

## Research report

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

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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.

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## 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 (Cyranski 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

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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

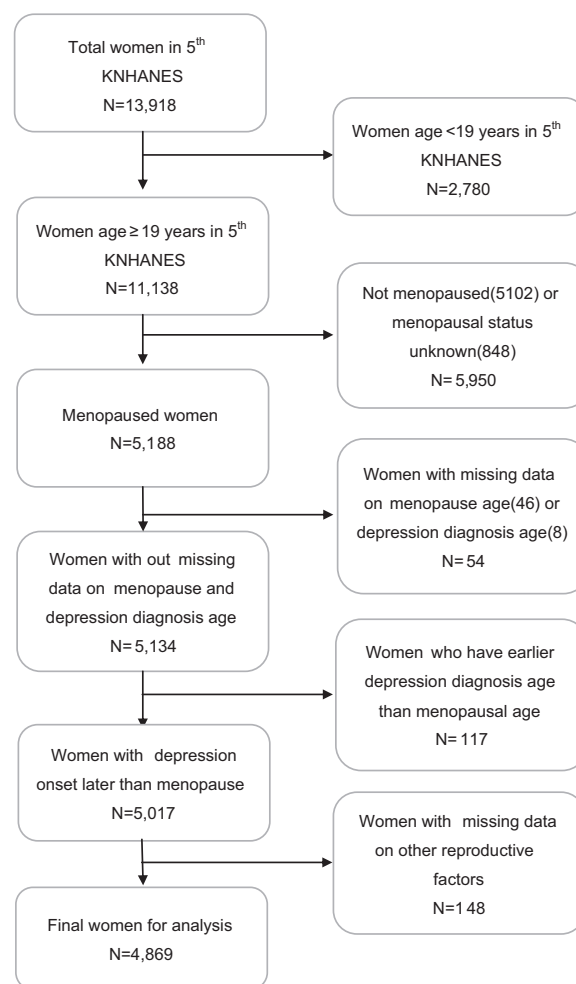


Fig. 1. Selection of participants for analysis.

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.

### 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

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