



# BMJ Open Population-based study of the association between asthma and exogenous female sex hormone use

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## ABSTRACT

**Objectives** Several studies have suggested the influence of exogenous hormones on asthma, but the results are still conflicting. Moreover, there has been little associated research on Asian population. This study aimed to assess the association between use of exogenous female sex hormones and asthma in Korean women.

**Design** Korea National Health and Nutrition Examination Survey (KNHANES) is a nationwide programme to assess national health and nutritional status in Korea. A population-based study was conducted to analyse the relationship between self-reported asthma and exogenous hormones using the KNHANES between 2007 and 2012.

**Participants** The study sample included 6874 premenopausal and 4912 postmenopausal women aged 30–65.

**Outcome measures** KNHANES data comprised health interviews and physical examinations. Questionnaires regarding asthma, reproductive factors and exogenous hormones were included.

**Results** Among postmenopausal women, 3.4% reported doctor-diagnosed asthma. Hormone replacement therapy (HRT) was associated with increased odds of doctor-diagnosed asthma (OR 1.56; 95% CI 1.04 to 2.35), while the association between HRT and wheeze in the last 1 year was not significant (OR 1.37; 95% CI 0.95 to 1.96). In premenopausal women, the prevalence of asthma was 2.3%. Use of oral contraceptives (OCs) was associated with an increased odds of doctor-diagnosed asthma (OR 1.67; 95% CI 1.01 to 2.76) and wheeze in the last 1 year (OR 1.88; 95% CI 1.31 to 2.69). These associations were dominant among non-obese women (body mass index <25 kg/m<sup>2</sup>; OR 2.36; 95% CI 1.34 to 4.17 for asthma and OR 2.15; 95% CI 1.43 to 3.23 for wheeze).

**Conclusions** HRT and OCs were associated with increased asthma in postmenopausal and premenopausal women, respectively. The association between OC use and asthma was strong in non-obese premenopausal women.

## INTRODUCTION

Over 300 million people are estimated to suffer from asthma worldwide.<sup>1 2</sup> Asthma is a chronic inflammatory airway disease that can have serious respiratory symptoms like shortness of breath and an adverse impact on quality of life.<sup>1</sup> Asthma is more common and severe in postpubertal women than in men.<sup>3–6</sup>

## Strengths and limitations of this study

- Use of reliable large nationwide data representing the general population in Korea.
- The first population-based study to investigate the association between exogenous female sex hormones and asthma in an Asian population.
- Large samples including premenopausal and postmenopausal women.
- Not possible to establish a true cause and effect relationship as a cross-sectional observational design.
- Insufficient information about exogenous female sex hormones and asthma control.

Additionally, symptoms of asthma have a greater impact on the quality of life in women than in men.<sup>4 6</sup> This is likely to be caused by female sex hormones and hormonal changes through the female reproductive life including menarche, menstruation cycle, pregnancy and menopause.<sup>3–6</sup> Although the underlying mechanisms have not been clearly defined, there have been several studies verifying the association between reproductive factors and asthma among women.<sup>7–10</sup> Several studies have reported a positive association between early menarche and risk of asthma.<sup>7–9</sup> A recent meta-analysis revealed that menopause was associated with an increased risk of asthma compared with premenopause.<sup>10</sup>

Endogenous female sex hormones appear to influence asthma prevalence in women, and several studies have suggested that exogenous sex hormones also affect it. Oral contraceptives (OCs) and hormone replacement therapy (HRT) containing exogenous sex hormones have been widely used and have both beneficial and harmful effects on several medical conditions. Although relatively less attention has been paid to this association, there have been reports on the impact of OCs and HRT on asthma. Exogenous sex hormones, such as OCs and HRT, for menopausal women have reportedly increased odds

of asthma and its severity.<sup>11–16</sup> In contrast, several studies reported conflicting results of no association between OCs and asthma or lesser prevalence of asthma in those using OCs.<sup>17 18</sup> Furthermore, the occurrence of asthma and its characteristics may vary depending on races/ethnicities and social/environmental factors. There have been very few studies on the relationship between asthma and exogenous sex hormones in Asia to date. Therefore, we investigated the association between use of exogenous sex hormones and asthma in women using the Korea National Health and Nutrition Examination Survey (KNHANES) data designed to assess national health and nutrition levels accurately.

## METHODS

### Study design and subjects

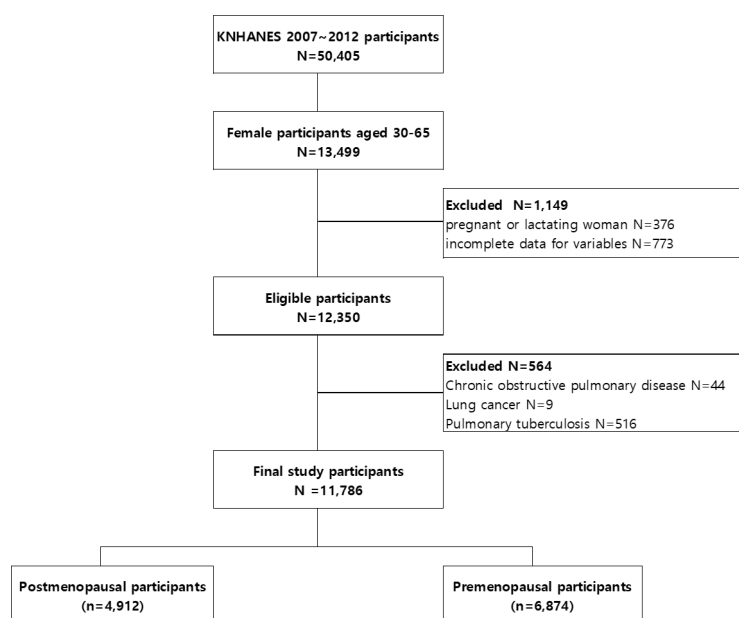
The data used in this study were collected from the 2007–2012 KNHANES, which is a nationwide cross-sectional survey designed to evaluate national health and nutrition status and was conducted by the Korean Centers for Disease Control and Prevention for Health Statistics. The survey consists of a health interview, nutritional survey and health examination. This is a population-based national study of a representative sample of Korea that includes approximately 10 000 individuals each year as a new survey sample. A stratified, multistage, cluster sampling design with proportional allocation based on geographic area, sex and age from the National Census Registry was used for the selection of survey participants to represent the entire non-institutionalised civilian population in Korea. The primary sample units (PSUs) were selected from a sampling frame of all census blocks or resident registration addresses. Each PSU consisted of approximately 50–60 households, and final 20 target households

were sampled for each PSU using systematic sampling. The final stage of selection occurred in the household, where all members aged 1 year and above were targeted.<sup>19</sup>

The sample included 13 499 women aged 30–65 years. Among them, 376 women who were pregnant or lactating were excluded from the study. The study further excluded 564 women who were diagnosed with chronic obstructive lung disease, pulmonary tuberculosis and lung cancer. Furthermore, 773 women who did not complete the health survey sections related to asthma and exogenous sex hormones were excluded. The final study sample for current analysis comprised 6874 premenopausal and 4912 postmenopausal women (figure 1).

### Questionnaire and examination

Self-reported answers to the questionnaire were collected and evaluated. The questionnaire contained data on items related to asthma such as doctor-diagnosed asthma, wheeze and treatment of asthma. The survey questions included: ‘Have you ever had asthma diagnosed by a doctor?’, ‘Have you had wheeze in your chest in the last 12 months?’ and ‘Have you been treated for asthma in the last 12 months?’. The questionnaire concerning hormonal status in women was also included. Questions on OC use, current pregnancy, menopausal status and use of HRT were included. The use of OCs or HRT was determined based on self-reported answers to the questions: ‘Have you ever used HRT?’ and ‘Have you ever taken OCs?’. Menopause was defined at the interview as no menstruation in the past 12 months. The types of menopause that can be divided into natural and surgical menopause were ascertained. Additionally, demographic information, smoking status and residential status were ascertained. Smoking status was divided into three groups: non-smokers, current smokers and ex-smokers.



**Figure 1** Flow chart for selection of the participants in the present study. KNHANES, Korea National Health and Nutrition Examination Survey.

Non-smokers included both never smokers and smokers who had smoked under 100 cigarettes in their lifetime. Residential status was classified into rural or urban areas. Anthropometric measurements for height and weight were performed by trained examiners. Body mass index (BMI) was calculated as weight in kilograms per square of height in metres ( $\text{kg}/\text{m}^2$ ).

### Statistical analysis

All analyses in the study were performed considering the complex survey design to acquire nationally representative estimates. To analyse the sample over multiple years, we averaged the survey sample weights over the sampled year. The results of the analyses were presented as weighted mean (SEM) or sample frequency (weighted proportion) for continuous and categorical variables, respectively. Logistic regression analyses were applied to evaluate the association between use of exogenous sex hormones and asthma. Multiple logistic regressions were performed with each of the asthma indicators as the dependent variable, use of hormones as the independent variable of interest, and age, place of residence, smoking status and BMI as the covariates. The type of menopause was added as a covariate in the models for HRT use. The ORs and 95% CIs for OR were calculated using participants not using hormones as the reference. Additional analyses for odds of asthma were conducted in each subgroup stratified according to obesity or residence. We evaluated interactions by multiple logistic regression model including interaction term between stratification group (BMI, region, smoking) and HRT use and OC use. The SAS V.9.4 (SAS Institute) survey procedure was used for statistical analysis using sample weights. All reported p values were based on two-sided tests of significance and a p value  $<0.05$  was considered statistically significant.

### Patient and public involvement

Patients or the public were not involved in this specific research project.

## RESULTS

### Characteristics of the study population

The prevalence of doctor-diagnosed asthma in 4912 postmenopausal women and 6874 premenopausal women was 3.4% and 2.2%, respectively, while incidence of self-reported wheeze was 6.1% and 3.3%, respectively, and self-reported treatment of asthma was reported in 1.2% and 0.4% of the study population, respectively. The median age of the postmenopausal and premenopausal women was 56.0 and 40.4 years, respectively. Among the postmenopausal women, 1037 (21%) had used HRT, while 983 (14.3%) premenopausal women were on OCs. The general characteristics of women consuming or not consuming exogenous sex hormones are shown in [table 1](#). Postmenopausal women taking HRT were more likely to have a lower BMI, and to live in urban areas than those not taking HRT. Premenopausal women taking OCs were more likely to be older and to be smokers than those not taking OCs.

### HRT and self-reported asthma in postmenopausal women

The prevalence of doctor-diagnosed asthma in postmenopausal women taking HRT and not taking HRT was 4.4% and 3.0%, respectively. Significant association between HRT use and doctor-diagnosed asthma (OR 1.56; 95% CI 1.04 to 2.35;  $p=0.032$ ) was found among menopausal women, after adjusting for age, place of residence, smoking status, BMI and menopausal type. HRT use showed a tendency to increase the odds of wheeze (OR 1.37; 95% CI 0.95 to 1.96;  $p=0.088$ ), although it was not significant ([table 2](#)). When stratified by BMI, use of HRT showed a tendency to increase odds of doctor-diagnosed

**Table 1** Characteristics of premenopausal and postmenopausal women according to exogenous hormone consumption

Characteristics	Postmenopausal women (n=4912)			Premenopausal women (n=6874)		
	HRT (n=1037)	No HRT (n=3875)	P value	OCs (n=983)	No OCs (n=5891)	P value
Age (years), mean (SE)	56.1 (0.21)	55.9 (0.12)	0.428	41.0 (0.25)	40.2 (0.11)	0.001
BMI ( $\text{kg}/\text{m}^2$ ), mean (SE)	24.1 (0.11)	24.5 (0.07)	0.002	23.2 (0.13)	23.1 (0.06)	0.404
Obesity (BMI $\geq 25$ ), n (%)	356 (32.5)	1524 (39.8)	$<0.001$	243 (24.9)	1364 (24.2)	0.700
Smoking, n (%)			0.753			$<0.001$
Current smoker	34 (4.7)	160 (5.0)		92 (10.0)	240 (5.1)	
Ex-smoker	18 (2.0)	57 (1.6)		49 (5.8)	166 (3.1)	
Non-smoker	963 (93.2)	3594 (93.4)		811 (84.2)	5269 (91.8)	
Place of residence, n (%)			$<0.001$			0.714
Urban	838 (83.0)	2800 (76.5)		806 (83.8)	4953 (84.4)	
Rural	199 (17.0)	1075 (23.5)		177 (16.2)	938 (15.6)	

Values are weighted mean (SEM) or frequency (weighted proportion).

BMI, body mass index; HRT, hormone replacement therapy; OC, oral contraceptive.

**Table 2** Asthma according to use of HRT in postmenopausal women

	No HRT (n=3875)	HRT (n=1037)	Crude OR (95% CI)	Adjusted OR* (95% CI)	P value*
	n (%)	n (%)			
Doctor-diagnosed asthma	115 (3.0)	51 (4.4)	1.49 (1.004 to 2.22)	1.56 (1.04 to 2.35)	0.032
Treatment of asthma	44 (1.2)	14 (1.3)	1.07 (0.54 to 2.10)	1.16 (0.59 to 2.28)	0.663
Wheeze	233 (5.7)	69 (7.7)	1.39 (0.97 to 1.98)	1.37 (0.95 to 1.96)	0.088

n (%) represents sample frequency (weighted proportion).

\*Adjusted for age, place of residence, smoking status, body mass index and menopausal type.

HRT, hormone replacement therapy.

asthma, wheeze and treatment of asthma among both obese and non-obese women, although it was not significant. When stratified by place of residence, significant association between HRT use and increased incidence of doctor-diagnosed asthma (OR 1.58; 95% CI 1.01 to 2.48;  $p=0.048$ ), and non-significant association between HRT use and increase in wheeze (OR 1.42; 95% CI 0.94 to 2.14;  $p=0.095$ ) were found in urban areas (table 3). Interaction between region and HRT use was not significant. Significant association between HRT use and asthma (OR 1.71; 95% CI 1.14 to 2.58;  $p=0.010$ ) was found in non-smokers.

#### OCs and self-reported asthma in premenopausal women

The prevalence of doctor-diagnosed asthma in premenopausal women taking OCs and not taking OCs was 3.4% and 2.0%, respectively. Use of OCs was significantly associated with higher odds of doctor-diagnosed asthma (OR 1.67; 95% CI 1.01 to 2.76;  $p=0.045$ ) and wheeze (OR 1.88; 95% CI 1.31 to 2.69;  $p<0.001$ ) after adjusting for age, place of residence, smoking status and BMI (table 4). When stratified by BMI, use of OCs was more strongly associated with doctor-diagnosed asthma (OR 2.36; 95% CI 1.34 to 4.17;  $p=0.003$ ) and wheeze (OR 2.15; 95% CI 1.43 to 3.23;  $p<0.001$ ) in non-obese women. However, there was no significant association between OCs and doctor-diagnosed asthma and wheeze in obese women. The interaction of OC use with BMI was significant ( $p=0.022$ ). In urban

areas, use of OCs was significantly associated with wheeze (OR 1.98; 95% CI 1.31 to 3.01;  $p<0.001$ ), and showed a non-significant increase in doctor-diagnosed asthma (OR 1.67; 95% CI 0.93 to 3.00;  $p=0.088$ ) (table 5). Interaction was not significant with respect to place of residence.

#### DISCUSSION

This nationwide study based on the representative sample population of Korea showed that use of exogenous female sex hormones was significantly associated with an increased odds of asthma, after adjusting for potential confounding factors. In postmenopausal women, HRT was associated with an increased prevalence of asthma. Additionally, OC use was associated with increased asthma in premenopausal women, especially in non-obese women.

Our results agree with those of previous reports. In the US Nurses' Health Study, postmenopausal women who use HRT had a significantly higher risk of asthma than premenopausal women. HRT increased the risk of asthma compared with postmenopausal women not undergoing HRT.<sup>11</sup> In addition, several recent studies have shown that HRT is associated with an increased asthma incidence and symptoms.<sup>11–15 20</sup> In a recent meta-analysis, McCleary *et al* also reported that HRT was associated with an increased

**Table 3** Asthma according to use of HRT, stratified BMI and residential area in postmenopausal women

	No HRT (n=3875)	HRT (n=1037)	Crude OR (95% CI)	Adjusted OR* (95% CI)	P value*
	N (%)	n (%)			
<b>BMI <math>\geq 25</math> kg/m<sup>2</sup></b>	<b>1524</b>	<b>356</b>			
Doctor-diagnosed asthma	50 (3.3)	23 (5.4)	1.69 (0.92 to 3.09)	1.52 (0.79 to 2.92)	0.206
Treatment of asthma	15 (0.9)	5 (1.4)	1.64 (0.54 to 4.95)	1.78 (0.58 to 5.45)	0.311
Wheeze	120 (6.9)	32 (10.5)	1.58 (0.93 to 2.69)	1.41 (0.83 to 2.40)	0.201
<b>BMI <math>&lt; 25</math> kg/m<sup>2</sup></b>	<b>2342</b>	<b>679</b>			
Doctor-diagnosed asthma	65 (2.9)	28 (4.0)	1.41 (0.81 to 2.47)	1.48 (0.84 to 2.62)	0.174
Treatment of asthma	29 (1.4)	9 (1.2)	0.85 (0.37 to 1.98)	0.92 (0.40 to 2.12)	0.852
Wheeze	113 (4.9)	37 (6.4)	1.33 (0.82 to 2.14)	1.32 (0.81 to 2.16)	0.267

n (%) represents sample frequency (weighted proportion).

\*In the subgroups stratified by BMI, adjusted for age, place of residence, smoking status and menopausal type; p value for adjusted OR.

BMI, body mass index; HRT, hormone replacement therapy.



**Table 4** Asthma according to use of OCs in premenopausal women

	No OCs (n=5891)	OCs (n=983)	Crude OR (95% CI)	Adjusted OR* (95% CI)	P value*
	N (%)	n (%)			
Doctor-diagnosed asthma	122 (2.1)	26 (3.4)	1.67 (1.03 to 2.73)	1.67 (1.01 to 2.76)	0.045
Treatment of asthma	27 (0.5)	3 (0.7)	1.45 (0.41 to 5.11)	1.71 (0.49 to 5.93)	0.398
Wheeze	176 (2.9)	48 (5.6)	1.96 (1.37 to 2.81)	1.88 (1.31 to 2.69)	0.001

n (%) represents sample frequency (weighted proportion).

\*Adjusted for age, place of residence, smoking status, body mass index and menopausal type.

.OC, oral contraceptive.

odds of current asthma (OR 1.42; 95% CI 1.18 to 1.70) and wheeze (OR 1.40; 95% CI 1.22 to 1.61).<sup>10</sup> The OR in this meta-analysis was very similar to the OR in our study. Similar to the Copenhagen City Heart Study, our study also showed that asthma was related to HRT in non-smokers.<sup>18</sup>

The results of studies on the use of hormonal OC have been inconsistent with reports of both increased and decreased risks of asthma. Unlike HRT, Lange *et al* reported no relationship between use of OCs and asthma.<sup>18</sup> In another cross-sectional study, Nwaru *et al* reported that use of OCs was associated with a reduced risk of asthma, whereas several studies have suggested an association with increased risk.<sup>21 22</sup> A study conducted in Japan suggested that maternal use of OCs was associated with asthma (OR 1.65; 95% CI 1.02 to 2.65) and wheeze (OR 1.59; 95% CI 1.01 to 2.50) in children.<sup>23</sup> Our study results also revealed similar findings that OC consumption was associated with an increased odds of asthma and wheeze in premenopausal women.

Further, we observed that the association between asthma and OCs was present in non-obese women (BMI <25 kg/m<sup>2</sup>). An OR value >2.0 in asthma, wheeze and treatment of asthma indicates a very high association with OCs. In a Nordic-Baltic population study, the association was not significant in lean women, which could be due to small samples.<sup>22</sup> Interestingly, one study reported a

higher postmenopausal asthma risk in non-obese women than in obese women using HRT. This and our result could be explained by van den Berge's suggestion of a possible relevant relationship between asthma, exogenous sex hormones and metabolic factors. He suggested that in non-obese women without insulin resistance, proinflammatory effects of oestrogen could predominate. On the contrary, in obese women, the proinflammatory effects of oestrogen could be counterbalanced by an increased insulin resistance.<sup>24</sup>

To the best of our knowledge, this is the first nationwide population-based study to evaluate the association between exogenous sex hormones and asthma in an Asian population. Asthma prevalence and symptoms vary across racial and ethnic groups. Several global reports found that Asians have the lowest rate of asthma prevalence and symptoms.<sup>25 26</sup> Genetic predisposition and environments, which are core factors in the pathophysiology of asthma, could vary in racial/ethnic groups and different ethnicities will provide different clinical outcomes and medical issues. Thus, a study evaluating the association between use of OCs and HRT and asthma was required in Asian countries. In our study, the association between HRT and asthma in Korea was similar to that in previous western studies. In contrast to inconsistent findings in the western studies, a positive association between OCs and asthma was shown, and was especially strong in non-obese Korean women.

**Table 5** Asthma according to use of OCs, stratified BMI and residential area in premenopausal women

	No OCs (n=5891)	OCs (n=983)	Crude OR (95% CI)	Adjusted OR* (95% CI)	P value*
	N (%)	n (%)			
<b>BMI ≥25 kg/m<sup>2</sup></b>	<b>1364</b>	<b>243</b>			
Doctor-diagnosed asthma	42 (3.3)	6 (2.2)	0.65 (0.25 to 1.71)	0.63 (0.24 to 1.69)	0.362
Treatment of asthma	9 (0.7)	0 (0.0)	–	–	–
Wheeze	56 (4.1)	11 (5.7)	1.43 (0.65 to 3.13)	1.34 (0.60 to 2.98)	0.472
<b>BMI &lt;25 kg/m<sup>2</sup></b>	<b>4511</b>	<b>736</b>			
Doctor-diagnosed asthma	80 (1.7)	20 (3.9)	2.34 (1.35 to 4.07)	2.36 (1.34 to 4.17)	0.003
Treatment of asthma	18 (0.4)	3 (0.9)	2.32 (0.64 to 8.49)	2.87 (0.78 to 10.52)	0.112
Wheeze	120 (2.6)	37 (5.6)	2.24 (1.48 to 3.38)	2.15 (1.43 to 3.23)	<0.001

n (%) represents sample frequency (weighted proportion).

\*In the subgroups stratified by BMI, adjusted for age, place of residence and smoking status; p value for adjusted OR.

BMI, body mass index; OC, oral contraceptive.



Experimental evidence has suggested that female sex hormones influence the airway inflammation and airway diseases such as asthma;<sup>27</sup> however, the effects of these hormones are complicated and incompletely understood. Study by Newcomb showed that interleukin (IL)-17A-producing memory TH17 cells increased in women with severe asthma compared with those in men. And it also indicated that oestrogen and progesterone enhanced TH17 cell differentiation and increased the IL-17A-mediated neutrophilic airway inflammation in mice.<sup>28</sup> Oestrogen has been shown to increase IL-4 and IL-13 production in human studies as well.<sup>29</sup> These cytokines are related to allergic airway inflammation of asthma.<sup>28</sup> These results demonstrate the importance of female hormones in inducing allergic airway inflammation. These experimental studies provide a possible mechanism for explaining our findings on the significant relationship between exogenous sex hormones and asthma.

There are several weaknesses of our study. First, the definition of asthma is solely based on self-reported answers to questions; doctor-diagnosed asthma, wheeze in breathing in the last 1 year and current treatment. These are subject to misclassification bias. However, the questionnaire responses of physician-diagnosed asthma used in our study have been the most widely accepted, simple and validated method for asthma estimates in epidemiological studies.<sup>30</sup> Second, the study does not provide information about type and dose of exogenous female hormone. However, there were no differences in asthma prevalence regarding the type of HRT and OC in previous studies.<sup>12 17</sup> Third, as a cross-sectional study, it is not known whether the HRT or OC came before or after the asthma. Fourth, we could not investigate asthma control and exacerbation due to insufficient data about asthma medication and asthma-related healthcare utilisation. Fifth, we lack data on several potential confounders including socioeconomic status and family history of asthma. Despite these limitations, this study is a reliable national population study based on the KNHANES data representing the general population in Korea, with its strength being that data of both OCs and HRT were collected in premenopausal and postmenopausal women.

In conclusion, our study demonstrated a positive association between use of exogenous female sex hormones and asthma in large nationally representative data of Korea. In postmenopausal women, HRT was associated with increased prevalence of asthma. Moreover, use of OCs was associated with increased asthma in non-obese premenopausal women. To affirm causality and clarify the impact of exogenous sex hormones on asthma, further longitudinal studies with detailed information are required.

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conceptualisation, data curation, and review and editing of the draft manuscript. SIC contributed to data curation, visualisation, and review and editing of the draft manuscript. EJJ contributed to investigation, and review and editing of the draft manuscript. JC contributed to data curation, formal analysis and methodology. WJJ is the guarantor of this work.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** The survey adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all KNHANES participants. The research protocol was approved by the Institutional Review Board (No 2019AN0048) of Anam Hospital, Korea University. The requirement for informed consent for this study was exempted because it was a secondary analysis using the pre-existing KNHANES data set.

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**Data availability statement** No data are available. No additional data available.

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