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Research report

Hormone-related factors and post-menopausal onset depression: Results from KNHANES (2010–2012)

Sun Jae Jung [a], Aesun Shin [b], Daehee Kang [c,*]

[a] Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Republic of Korea
[b] Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
[c] Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background: Although hypotheses have been proposed regarding the biological mechanisms of hormonal fluctuations in mood disorders, few epidemiological studies have addressed this issue. The aim of this study was to examine the association between hormone-related life events and postmenopausal depression.

Methods: Of 13,918 women who participated in the Korean National Health and Nutrition Examination Survey (KNHANES) V, a total of 4869 post-menopausal women who had completed information on depression onset age and additional reproductive factors were included in the analysis. A multivariate logistic regression was applied to calculate the odds ratios between reproductive factors and post-menopausal onset depression.

Results: A total of 276 women (5.7%) were diagnosed with depression after menopause. Longer reproductive years were associated with a reduced risk of depression (for more than 35 reproductive years: OR=0.41, 95% CI: 0.27–0.62, *P*-trend < 0.001). Similarly, a later age of menopause (52 years and older) corresponded to a decreased risk of depression (OR=0.35, 95% CI: 0.22–0.55) compared to the women with a menopausal age younger than 46 years. Greater numbers of pregnancies and exogenous hormone use were also associated with increased risk of depression.

Limitations: All data were collected from interviews using questionnaires. There may be some inaccuracies in recall of lifetime reproductive events, but women generally recalled their hormonal events correctly.

Conclusion: Early menopause and the use of exogenous hormones were associated with the risk of post-menopausal depression. Clinicians should closely monitor and consider further screening for depressed women who undergo early menopause or those with exogenous hormone use.

1. Introduction

Depression is a major health problem worldwide, and it is expected to be the main contributor to the burden of disease in the future (Mathers and Loncar, 2006). In the National Comorbidity Survey (NCS) of the United States, the lifetime prevalence of major depressive disorder (MDD) was 12.7% for men and 21.3% for women (Kessler et al., 1993), and more recent data presented a nearly doubled lifetime risk of MDD in women (OR=1.7, 95% CI 1.5–2.0) (Kessler et al., 2003). Several studies have interpreted these phenomena to be related to female-specific reproductive events (Cyranowski et al., 2000; Soares and Zitek, 2008). Women are particularly susceptible to depression at times of hormonal fluctuations, such as the transitions between the premenstrual, postnatal and peri-menopausal phases (Bromberger et al., 2010; Burt and Stein, 2002; Gibbs et al., 2012). Several articles have been published based on the assumption that fluctuations in sex hormones in female reproductive events can affect neurochemical pathways related to depression (Bloch et al., 2000; Noble, 2005; Soares and Zitek, 2008).

A series of studies support the idea that there is an increased risk of depression related to reproductive life events in women who are more sensitive to hormonal changes (Bloch et al., 2000; Halbreich, 2003). Women's particular susceptibility to mood disorders during stages of hormone changes is explained by the neuro-modulating effect of estrogen within interactions with serotonergic system (Amin et al., 2005). Hormonal changes in

* Correspondence to: Department of Preventive Medicine Seoul National University College of Medicine 103 Daehak-ro, Jongno-gu, Seoul 110-799, Republic of Korea. Tel.: +82 2 740 8326; fax: +82 2 747 4830.
E-mail address: dhkang@snu.ac.kr (D. Kang).

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reproductive events contribute to the dysregulation of the serotonergic and noradrenergic systems involved in mood and behavior (Cohen et al., 2006b; Deecher et al., 2008). It has been hypothesized that a reduced capacity to adapt to fluctuations of estradiol or progesterone may predispose certain women to depression (Deecher et al., 2008).

However, the relationship between hormonal events and depressive illness in women remains controversial. A French study showed that early menopause was associated with a higher risk of late-life depression (Ryan et al., 2008), and a study from the U.S. demonstrated that women with more children had a lower risk of depression (Harlow et al., 1999). Furthermore, although pregnancy is believed to be protective against psychiatric disorders, there is accumulating evidence that supports the opposite conclusion (Cohen et al., 2006a). However, there is not enough evidence to prove the effects of natural reproductive hormones on developing depression, and few epidemiological studies have been conducted on this issue, especially in Asian women. For exogenous hormones, a meta-analysis analyzed 26 studies and summarized that hormone replacement therapies (HRTs) have beneficial effects in reducing depressed mood among postmenopausal women (Zweifel and O'Brien, 1997). Still, a subsequent study argued that these studies had predominantly poor methodological quality (Stoppe and Doren, 2002).

Menopause is a particularly influential period during which women have to adapt to a new biological transition. Women with postmenopausal depression tend to have lower estradiol and serotonin concentrations, in contrast to high levels of follicle stimulating hormone (Jasienska et al., 2005). These hormones are able to alter the functions of the nervous system (Jasienska et al., 2005). Additionally, many publications have reported on the protective effects of hormone replacement therapy on depressive symptoms (Hlatky et al., 2002; Kugaya et al., 2003; Morrison et al., 2004; Schmidt et al., 2000; Soares et al., 2001; Wihlback et al., 2001), and many studies have focused on the hormonal treatment of postmenopausal depression. Even if the protective effects of estrogen towards neuronal systems were proven by experimental studies, the protective effects of hormone replacement therapy in women who undergo menopause remain controversial (Ancelin et al., 2007). Additionally, because many studies on the effects of hormone replacement therapy and depression have primarily consisted of Western populations, evidence among Asian women is minimal.

The objectives of this study were to estimate the association between reproductive factors and the onset of postmenopausal depression in the Korean population and to further elucidate the role of hormone-related factors on post-menopausal onset depression.

2. Materials and methods

2.1. Study participants

The data used in this study were derived from the Korean National Health and Nutritional Examination Survey (KNHANES) V (2010–2012). Based on the National Health Promotion Act announced in 1995, KNHANES began in 1998. Samples were recruited using a multi-stage clustered probability design. From approximately 200,000 primary sampling units (PSU) defined by geographical regions in the entire country, the final PSU for the actual survey were extracted. The survey used data of approximately 10,000 individuals each year between 2010 and 2012. The sample weights were used to calculate all statistics of this survey. To represent the Korean population with sample participants, sample weights were created, considering survey non-response, complex survey design and post-stratification. KNHANES is a series of nationwide cross-sectional studies that targeted a nationally representative population who are non-institutionalized residents in Korea. Trained interviewers conducted all the interviews using structured questionnaires to obtain information including sociodemographic factors, health-related factors, lifestyle factors, the use of medical services and female reproductive factors. Further information about KNHANES can be found elsewhere (Kweon et al., 2014). A total of 13,913 women participated in the KNHANES V (2010–2012) survey. The analysis in this study was confined to a total of 4869 respondents over 19 years old who had gone through menopause and had no missing values for the reproductive factors and outcome variables (Fig. 1). Only those who had a first depression diagnosis after menopause were considered, and those who had a depression diagnosis before menopause were excluded from the analysis.

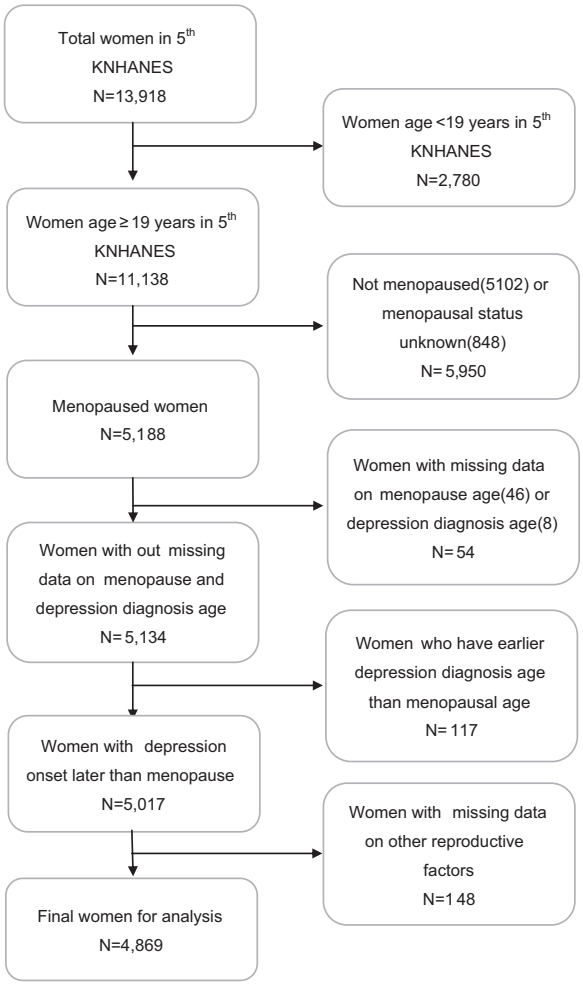

Fig. 1. Selection of participants for analysis.

2.2. Measures

The presence of depression was determined by the question, "Have you ever been diagnosed with depression confirmed by a physician?"; those who provided information regarding their age at first diagnosis were included in the analysis. The endogenous hormone-related factors included menarche and menopause age, total reproductive years, number of pregnancies, first birth age and breastfeeding duration. The number of pregnancies was classified as total pregnancies including abortions and pregnancy without any abortion. The number of abortions were classified as the total number of abortions, including spontaneous and artificial

abortions, number of spontaneous abortions only and number of artificial abortions only. The total number of reproductive years was calculated based on the menarche age and menopause age. The exogenous hormone-related factors included oral contraceptive (OC) usage duration and HRT starting age and duration.

Information on age, household income, educational level, marital status, occupation, number of family members, number of generations living together, education of both parents, other comorbid diseases and the Alcohol Use Disorders Identification Test (AUDIT) score (Barbor et al., 2001) was obtained to provide a sociodemographic background and the medical conditions of the participants. Age was classified into four groups by quartile (≤ 56 years, 57–63 years, 64–71 years or >71 years). Education was classified by attainment years (≤ 6 years, 7–9 years, 10–12, and >12 years). Marital status was classified into three groups: never married, married and living with a spouse or married but living alone due to divorce or the death of a spouse. Comorbid diseases were: coronary heart disease, stroke, diabetes mellitus, chronic renal failure, cancers of stomach, liver, colorectum, breast, uterine cervix, lung and thyroid and chronic hepatitis B or C virus infection.

2.3. Statistical analysis

Because KNHANES represents the total population of South Korea, population weights were used. By applying the PROC SURVEY in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA), the distributions of the cluster sample, covariance and significance were corrected. The percentages of participants were calculated based on the sociodemographic characteristics to provide descriptions of the data. Generally, participants were excluded from the study if they had any missing values in the diagnosis of depression or age of depression diagnosis. Similarly, if women had no value on each reproductive factor, such as menarche age, menopause age, menopause status, type of menopause, first pregnancy age, pregnancy number among ever pregnant women, first birth age, last birth age, breast feeding duration among ever parous women, OC usage duration among OC users and HRT usage duration among HRT users, they were excluded from the analysis. For covariates in the model, missing values were coded separately to be applied in the final model. The stepwise likelihood ratio test was conducted and the final model included age, occupational status, marital status, comorbidity and AUDIT score for adjustment variables. Variables for hormonal events were categorized as followed: menarche age (≤ 14, 15–16, 17, ≥ 18 years old), menopause age (<46, 46–49, 50–51, ≥ 52 years old), first birth age (≤ 21, 22–23, 24–25, ≥ 26 years old), last birth age (≤ 27, 28–30, 31–33, ≥ 34 years old), OC usage duration (never, 10, 11–22, ≥ 23 months) and HRT duration (never, ≤ 7, 8–35, ≥ 36 months). The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a multivariate logistic regression analysis to evaluate the associations between endogenous hormonal factors, exogenous hormonal factors and depression onset, with adjustments made for the covariates. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA), and the level of significance was $P<0.05$.

2.4. Ethics

All participants agreed to provide written consent to participate in KNHANES. The Institutional Review Board of the Seoul National University Hospital in Seoul, Korea, approved the use of publicly available data for statistical analysis. (IRB no. 1406-058-586)

3. Results

3.1. Baseline characteristics of the study population

A total of 276 participants (weighted percentage 5.1%) were diagnosed with depression after menopause. The mean age in the depression group was 64.4 years, and the mean age in the non-depression group was 63.9 years. As shown in Table 1, there was a

Table 1
Characteristics of post-menopausal women who ever had menstruation stratified by depression using the Korea NHANES 2010–2012 (weighted).

Variables	($n=4869$, weighted $N=7{,}065{,}898$)		*P*-value
	Never diagnosed depression ($n=4593$, 94.3%) (weighted $N=6{,}704{,}673$, 94.9%)	Post-mentsrual onset depression ($n=276$, 5.7%) (weighted $N=361{,}225$, 5.1%)	
General factors	**Weighted %**[a]	**Weighted %**[a]	
Age (Years)			0.118
≤56	33.2	32.2	
57–63	23.4	22.8	
64–71	20.6	27.4	
>71	22.7	17.5	
Family income percentile[b]			0.219
<25%	25.7	31.3	
25–50%	26.4	22.5	
51–75%	25.1	27.6	
>75%	22.8	18.6	
Education attainment years			0.051
≤6	58.3	61.6	
7–9	16.9	11.7	
10–12	18.4	23.3	
>12	6.4	3.4	
Marital status			0.204
Never married	0.8	0.1	
Married–living together	67.9	71.5	
Married–others	31.3	28.4	
Occupation			0.373
Wage working	21.8	17.5	
Self-supporting	12	12.2	
House-employed	10.7	7.8	
No financial activity	55.5	62.5	
Number of family members			0.753
Living alone	12.9	12.4	
Living with one family member	36.9	39.7	
Living with more than one member	50.2	47.9	
AUDIT[c] score			0.061
0–7	62.8	62.0	
8–19	5.3	4.8	
20–40	0.5	2.2	
Number of comorbid disease			0.100
0	76.9	70.9	
1	19.6	23.2	
≥2	3.4	6.0	

Number of diseases was counted among coronary heart disease, stroke, diabetes mellitus, chronic renal failure, solid cancers (gastric, liver, colon, breast, cervix, lung and thyroid) and hepatitis virus (HBV and HCV) infection.

[a] Sum of numbers can miss the total number in group due to missing values.
[b] Each income amount in quartile is different by age strata.
[c] The Alcohol Use Disorders Identification Test.

smaller proportion of participants who had at least some college education in the depression group (3.4%) compared to the non-depression group (6.4%), and a larger percentage of those who had less than an elementary school education were in the depression group (61.6%) than in the non-depression group (58.3%). Similarly, the percentage of women without a regular job by which to participate in financial activity was larger in the depression group (62.5%) than in the non-depressed group (55.5%). The distribution of number of comorbid diseases and AUDIT score were presented in the Table 1. As shown in Table 1, no statistically significant differences were observed between the groups based on family income quartile, marital status or number of family members. Likewise, there were no significant differences in the number of generations living together and the education level of both parents after adjusting for age (data not shown).

3.2. Endogenous hormone-related factors

In the multivariate analysis (Table 2), there was a statistically significant trend relating the total number of reproductive years to post-menopausal onset depression (P-trend <0.001). As the period of reproductive years increased, the odds ratio of depression decreased. Women with a total number of reproductive years greater than 35 had an OR of 0.41 (95% CI: 0.27–0.62) compared to those with less than 30 reproductive years after adjusted for age. The age at menarche showed no significant trend in post-menopausal onset depression. However, compared to those who experienced menopause before 46 years old, women who underwent menopause at 52 years old or later had an OR of 0.35 (95% CI: 0.22–0.55).

Compared to the women who had no pregnancies or at least 3 pregnancies, including abortions, women who had 7 or more pregnancies had a 1.3-fold increased risk of depression onset (95% CI: 0.84–2.04). If limited to pregnancies without abortion, no group showed significant results in OR. Compared to those who had no abortion during their pregnancies, women who underwent abortion more than 3 times showed an increased likelihood of depression (OR 1.74, 95% CI 1.12–2.70). There was no significant association between the first birth age groups. There was no significant association between depression onset and increased duration of breastfeeding.

3.3. Exogenous hormone-related factors

Compared to the group who had never used oral contraceptives in their lifetime, women who continued their oral contraceptive use for 23 months or longer had an odds ratio of 1.55 (95% CI: 0.94–2.55). If women began using HRT at 48 years old or younger, the odds ratio increased to 3.86 (95% CI: 2.10–7.09) compared to the women who had never used HRT (data not shown). Likewise, as the duration of HRT increased, the odds ratio increased (P-trend, <0.001). In particular, if the duration of HRT was longer than 8 months, the odds ratio increased with statistical significance (for an HRT duration of 8–35 months, OR=2.89, 95% CI: 1.54–5.44; for an HRT duration $\geq$36 months, OR=2.37, 95% CI: 1.38–4.08).

4. Discussion

In this study, an earlier menopause age was associated with post-menopausal onset depression. For exogenous hormone-related factors, longer oral contraceptive and hormone replacement therapy usage were associated with an increased risk for depression. In particular, for those who used hormone replacement therapy, those who started using HRT at a younger age had the highest risk for depression. Despite that depression has multiple etiologies in its disease onset, this study suggests the obvious associations between several factors related to the female hormonal system and post-menopausal onset depression.

In our study, mean reported age of menarche was 16 years, and this age is older than what is reported in the current Caucasian population. However, the age at menarche in our study is consistent with a previous report that showed that approximately 56.5% of women who were born between 1940 and 1949 had menarche at 15–16 years (Park et al., 2006).

In this study, there was a significant trend between a longer period of reproductive years and a reduced risk of depression onset. Menopausal age, but not menarche age, was the major determinant in this relationship. This result is very similar to a study conducted in the European population (Ryan et al., 2008). There are few studies that have focused on the effects of reproductive factors on depression onset, and one study asserted that early menopause increases the risk of depression (Harlow et al., 2003). Because the age of menarche has a narrower distribution range compared to the age of menopause, the protective effect seems to have been masked. Some studies have indicated that women are more susceptible to depression if they start menstruation at a younger age (Harlow et al., 2004), but our findings were not statistically significant.

In this study, the mean age of depression diagnosis was approximately 58.7 years. Several studies have reported that the age of menopause alters the risk of diseases, such as ischemic stroke and breast cancer, after age 60 (Lisabeth et al., 2009; Shin et al., 2011). Late menopause extends reproductive years and lengthens lifetime estrogen exposure, which increases the risk of hormone-related diseases. It is known that early menopause is associated with adverse socio-economic factors, such as manual working class (Parazzini and Progetto Menopausa Italia Study Group, 2007) or low educational level (Lawlor et al., 2003) which can also affect the onset of depression. However, we controlled for these factors in the final adjusted model.

Menopause that occurs by artificial factors, such as surgery, exhibits a significantly increased odds ratio of approximately 80% compared to natural menopause. This finding supports previous studies that have suggested that menopause provoked by other artificial causes results in rapid changes in the hormonal system, which encompasses more severe depressive symptoms (Unsal et al., 2011). In addition to biological explanations limited to hormonal effects, some argue that this phenomenon can be based on complications of surgery, body image alteration, inability to reproduce, and negative effects on sexual life and pain (Azadeh-Ghamsari et al., 2002; Vrzackova et al., 2010).

Although we demonstrated a marginal significance, our results regarding the number of pregnancies is not consistent with the results from a previous study (Vesga-Lopez et al., 2008) that showed a decreased risk of mood disorders among pregnant women compared to non-pregnant women. However, more recent meta-analysis and systematic reviews (Bennett et al., 2004; Ross and McLean, 2006) report heterogeneity in results regarding the association between number of pregnancies and depression. There are several studies showing no typical harmful effect of pregnancy to women's mental health similar to this study. One longitudinal study conducted in Australia showed that there was no association between pregnancy and increased symptoms of depression (Leach et al., 2014). Another prospective cohort study showed no alteration in psychological distress during the time of pregnancy (van Bussel et al., 2006). One study conducted within twins identified no biological associations between increased parity and the risk of psychiatric illnesses, and it suggested that social factors are a major determinant in the higher prevalence of psychiatric diseases in married women (Dean and White, 1996). Another study

Table 2
Odds ratios for the association between each reproductive factors and 276 post-menopausal onset depression of menopaused women in South Korea NHANES 2010–2012. (weighted).

Variables	Depression (−)	Depression (+)	Odds ratio[a] (95% CI)	Odds ratio[b] (95% CI)	Odds ratio[c] (95% CI)
Endogenous hormonal factors					
Menstruation duration					
< 30 years	1016	81	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–33 years	889	56	0.66 (0.41–1.05)	0.66 (0.41–1.05)	0.66 (0.41–1.05)
34–35 years	1158	68	**0.61 (0.40–0.95)**	**0.58 (0.37–0.90)**	0.56 (0.36–0.88)
> 35 years	1530	71	**0.44 (0.29–0.67)**	**0.41 (0.27—0.64)**	**0.41 (0.27–0.62)**
		P-trend	< 0.001	< 0.001	< 0.001
Menarche age					
≤ 14 years	1016	57	1.00 (ref)	1.00 (ref)	1.00 (ref)
15–16 years	1599	102	0.98 (0.65–1.48)	0.98 (0.64–1.49)	0.98 (0.64–1.49)
17 years	850	54	0.83 (0.50–1.36)	0.80 (0.48–1.34)	0.82 (0.49–1.38)
≥ 18 years	1128	63	0.76 (0.48–1.20)	0.75 (0.48–1.18)	0.77 (0.48–1.21)
		P-trend	0.178	0.144	0.183
Menopause age					
< 46 years	999	78	1.00 (ref)	1.00 (ref)	1.00 (ref)
46–49 years	1156	84	0.82 (0.55–1.21)	0.80 (0.54–1.21)	0.79 (0.53–1.19)
50–51 years	953	47	**0.47 (0.30–0.72)**	**0.44 (0.28–0.69)**	**0.43 (0.28–0.67)**
≥ 52 years	1485	67	**0.39 (0.24–0.61)**	**0.36 (0.23–0.57)**	**0.35 (0.22–0.55)**
		P-trend	< 0.001	< 0.001	< 0.001
Type of menopause					
Natural	4027	227	1.00 (ref)	1.00 (ref)	1.00 (ref)
Artificial	566	49	**1.79 (1.16–2.75)**	**1.77 (1.17–2.69)**	**1.75 (1.16–2.66)**
Duration between menarche and first pregnancy among ever pregnant women					
≤ 4 years	1068	57	1.00 (ref)	1.00 (ref)	1.00 (ref)
5–7 years	1187	88	1.52 (0.96–2.40)	1.51 (0.95–2.41)	1.48 (0.93–2.36)
8–10 years	1135	72	1.24 (0.76–2.04)	1.22 (0.72–2.07)	1.17 (0.68–2.01)
≥ 11 years	1082	55	1.30 (0.79–2.15)	1.28 (0.75–2.19)	1.21 (0.70–2.10)
		P-trend	0.519	0.644	0.810
Total pregnancy (number) including abortion					
0–3	1407	64	1.00 (ref)	1.00 (ref)	1.00 (ref)
4	868	56	1.21 (0.71–1.98)	1.22 (0.74–2.01)	1.20 (0.73–1.98)
5–6	1345	85	1.09 (0.73–1.62)	1.11 (0.74–1.68)	1.09 (0.72–1.64)
≥ 7	973	71	1.25 (0.82–1.90)	1.31 (0.84–2.05)	1.30 (0.84–2.04)
		P-trend	0.395	0.302	0.330
Pregnancy (number) without any abortion					
0–2	1768	91	1.00 (ref)	1.00 (ref)	1.00 (ref)
3	1085	82	1.10 (0.76–1.59)	1.04 (0.70–1.52)	1.05 (0.71–1.54)
4	733	42	0.79 (0.50–1.24)	0.74 (0.46–1.20)	0.77 (0.47–1.25)
≥ 5	927	57	0.95 (0.62–1.45)	0.99 (0.55–1.78)	1.05 (0.58–1.89)
		P-trend	0.577	0.730	0.888
Total abortion (number) among ever pregnant women					
0	1312	51	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1197	73	1.62 (1.02–2.56)	1.57 (0.98–2.52)	1.66 (0.98–2.51)
2	981	61	1.50 (0.93–2.43)	1.46 (0.90–2.39)	1.44 (0.89–2.36)
≥ 3	1023	87	**1.89 (1.24–2.89)**	**1.79 (1.15-2.77)**	**1.74 (1.12–2.70)**
		P-trend	0.005	0.014	0.021
Spontaneous abortion among ever pregnant women					
Never	3464	205	1.00 (ref)	1.00 (ref)	1.00 (ref)
Ever	1049	67	1.12 (0.79–1.60)	1.10 (0.77–1.58)	1.10 (0.77–1.57)
Artificial abortion among ever pregnant women					
Never	1882	89	1.00 (ref)	1.00 (ref)	1.00 (ref)
Ever	2631	183	**1.40 (1.03–1.90)**	1.35 (0.98–1.87)	1.33 (0.97–1.84)
First birth age among ever parous women					
≤ 21 years	1189	61	1.00 (ref)	1.00 (ref)	1.00 (ref)
22–23 years	970	84	1.75 (1.10–2.78)	1.71 (1.05–2.77)	1.68 (1.03–2.75)
24–25 years	1020	59	1.03 (0.63–1.70)	1.01 (0.59–1.73)	0.98 (0.57–1.70)
≥ 26 years	1293	68	1.10 (0.69–1.76)	1.06 (0.63–1.80)	1.02 (0.60–1.75)
		P-trend	0.731	0.604	0.489
Last birth age among ever parous women					
≤ 27 years	1126	71	1.00 (ref)	1.00 (ref)	1.00 (ref)
28–30 years	1300	81	1.02 (0.67–1.56)	1.01 (0.67–1.52)	0.99 (0.65–1.50)
31–33 years	923	65	0.92 (0.60–1.40)	0.90 (0.58–1.39)	0.87 (0.56–1.37)
≥ 34 years	1103	53	0.72 (0.46–1.15)	0.74 (0.44–1.25)	0.74 (0.43–1.26)
		P-trend	0.145	0.229	0.232
Breastfeeding duration among ever parous women					
0–27 months	856	46	1.00 (ref)	1.00 (ref)	1.00 (ref)
24–41 months	1189	75	0.87 (0.59–1.60)	0.93 (0.57–1.53)	0.95 (0.57–1.58)

Table 2 (*continued*)

Variables	Depression (−)	Depression (+)	Odds ratio[a] (95% CI)	Odds ratio[b] (95% CI)	Odds ratio[c] (95% CI)
42–77 months	1,057	69	0.88 (0.53–1.46)	0.77 (0.43–1.36)	0.81 (0.44–1.49)
≥ 78 months	1,045	58	0.91 (0.56–1.48)	0.81 (0.43–1.55)	0.86 (0.44–1.70)
		P-trend	0.622	0.445	0.594
Exogenous hormonal factors					
Oral contraceptive usage duration (months)					
Never	3,605	198	1.00 (ref)	1.00 (ref)	1.00 (ref)
≤ 10 months	326	19	1.23 (0.67–2.26)	1.15 (0.64–2.08)	1.15 (0.63–2.09)
11–22 months	253	22	1.24 (0.70-2.18)	1.15 (0.65–2.03)	1.15 (0.65–2.03)
≥ 23 months	409	37	**1.73 (1.08–2.77)**	1.56 (0.95–2.58)	1.55 (0.94–2.55)
		P-trend	0.021	0.080	0.088
Hormone replacement therapy duration (months)					
Never	3,906	206	1.00 (ref)	1.00 (ref)	1.00 (ref)
≤ 7 months	228	18	1.55 (0.85–2.83)	1.54 (0.82–2.88)	1.55 (0.82–2.94)
8–35 months	190	26	**2.89 (1.59–5.27)**	**2.95 (1.58–5.51)**	**2.89 (1.54–5.44)**
≥ 36 months	269	26	**2.49 (1.44–4.32)**	**2.45 (1.43–4.21)**	**2.37 (1.38–4.08)**
		P-trend	< 0.001	< 0.001	< 0.001

[a] Crude odds ratio.
[b] Adjusted with age, comorbidity and alcohol use(AUDIT score).
[c] Adjusted with age, comorbidity, alcohol use(AUDIT score), occupational status and marital status.

suggested that even pregnancy might affect depression and that childbirth may prevent harmful effects (Evans et al., 2001). It is also possible that living with many children might reduce the risk of depression which might have been affected by the pregnancy itself, but we were unable to compare the number of living children with total parity due to a lack of information. Further research should be conducted to evaluate the true meaning of the biological effects of parity on the development of depression.

Breastfeeding is well recognized for its beneficial effects on mothers' mental health, and several studies report that breastfeeding mothers have lower susceptibility to depression (Assarian et al., 2014). Another study suggests that breastfeeding can increase the negative mood of women (Mezzacappa and Katlin, 2002). Additional researchers suggested that breastfeeding may provide an anti-depressive effect (Field, 2008). Research has also proposed that breastfeeding diminishes the hormonal and psychological risk conditions for postpartum depression (Figueiredo et al., 2013). Other studies claim that breastfeeding weakens the stress response related to the cortisol pathway, which can protect against maternal depression (Heinrichs et al., 2002; Tu et al., 2006). Hormones related to breastfeeding, such as oxytocin and prolactin, seem to have an anxiolytic or antidepressant effect (Mezzacappa and Katlin, 2002).

For exogenous hormone-related factors, the results were more pronounced than those of the endogenous hormone-related factors. There have previously been many contradictory results regarding the effects of oral contraceptives. In Finland, the use of hormonal contraception was not associated with a negative impact on mental health (Toffol et al., 2012). However, this study was conducted in a large population and used the Beck Depression Inventory-13 as a diagnostic tool, which can produce relatively subjective results. Furthermore, there was no clear association between the duration of oral contraceptive usage and mental health effects in this study. Additionally, a recent meta-analysis states that there are limited data on evaluating hormonal contraception and depression (Bottcher et al., 2012). Contrary to previous outcomes, which showed a decreased risk of depression as the duration of oral contraceptive usage increased beyond 10 years (Ryan et al., 2008), our results show that the odds ratio increases as the duration of oral contraceptive usage increases. If women used oral contraceptives for 23 months or longer, the odds ratio of depression increased by approximately 55%. There are warnings that the synthetic female sex hormones used in oral contraceptives may be associated with the risk of adverse effects on mental health. In several reports, it has been mentioned that certain women developed depressive symptoms after they used hormonal contraceptives (Andersen et al., 2014). Our results support these previous reports and suggest clear implications of the possible hazardous impact of oral contraceptives on mental health.

There have been consistent claims of the beneficial effects of HRT on depressive mood (Whooley et al., 2000). A pilot study was previously conducted in Korea that also supported the protective effects of HRTs on depression (Lim et al., 2006). Several articles proposed the use of estrogen in women with a reproductive depression disorder (Studd and Panay, 2009). As stated in the previous study, this study agrees with only a few reports suggesting that the use of HRTs may increase the risk of depression (Ryan et al., 2008). Based on our results, the starting age and duration of HRT use seems to influence the odds ratios for depression. In particular, if women started their HRT at 48 years old or younger, the odds ratio was more than three times greater. Because women tend to begin HRT after suffering from post-menopausal symptoms, such as hot flashes, the early use of HRT may reflect early menopause. In our data, we showed a linear correlation between menopause age and the starting age of HRT in the HRT group (data not shown). Therefore, further research is needed to evaluate the true factors affecting the onset of depression. However, it seems evident that the use of HRTs increases the risk of post-menopausal depression. Additionally, the previous study conducted in Korea was conducted in only 65 women and reported a marginal significance of a reduced risk of HRTs on depression (Lim et al., 2006).

This study has various strengths. First, KNHANES is a nationally representative large survey in Korea, and the questionnaires were conducted by trained interviewers in a standardized manner. With the large population used in this study, some results, such as the increased duration of hormone replacement therapy that was not statistically significant in a previous study (Ryan et al., 2008), had a significant result in this study. Additionally, because the questionnaires in KNHANES contain a large amount of information, we were able to access many factors, such as the presence of comorbid diseases or the education of parents, which were previously known to be related to depression and were found to be effective covariates to include in the model.

However, this study was based on a cross-sectional design; therefore, we could only interpret the results pertaining to certain temporal relationships based on the time information regarding menopause and the onset of depression. Additionally, this study is one of only a few studies that address depression diagnosed by a

physician in a large population. Several studies have failed to differentiate between major depressive disorder, according to the clinical diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), and other symptoms such as simple depressive mood (Bloch et al., 2000; Figueiredo et al., 2013; Ryan et al., 2008; Unsal et al., 2011). However, there remains a chance of underestimation if women answered 'yes' to the question: "Have you ever been diagnosed with depression? If so, when?" This question may be more accurate in assessing depressive disorder.

5. Limitations

There are several limitations in this study. All data were collected from interviews using questionnaires and were reviewed retrospectively. Some inaccuracies may occur, especially because participants had to remember their entire lifetime of reproductive events. Retrospective reports of age at menarche are quiet inaccurate, so the validity of certain exposure variables are somewhat questioned. However, one study conducted in the Korean Multi-Center Cancer Cohort (KMCC) study showed a strong percent agreement (69.4%) in age at menarche even if the error range was set less than 1 year (Ko et al., 2008). Therefore, the reproducibility of the data according to menarche age is considered to be acceptable. Likewise, it is possible that women with depression may tend to answer less accurately. However, the KNHANES contains many items related to the history of participants, and there is no particular reason for depressed women to answer more inaccurately on the questions involved in this study than other questions because they were not aware of the objective of this study. Furthermore, all questions were asked by trained interviewers to prevent illogical replies. Therefore, we estimated that there were no significant errors contributing to biased results.

Similarly, because we excluded those women with unknown menopausal statuses, there may be a potential bias. Because it was difficult to interpret certain temporalities between hormone-related factors and depression in the pre-menopause population, we likely excluded some women who were not menopausal. In those women with an unknown menopause status, some may have had depression after menopause, which would have reduced the overall power of this study.

In the process of building models including possible confounders, items such as family history of depression or drug use pattern, were unable to be applied in the final model. In KNHANES 2010–2012, there is no information for family history of depression. Only the familial history for hypertension, hyperlipidemia, ischemic heart disease, stroke and diabetes is included. Similarly, only information on drug prescriptions in the past 2 weeks was available. As it is not adequate to assume effect of relatively short period of drug prescription on depression, which is a chronic state, we did not include this factor in the final model. However, this element might have caused missed possible effects of these confounders on the associations between the reproductive factors and depression.

A total of 276 participants (5.1%) were diagnosed with depression after menopause, which is less than previous reports (6.7%) (Cho, 2011). Because the participants in KNHANES were limited to only non-institutionalized people, fewer people with depression may be included in this study. The results of the present study might therefore underestimate the true prevalence.

6. Conclusions

In conclusion, in this study of Korean women, hormone-related factors such as age at menopause and hormone replacement therapy were associated with post-menopausal onset depression. According to our results, we suggest that careful psychiatric screening for depression should be provided to women who undergo early menopause, menopause by artificial procedures or have a large number of pregnancies. Additionally, women who use oral contraceptives or HRTs for longer than a particular duration or women who start HRT early should also be carefully observed for depression development.

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Conflict of interest

None.

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