

Association between premature ovarian insufficiency, early menopause, socioeconomic status in a nationally representative sample from Korea

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ABSTRACT

Objective: We investigated whether, in the Korean population, the risk of premature ovarian insufficiency (POI) and early menopause varies with a woman's socioeconomic status, evaluated in relation to income, education, and occupation.

Methods: This cross-sectional, population-based study involved 31,508 women aged > 19 years registered in the Korea National Health and Nutrition Examination Survey (KNHANES) (2007–2016). Menopausal status and socioeconomic status were obtained from self-reported KNHANES data. A logistic regression model was applied to test whether POI and early menopause varied with socioeconomic status.

Results: The prevalence of POI was 2.41% and of early menopause was 5.89%. The annual incidence of POI during the investigation period plateaued, while that of early menopause showed a linear trend. The risk of POI was significantly higher among participants with lower household incomes (odds ratio [OR], 95% confidence interval [CI]; 1.44, 1.16–1.78) and lower levels of education (OR, 95% CI: 1.75, 1.16–2.65) after adjustment for age.

Conclusion: The prevalence of POI in the Korean population was almost twice that reported in a previous study. Lower socioeconomic status was associated with an increased risk of POI and early menopause. Further studies are warranted to investigate this association.

1. Introduction

Premature ovarian insufficiency (POI) refers to the amenorrhea status due to the loss of ovarian function before 40 years of age. This age is agreed conventionally and is supported by a statistical view of clinical observation. It is approximately 2 standard deviation below the mean age of natural menopause [1]. Thus, POI occurs at least 10 years faster compared to the average age of menopause, which is 51.4 years [2]. In other words, women with POI experience the effects of oestrogen deprivation longer, resulting in medical issues related to oestrogen deficiency. Previous studies have reported that POI can cause coronary heart disease [3] and increased early mortality [4–6] than natural menopause. Recent evidence suggested that POI is closely linked to long-term health effects, including depressive symptoms and poor quality of life [7]. Although the significant association between POI and women health status is reported, very little is currently known about how many women are affected by POI, especially in the Asian population.

POI is a condition triggered by highly heterogeneous causes. In 2015, the European Society of Human Reproduction and Embryology (ESHRE) guideline development group classified the aetiology of POI into the following six categories: chromosomal or genetic defects, autoimmune disorders, infections, iatrogenic causes, environmental factors, and idiopathic factors [1]. POI due to environmental factors, such as smoking and alcohol, were reported as well [8,9]. The socioeconomic environment is one of the fundamental environmental factors and could play a key role as a health determinant in women [10]. However, research to date has not yet known the impact of socioeconomic status on POI or early menopause.

The objective of this study was to determine the prevalence of POI and early menopause in the general population and to investigate the association between socioeconomic status and POI or early menopause among women aged 19 years or older through a cross-sectional study using a national representative data in Korea between 2007 and 2016.

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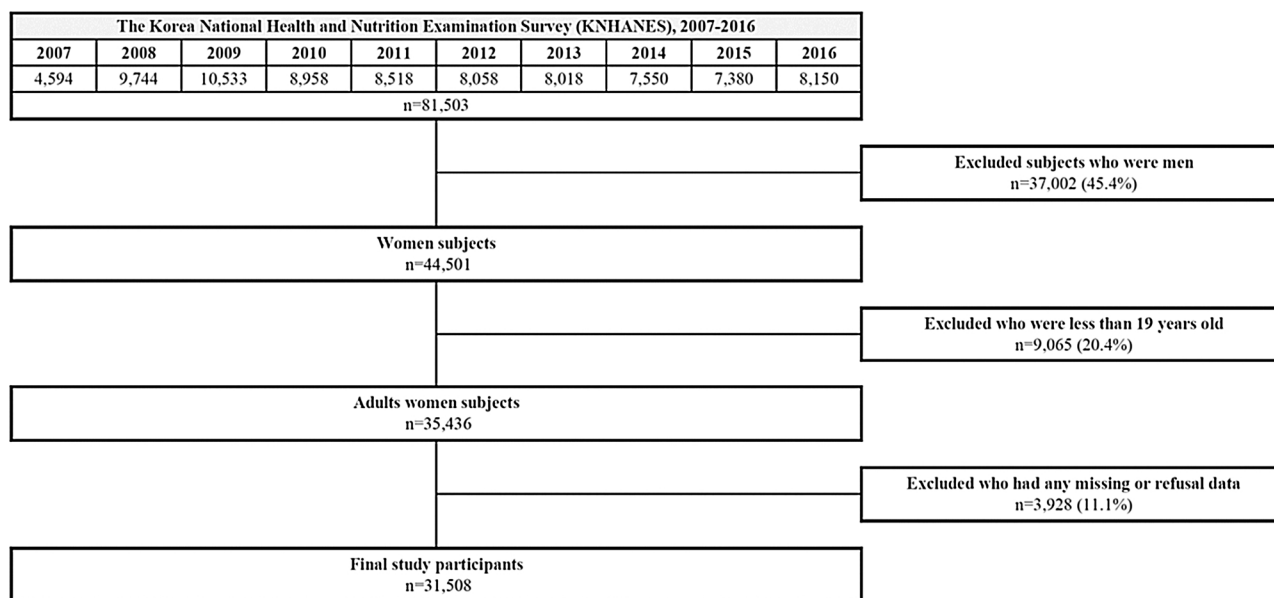


Fig. 1. Schematic diagram depicting study population.

2. Materials and methods

2.1. Data collection and study participants

The current study used the data from the Korea National Health and Nutrition Examination Survey (KNHANES), which is a series of nationally representative, cross-sectional, and population-based surveys of the health and nutritional status of Koreans by the Korea Centres for Disease Control and Prevention [11]. This study used the 2007–2016 KNHANES data, which included socioeconomic status and women's health specific survey. The study participants and exclusion criteria are presented in Fig. 1.

2.2. Menopausal status

Data of menopausal status were collected from the women's health survey of the KNHANES. The survey was conducted through a face-to-face interview by trained staff of the KNHANES. We used the self-reported questionnaire, which included whether the women had menopause or not and menopause age, to assess the menopausal status excluding artificial menopause. The menopausal status was divided into the following four categories: premenopausal (including pregnancy or breastfeeding), POI, early menopause, and menopause according to menopause age (none, < 40 years, 40–45 years, and > 45 years).

2.3. Socioeconomic status

The KNHANES calculated the household income level based on the standardised classification by sex, residence, and five-year age groups, and the value was compared with the standard income level of Korean citizens. The total household income was divided into quartiles from lower to higher. Educational level was classified as less than elementary, middle, high school, and college or more. Marital status was categorised as married and separated or never. The separated or never group also included divorced women. Occupation was categorised as unemployed, non-manual (white-collar workers), or manual (blue-collar workers). The unemployed women were classified as 'no job', students, and homemakers. Managers, experts and related workers, and office workers were classified as non-manual workers. Workers in sales and services, agriculture, forestry, fishery, engineering, assembling, technical work, and manual labour were classified as manual workers.

Residence was categorised as urban or rural according to the population size of the registered province.

2.4. Health behavioural status

Smoking status was categorised into the following three categories: none, past, and current. Current smokers were defined as those who were smoking during the survey. Past smokers were those who discontinued smoking but had smoked in the past. Those who smoked fewer than 100 cigarettes in their lifetime were classified under the none category. Drinking at least 5 glasses of alcohol 2 or more times per week was defined as severe alcohol drinking. Body mass index (BMI, m^2/kg) was categorised into three groups according to the standard for Asian population: underweight (< 18.5), normal (< 25), and obesity (≥ 25).

2.5. Statistical analyses

The weighted prevalence and standard errors (SEs) according to each menopausal status were calculated using a sampling clustering weight that was estimated from the KNHANES's complex sampling design to estimate the approximation of the South Korean participants. Chi-squared test with both weighted and unweighted values was used to compare the differences in socioeconomic characteristics according to menopausal status. The yearly trend of weighed prevalence and crude linear trend were calculated by menopausal status. The women had various ages during their participation to the KNHANES, which differed from the menopausal age. Thus, we used age during the survey period and adjusted logistic regression models to assess the relationship between socioeconomic characteristics and menopausal status. To estimate the effect of household income level on menopause age, we calculated the cumulative prevalence rate after stratification of household income level. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). For all statistical calculations, a p -value < 0.05 in both tails was considered statistically significant.

3. Results

A total of 31,508 Korean women were included in the final analysis after excluding men ($n = 37,002$), women aged < 19 years ($n = 9065$), or women with missing data or who refused ($n = 3928$) from the

Table 1
Weighted menopausal status per 100 adults aged 19 years or older in the Korean women according to socioeconomic status, 2007–2016.

	Total No. ^a	Premenopausal status			POI (Age < 40 year-old)			Early menopause (Age 40-45 year-old)			Menopause (Age > 45 year-old)		
		n ^a	% (SE) ^b	P-value ^c	n ^a	% (SE) ^b	P-value ^c	n ^a	% (SE) ^b	P-value ^c	n ^a	% (SE) ^b	P-value ^c
Overall	31,508	15,870	59.26 (0.42)		914	2.41 (0.10)		2,298	5.89 (0.15)		12,426	30.43 (0.37)	
Household income													
1st quartile	6,596	1,197	8.01 (0.33)	< .0001	400	38.97 (1.91)	< .0001	957	37.26 (1.29)	< .0001	4,042	29.07 (0.56)	< .0001
2nd quartile	8,000	3,893	25.58 (0.52)		215	24.14 (1.85)		587	25.82 (1.05)		3,305	26.73 (0.53)	
3rd quartile	8,401	5,293	33.21 (0.53)		159	19.59 (1.69)		387	18.25 (1.04)		2,562	22.11 (0.49)	
4th quartile	8,511	5,487	33.13 (0.63)		140	17.31 (1.51)		367	18.67 (1.17)		2,517	22.09 (0.57)	
Education													
Elementary school	9,636	646	3.44 (0.17)	< .0001	603	57.93 (2.08)	< .0001	1,519	60.12 (1.38)	< .0001	6,868	50.63 (0.66)	< .0001
Middle school	3,246	917	5.87 (0.23)		85	10.85 (1.36)		295	14.36 (0.99)		1,949	16.49 (0.42)	
High school	10,175	7,134	46.67 (0.54)		158	21.57 (1.73)		344	18.25 (1.13)		2,539	23.13 (0.52)	
College	8,451	7,173	44.01 (0.56)		68	9.64 (1.38)		140	7.27 (0.71)		1,070	9.74 (0.41)	
Marital status													
Married	21,624	11,414	67.59 (0.55)	< .0001	547	61.70 (1.86)	< .0001	1,361	59.84 (1.29)	< .0001	8,302	67.21 (0.56)	< .0001
Separated or never	9,884	4,456	32.41 (0.55)		367	38.30 (1.86)		937	40.16 (1.29)		4,124	32.79 (0.56)	
Occupation													
Unemployed	16,396	7,183	45.27 (0.52)	< .0001	547	60.02 (2.10)	< .0001	1,397	89.87 (1.27)	< .0001	7,269	56.90 (0.59)	< .0001
Non-manual	9,558	6,996	44.47 (0.51)		134	17.13 (1.72)		282	15.22 (0.96)		2,146	20.20 (0.49)	
Manual	5,554	1,691	10.26 (0.32)		233	22.85 (1.72)		619	24.91 (1.12)		3,011	22.90 (0.56)	
Residence													
Urban	24,836	13,488	85.91 (0.88)	< .0001	596	72.83 (1.90)	< .0001	1,831	71.65 (1.48)	< .0001	9,221	77.14 (1.03)	< .0001
Rural	6,672	2,382	14.09 (0.88)		318	27.17 (1.90)		767	28.35 (1.48)		3,205	21.86 (1.03)	
Smoking													
None	28,022	13,674	84.69 (0.37)	< .0001	789	85.11 (1.59)	< .0001	2,080	89.38 (0.81)	< .0001	11,470	91.47 (0.34)	< .0001
Past	1,741	1,054	7.44 (0.28)		70	10.37 (1.49)		112	5.57 (0.59)		505	4.69 (0.26)	
Current	1,745	1,142	7.87 (0.26)		46	4.52 (0.74)		106	5.05 (0.63)		451	3.84 (0.22)	
Drinking													
None	11,895	3,748	22.73 (0.41)	< .0001	508	51.94 (2.12)	< .0001	1,275	52.78 (1.32)	< .0001	6,364	48.32 (0.59)	< .0001
Moderate	18,287	11,094	70.31 (0.45)		389	46.28 (2.11)		982	44.59 (1.32)		5,822	49.36 (0.60)	
Severe	1,326	1,028	6.96 (0.25)		17	1.78 (0.50)		41	2.63 (0.46)		240	2.32 (0.18)	
Body mass index													
Underweight (< 18.5)	1,696	1,305	9.19 (0.29)	< .0001	36	4.04 (0.79)	< .0001	59	2.56 (0.38)	< .0001	296	2.35 (0.16)	< .0001
Normal (< 25)	20,657	11,215	70.22 (0.43)		533	57.05 (2.02)		1,365	60.70 (1.25)		7,544	61.33 (0.56)	
Obesity (≥ 25)	9,155	3,350	20.59 (0.39)		345	38.91 (1.99)		874	36.74 (1.24)		4,586	36.31 (0.56)	

POI: Premature ovarian insufficiency.

SE: standard errors.

^a Unweighted No.

^b Weighted prevalence.

^c Calculated using the F test.

81,503 baseline dataset of the KNHANES 2007–2016 (Fig. 1). The weighted prevalence and SE are demonstrated in Table 1. Most of the women were premenopausal (59.26%). The prevalence POI and early menopause was 2.41% and 5.89%, respectively. There was statistically significant increased prevalence of POI or early menopause in women with lower income, those with lower educational level, married, unemployed, those residing in urban areas, past smokers, none drinkers, and those with obesity.

In Fig. 2, according to the wave of the KNHANES, prevalence of the POI showed a plateau, which was closed to 2.5%. However, prevalence of early menopause or both early menopause and POI had an increased trend crudely according to survey year [beta (p-value) of linear trend was 0.2133 (0.0092) and 0.1996 (0.0103)].

As shown in Table 2, there was a statistically significant increased association between POI, early menopause, or both and socioeconomic status even after adjustment for the survey participating age. The odds ratio (OR) [95% confidence interval (CI)] for POI, early menopause, and both were 1.44 (1.16–1.78), 1.15 (1.00–1.32), and 1.25 (1.11–1.41), respectively, in the 1st quartile of household income. In terms of educational level, participants with less than elementary school level had higher OR in POI, early menopause, and both POI and early menopause compared to those with over college level. The manual worker group showed a higher OR (95% CI) than the unemployed group, in POI (1.29 (1.10–1.51)), early menopause (1.39 (1.26–1.39)), and both POI and early menopause (1.34 (1.23–1.45)). In the health behaviour, compared with the none smokers' group as

reference, OR (95% CI) of the POI was 1.86 (1.44–2.40) in the past smokers' group. The obesity group has higher OR (95% CI) than the normal body weight group in early menopause and both POI and early menopause with statistical significance.

Fig. 3 shows the results of cumulative prevalence rate by menopause age after household income-stratified analysis. Women who were in the 1st quartile of household income had earlier menopause age than those in the 4th quartile of household income.

4. Discussion

To our knowledge, this is the first report to describe the prevalence of POI and early menopause in a South Korean population. Moreover, we verified that the prevalence of both POI and early menopause was statistically significantly associated with lower socioeconomic status, such as those with lower household income and lower educational levels.

In our analysis, POI prevalence in Korea (2.41%) was two times more than those of other studies (about 1%), except for the result of a Shanghai study (2.8%) [12,13]. The most recent study conducted between 2003 and 2013 in Estonia reported a POI prevalence of 0.91% [14]. Even a previous report about premature menopause in a multi-ethnic population from the Study of Women's Health Across the Nation (SWAN) demonstrated the prevalence of POI in Chinese and Japanese populations to be 0.5% and 0.14%, respectively [15]. These values in Asian individuals were below average. Furthermore, they analysed that

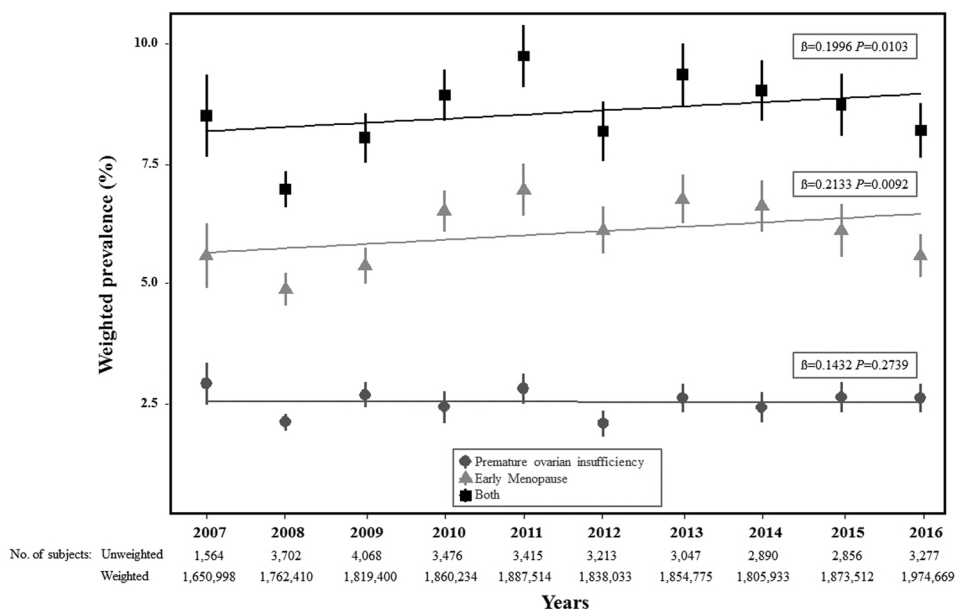


Fig. 2. Yearly weighed prevalence and crude linear trend of premature ovarian insufficiency, early menopause, and both in the Korean women aged 19 years and older, 2007–2016.

these values are consistent with the results that menopausal age of Japanese women in other reports from SWAN is significantly later. However, the number of Asian participants, consisting of Chinese and Japanese women aged 40–55 years, in this report is 1,319, which is far smaller than the 31,508 participants, consisting of Korean women aged

19 years or older, of the present study and 36,402 postmenopausal Chinese women aged 40–70 years enrolled in a previous Shanghai study. Moreover, the Asian study population of SWAN resided within USA. Considering that POI causes were multifactorial, despite that the participants had the same ethnicity, the results still varied because of

Table 2
The risk of association between menopausal status and socioeconomic status using age-adjusted logistic regression.

	Odds Ratio (95% confidence intervals)		
	POI	Early menopause	POI/Early menopause
House hold income			
1st quartile	1.44 (1.16-1.78)	1.15 (1.00-1.32)	1.25 (1.11-1.41)
2nd quartile	1.17 (0.94-1.46)	1.16 (1.01-1.33)	1.17 (1.03-1.32)
3rd quartile	1.10 (0.87-1.38)	1.00 (0.86-1.16)	1.03 (0.90-1.17)
4th quartile	Reference	Reference	Reference
Education			
Elementary school	1.75 (1.16-2.65)	1.94 (1.49-2.51)	1.87 (1.75-2.97)
Middle school	1.42 (0.92-2.20)	2.23 (1.69-2.92)	1.92 (1.37-2.38)
High school	1.41 (0.98-2.03)	1.49 (1.18-1.90)	1.45 (0.99-1.68)
College	Reference	Reference	Reference
Marital status			
Married	Reference	Reference	Reference
Separated or never	0.95 (0.82-1.09)	0.91 (0.83-1.01)	0.94 (0.86-1.02)
Occupation			
Unemployed	Reference	Reference	Reference
Non-manual	1.03 (0.83-1.27)	0.93 (0.80-1.07)	0.96 (0.85-1.09)
Manual	1.29 (1.10-1.51)	1.39 (1.26-1.55)	1.39 (1.26-1.52)
Residence			
Urban	Reference	Reference	Reference
Rural	1.37 (1.18-1.58)	1.26 (1.15-1.39)	1.34 (1.23-1.45)
Smoking			
None	Reference	Reference	Reference
Past	1.86 (1.44-2.40)	1.13 (0.92-1.39)	1.42 (1.19-1.69)
Current	1.07 (0.79-1.46)	0.94 (0.76-1.17)	1.00 (0.83-1.20)
Drinking			
None	Reference	Reference	Reference
Moderate	0.94 (0.81-1.09)	1.01 (0.92-1.11)	0.99 (0.91-1.07)
Severe	0.95 (0.58-1.57)	1.07 (0.78-1.48)	1.04 (0.79-1.38)
Body mass index			
Underweight (< 18.5)	1.19 (0.84-1.69)	0.74 (0.56-0.98)	0.88 (0.70-1.11)
Normal (< 25)	Reference	Reference	Reference
Obesity (≥25)	1.13 (0.98-1.30)	1.10 (1.00-1.21)	1.11 (1.03-1.21)

POI: Premature ovarian insufficiency.
Bold are statistical significance.

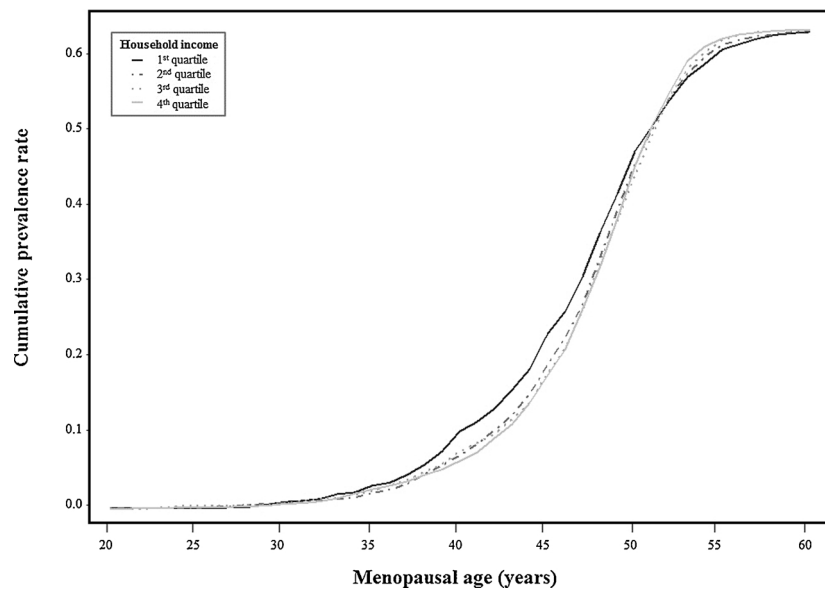


Fig. 3. Cumulative prevalence rate according to menopausal age and household income level, 2007–2016.

the different environment conditions that they lived in.

Early menopause is defined as menstrual cessation in women aged 40–44 years. Prevalence of early menopause in our data is 5.89%. In 1986, Coulam et al. reported that the prevalence of early menopause is ten times higher than that of POI [12]. In 2002, the proportion of women who experienced early menopause among SWAN participants is 4.2% [15], which is similar to the results of other previous studies [16,17]. They reported a range of 3.3% to 5%. In our study, we showed yearly weighed prevalence and crude linear trend of POI or early menopause in Korean women aged 19 years and older from 2007 to 2016. The prevalence of POI is constant, whereas that of early menopause tends to increase yearly. We found no recent studies demonstrating the trend prevalence of POI or early menopause. Although accumulating more data, our analysis suggests that early menopause women need to be informed regarding the long-term health risks of POI, which include overall mortality, cardiovascular diseases, neurological diseases, psychiatric diseases, osteoporosis, and other sequelae [4].

The association between POI and early menopause and socioeconomic status was also analysed. Women with lower household income and educational levels were significantly associated with increased prevalence of POI and early menopause in the current analysis. Several reports have shown that lower socio-economic status was associated with shortening of menopausal age [15,18–20]. In general, socioeconomic status has been positively correlated with individual and public health status [21]. In the individual level, a possible explanation for this association could be that higher socioeconomic status could bring better opportunities to protect them against unhealthy conditions by influencing lifestyle behaviours, positive attitudes about health, and access to preventive health services or information [22]. In the public level, it seems possible that better health status among high socioeconomic population is due to a higher likelihood of having safe and clean living conditions, which could affect health, especially in developing countries. In developed countries, the relationship between socioeconomic status and health status may be explained by the psychosocial factors, such as social dominance, autonomy, and the quality of social relations [23]. The shortening of menopause age is caused by multiple factors. Based on our results, the abovementioned socioeconomic effects on health could be a key aspect of women's health, especially on ovarian function.

One unanticipated finding was the occupational difference of risk of POI and early menopause. In general, workers are healthier than unemployed individuals in most health areas. This trend is very strong; in

fact, it is termed as 'healthy worker effect' in epidemiology [24]. However, the current analysis indicated that the manual worker group are more vulnerable to POI and early menopause even after adjustment for age, compared to the unemployed group. Considering the healthy worker effects, significantly increased risk of POI and early menopause linked to employment status could be underestimated. To date, only a limited number of occupational characteristics related to menopausal status has been identified. Further studies regarding the role of occupation in menopausal status would be worthwhile.

Smoking is a well-known risk factor of POI and early menopause [25–28]. Although our cross-sectional study reporting that past smoking is significantly related to premature ovarian insufficiency does not prove a causal relationship, some articles already showed that active smoking leads to diminished ovarian reserve [29–31]. In our analysis, we cannot confirm the association of alcohol drinking and POI or early menopause. Based on previous reports, long-term and more-than-moderate consumption of alcohol affect ovarian aging [31,32]. In 2018, a report analysing 11 prospective studies about BMI and age at natural menopause was published [33]. They reported that underweight women have twice the risk of early menopause, whereas obese women also have a high risk of early menopause, but was not statistically significant. We confirm that BMI is significantly associated with early menopause in women; however, in the underweight group, BMI was not associated with early menopause, unlike the previous results.

This is the first report about the prevalence of POI in Korea with socioeconomic factors. It may contribute in clarifying the difference of POI or early menopause according to ethnicities. However, these findings need to be interpreted with caution due to the following limitations. First, this study used a cross-sectional design with unmatched survey time and menopause period, in which causal relationships between menopause status and socioeconomic status remain unclear. A longitudinal study, such as well-controlled randomised study, is necessary to reveal any specific cause-and-effect factors between socioeconomic characteristics and POI and early menopause. Second, our study relied on subjective self-questionnaires for assessing the status of menopause without a specific medical examination for either condition. Although it makes the prevalence of menopause status from current study less generalisable, we excluded artificial menopause; and it is highly acceptable and validated in many studies to assess menopause status and age using simple self-reported questionnaires, similar to those used in the KNHANES [34,35]. Third, KNHANES did not conduct survey for the specific causes of POI such as autoimmune disease (type

1 diabetes or Addison's disease), genetic cause (Turner syndrome), infection (mumps or tuberculosis), and surgery (oophorectomy). Further work is needed to fully investigate the causes of POI.

In conclusion, the prevalence of POI in the Korean population is almost twice compared to that reported in a previous study. The lower socio-economic status is closely associated with increased risk for POI and early menopause. Further studies will be warranted to determine the difference of prevalence and causes of menopausal status according to the socioeconomic status.

Contributors

Young-Mee Lim conceptualised the study, analysed the data, and drafted and revised the manuscript.

Kyungah Jeong conducted the analysis and drafted the manuscript.

Sa Ra Lee contributed to developing the study design and revised the manuscript.

Hye Won Chung contributed to developing the study design and revised the manuscript.

Wanhung Lee conceptualised the study, analysed the data, and drafted and revised the manuscript.

Wanhung Lee is the corresponding author of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis.

All authors read and approved the final version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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All aspects of study design, data analysis, and manuscript writing were independent of funders.

Ethical approval

The study data were anonymised prior to release to the public from the Korea Centres for Disease Control and Prevention. This current analysis was approved by the Institutional Review Board of the Korea Centers for Disease Control & Prevention (IRB Nos. 2007-02-CON-04-P 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C, 2013-07CON-03-4C, 2013-12EXP-03-5C, and 2015-01-02-6C).

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

All data and related information of current study are accessible on the KNHANES website (<https://knhanes.cdc.go.kr/knhanes/index.do>).

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