant association between HRT use and depression, and the results of this study coincide with other previous studies conducted in Europe (Ryan et al., 2008) and Korea (Jung et al., 2015). In this study, former HRT users showed significantly increased odds ratios of depression defined by both physician diagnosis and CES-D. There was also a significant trend in prevalence of depression diagnosis with increased duration of HRT. Compared with women who had HRT for 4 months or less, women who took HRT for 41 months or longer showed an approximately 30% increase in depression likelihood. However, this trend with the duration of HRT was not shown when measuring depression with current CES-D scores. Additionally, as the odds ratio of depression diagnosed by a physician for current HRT users was greater than in former users, the magnitude of the odds ratio decreased in current HRT users compared with former users according to the CES-D results. It is possible that there is an inverse causality in this association, in which women with a past history of post-menopausal onset depression tend to seek more HRT. Because there is no information for initiation age of HRT, we were unable to compare with the age of depression diagnosis. Further research is needed to evaluate this issue.

We used two methods to define post-menopausal depression: physician diagnosed depression history and self-reported CES-D score. CES-D is a 20-item questionnaire measuring the number of depressive symptoms with its duration (Radloff, 1977). According to a validation study, it is known that the Korean population tend to not express their positive feelings, which translates to a higher standard cutoff point for epidemiologic studies than Western society (Cho and Kim, 1993). Using psychometrics such as CES-D is not exactly the same as a physician's diagnosis. In CES-D original version, the sensitivity and specificity was found to be 86 percent and 90 percent, respectively, with a positive predictive value showing 80% (Parikh et al., 1988). In the Korean version of the CES-D, the sensitivity and specificity was 96 percent and 69 percent, respectively. Although depression diagnosis by a physician seems to represent a more valid value of depression, there may be more fluctuation in defining depression due to personal differences in experience or knowledge between physicians (Cho and Kim, 1993). The results were generally similar between these two different measures of depression.

As longer reproductive years represent extended exposure to gonadal hormones in women, many publications focus on the role of estrogen in addition to its effect on mental health. In addition, it is known that the change in circulating estrogen during puberty is also related to the disturbances in mood (Susman et al., 1987), and the estrogen in puberty affects adolescent brain in mice (Sisk and Zehr, 2005). Estrogen is known to interact with the serotonergic system and processes related to norepinephrine in post-menopausal women (Halbreich, 1997). Among the receptors for estrogen, the beta-receptor plays a major role in emotional processes associated with the serotonergic system (McEwen, 2001). Estrogen receptors located in the central nervous system seems to play roles in cognition and mood (Kruijver et al., 2003). As estrogen lessens monoamine oxidase, the level of serotonin increases (Sherwin, 1996). As the estrogen was known to be protective in depression, there are several studies regarding the use of exogenous estrogen in postpartum depression. One study conducted in U.S. suggested to use transdermal estradiol in treating postpartum depression

(Moses-Kolko et al., 2009). In addition, a meta-analysis also recommended to use estrogen therapy to treat severe postpartum depression (Dennis et al., 2008).

A strength of this study was the large population. As there was enough power, items such as associations between age of menarche and depression were observed with significant results. In a previous study conducted in Korea, such an association was not significant (Jung et al., 2015). All the information was collected with trained interviewers with a standardized questionnaire. As the questionnaire contained a large number of exposure information, it was possible to consider particular covariates, such as the number of comorbidities or marital status. Additionally, this study applied two measures to define depression: past history of physician diagnosed depression and depressive symptoms defined by the CES-D score. As the depression diagnosis by physicians represents depression defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of diseases and Related Health Problems (ICD) as the gold standards, most of the studies used psychometrics alone to evaluate depression. The results may vary with these different measures; however, this study found stable results by comparing the results of two definitions.

5. Limitations

There are several limitations in this study. The recalled information of previous hormonal events may be less accurate, especially for the information of menarche. However, a cohort study conducted in Korea revealed that the percent agreement was robust on menarche information even with an error range of less than 1 year (Ko et al., 2008). Similarly, it is unlikely to have a differential misclassification on reproductive history in this study by depression diagnosis or CES-D score.

In the HEXA study, there were no items querying the family history of depression or psychiatric drug usage. Although these factors are possible confounders, we could not adjust them in the full model. As it was difficult to interpret the time-sequence in association with each hormonal factor and depression onset before menopause, we excluded the women with pre-menopausal depression. Additionally, we excluded women with unknown menopausal statuses, which may cause potential bias.

6. Conclusion

Our study found that both ages of menarche and menopause show increased likelihood of post-menopausal onset depression. However, the age of menopause seems to be more important in depression prevalence. Based on our results, we suggest that women with earlier menopause and increased number of abortions should be checked for depression carefully. Additionally, further research is needed to evaluate the true causality between HRT and depression, especially in Korea.

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