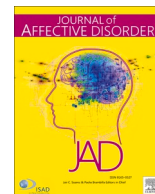




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Research paper

# Association between menstrual cycle irregularity and suicidal ideation among Korean women: Results from the Korea national health and nutrition examination survey (2010–2012)

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## ABSTRACT

**Background:** We aimed to evaluate the association between menstrual cycle irregularity and suicidal ideation in Korean women.

**Methods:** Data on 5,606 women from the 2010–2012 Korea National Health and Nutrition Examination Survey, a population-based cross-sectional study, were included. Menstrual cycle irregularity, suicidal ideation, current occupational status, age at menarche, education level, household income, and marital status were assessed through questionnaires with trained interviewers. A multivariate logistic regression analysis was performed after adjusting for age, socioeconomic status, smoking and drinking status, age at menarche, comorbid diseases, and physical activity.

**Results:** In the multivariate-adjusted models, we found significant associations between menstrual cycle irregularity and suicidal ideation (odds ratio [OR], 95% confidence interval [CI] = 1.44 [1.14–1.82]). This association was particularly noticeable in women aged 12 to 29 years (OR [95% CI] = 1.45 [1.04–2.03]), in those who had menarche at a relatively early age (aged 8–13 years) (OR [95% CI] = 1.60 [1.15–2.23]), and in those who were currently employed (OR [95% CI] = 1.46 [1.05–2.04]).

**Limitations:** Suicidal ideation was evaluated based on the participants' self-reports, and were therefore subjective in nature. Additionally, due to the cross-sectional design and use of retrospective data, causal relationships could not be drawn.

**Conclusion:** Women with irregular menstrual cycles were 1.42 times more likely to have suicidal ideation than those with regular cycles. More attention should be paid to menstrual cycle irregularity when attempting to improve levels of suicidal ideation.

## 1. Introduction

According to the World Health Organization, nearly 800,000 people die from suicide every year (WHO, 2019). The prevalence of suicidal ideation among women around the world is 2.2% to 2.4% (Borges et al., 2010), while that of Korean women is 20.4% (Park and Choi, 2013). In Korea, women are more than three times more likely to have suicidal ideation than men (Lee and Ham, 2018). Moreover, over the past 20 years, the suicide rate has increased 4.12 times for women and 3.44 times for men (Lim and Park, 2016). Several studies have interpreted these findings to be associated with female-specific events such as being

married, feeling hopeless (Xu et al., 2015), and depression (Lamis and Lester, 2013). In addition, subjective happiness and economic status have been shown to affect suicidal ideation among Korean women (Jo and Kim, 2016).

Women are particularly vulnerable to mental health issues, especially at times of significant hormonal changes, such as the transitions between pre-menstruation and menstruation and between menstruation and menopause. Several articles have been published considering that changes in sex hormones in female reproductive events could affect neurochemical pathways associated with mental health (Jung et al., 2015). An analysis of data on women aged 18 to 55 who participated in

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the 2002 National Health Interview Survey showed that about 19% of women experienced menstruation-related problems and reported that they had more frequent issues with mental health such as anxiety, depression, hopelessness, and worthlessness over the previous 12 months than women with no menstruation-related problems (Strine et al., 2005). The reproductive life cycle is characterized and influenced by the rhythm of the menstrual cycle and its related hormonal fluctuations. Any abnormalities in this rhythm may affect a variety of aspects of women’s lives. In particular, there seems to be a reciprocal relationship between mental health and reproductive features, such as the menstrual cycle phase and menstrual flow regularity (Akdeniz et al., 2010). Moreover, the prevalence of completed and attempted suicide is more common in the early menstrual and luteal phases (Baca-Garcia et al., 2000; Saunders and Hawton, 2006).

The few studies that have evaluated the association between menstrual cycle irregularity and suicidal ideation among Korean women have mostly focused on the relationship between the menstrual cycle and psychiatric admissions (Targum et al., 1991) or overall mental health (Lande and Karamchandani, 2002). The association between menstrual cycle irregularity and suicidal ideation has not been sufficiently studied.

Therefore, we aimed to investigate the association between menstrual cycle irregularity and suicidal ideation among Korean women using data from the Korea Health and Nutritional Examination Survey (KNHANES), a representative sample of South Korean women aged 12 to 65 years.

## 2. Methods

### 2.1. Study participants

This data was drawn from the fifth KNHANES (KNHANES 2010–2012). The KNHANES provides nationally representative data by selecting participants in South Korea using a complex stratified multi-stage clustered probability design. Of the total 13,918 female participants in the KNHANES 2010–2012, 8,302 were excluded because they had already reached menopause (n=5,506), they had not reached menarche (n=2,647), or information about menstruation status was not available (n=149). Among the remaining 5,616 participants, those without available data on menstrual cycle regularity (n=9) or suicidal ideation (n=1) were also excluded. The final study population comprised 5,606 participants (Fig 1).

### 2.2. Assessment of menstrual cycle irregularity & suicidal ideation

Menstrual cycle irregularity was determined by the question, “Do you currently have menstruation?” If participants answered yes, they were then asked whether the menstruation was regular or irregular. Additionally, they answered whether they went more than 3 months without menstruating or menstruated once every 3 months.

Suicidal ideation was determined by the question, “Within the past year, have you ever thought about killing yourself?” A “yes” or “no” response was used to assess whether the participants had suicidal thoughts. If participants answered yes, they were then asked “Within the past year, have you ever actually tried to kill yourself?” The participants

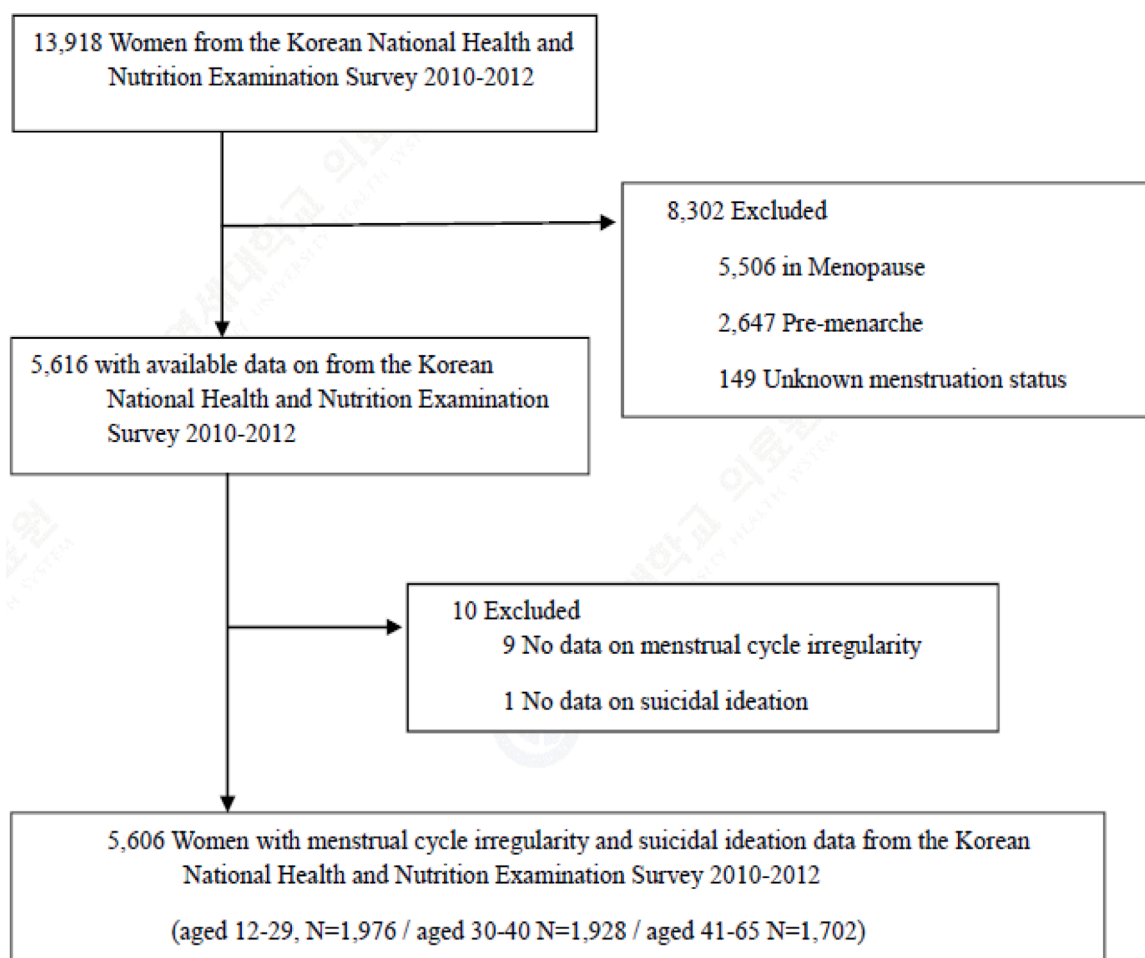


Fig. 1. Flow of persons in the Korean National Health and Nutrition Examination Survey 2010–2012.

answered yes or no. According to this information, we defined ‘suicidal attempt’.

### 2.3. Covariates

Participants were asked about their age, age at menarche, socioeconomic status (SES), lifestyle, and comorbid diseases by trained interviewers using structured questionnaires. Age (Duberstein et al. 1999) was classified into tertiles (12–29 years, 30–40 years, and 41–65 years). The age at menarche (Ortin and Miranda, 2020) was collected in response to the question “When did you start menstruating?” and was classified into tertiles (8–13 years, 14 years, and 15–21 years). SES (Kim et al., 2016; Kwak et al., 2019) included education level, monthly household income, marital status, and occupational status. Education level was divided into groups based on high school graduation (< high school graduation or ≥ high school graduation), and monthly household income was divided into quartiles. Marital status was classified into four groups: not married, married-living together, married-separate, and divorced or widowed. Occupational status was classified into currently employed or not employed. Lifestyle consisted of smoking status (Poorolajal and Darvishi, 2016) (three groups: non-smoker, former smoker, current smoker), drinking status (Conner et al., 2003) (two groups: non-drinker, current drinker), and physical activity (Vancampfort et al., 2018) (high intensity: at least 3 days a week, 20 min or more at a time, moderate intensity: at least 3 days a week, 20 min or more at a time) Comorbid diseases (Druss and Pincus, 2000), including hypertension; myocardial infarction; angina; hyperlipidemia; stroke; thyroid; diabetes mellitus; and cancers of the stomach, liver, breast, colorectum, uterine cervix, and lung were divided into groups of 0, 1, or 2+. A “0” indicated that the participant had never been diagnosed with any of the comorbid diseases, a “1” indicated one comorbid disease diagnosis, and a “2+” indicated that the participant had been diagnosed with two or more of the comorbid diseases.

### 2.4. Statistical analysis

This study applied population weights to all statistical computations to represent the total population of South Korea. Generally, participants were excluded from the study if they had any missing data regarding menstrual cycle regularity or suicidal ideation. To evaluate the overall association between menstrual cycle irregularity and suicidal ideation, the PROC SURVEYLOGISTIC procedure was used, which consecutively adjusts for potential confounders. Among 860 women who reported having suicidal ideation, 859 responded to the “suicidal attempt” item. Repeatedly, the PROC SURVEYLOGISTIC procedure was used to evaluate the association between menstrual cycle irregularity and suicide attempts among people who reported suicidal ideation. The weight was calculated as  $w_{10-12} = w_{10} * (1/3)$ ,  $w_{10-12} = w_{11} * (1/3)$ , and  $w_{10-12} = w_{12} * (1/3)$ , as given in the KNHANES. Model 1 was adjusted for age. Model 1 was adjusted for age. Then, SES (education, income, marital status, and occupational status), which seemed to have the greatest impact among all covariates, was further adjusted for in Model 2. Model 3 was adjusted for age, SES, age at menarche, and number of comorbidities. Model 4 was adjusted for all the previous factors and lifestyle factors (smoking status, drinking status, and physical activity). In addition, age and age at menarche variables were converted into tertiles when adjusting for each model: age (12–29 years, 30–40 years, and 41–65 years) and age at menarche (8–13 years, 14 years, and 15–21 years). The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariate logistic regression analyses to evaluate the association between menstrual cycle irregularity and suicidal ideation by age, age at menarche, and occupational status. All statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and the significance level was set at  $p < 0.05$ .

### 2.5. Ethical approval

All participants provided written informed consent for the KNHANES. All procedures and protocols of the study have been approved by the institutional review board (IRB no. 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C) of the Korean Center for Disease Control and Prevention since 2007. The study was conducted in accordance with the Declaration of Helsinki.

## 3. Results

Of the 5,606 women who had valid menstrual cycle regularity and suicidal ideation information available, 860 (weighted percentage, 15.3%) had episodes of suicidal ideation. The mean age of the suicidal ideation group was 31.6 years, and the mean age in the non-suicidal ideation group was 33.7 years. Women who had episodes of suicidal ideation were more likely to have menstrual cycle irregularity, lower household incomes, be less educated, and not be married (Table 1).

Table 2 shows the association between menstrual cycle irregularity and suicidal ideation, stratified by age, age at menarche and occupational status. The OR for suicidal ideation among women with irregular menstrual cycles compared with regular cycles was 1.44 (95% CI = 1.14–1.82), after adjusting for age, education level, household income, marital status, occupational status, age at menarche, comorbidities,

**Table 1**  
Descriptive characteristics of participants in KNHANES, 2010-2012 (N=5606).

Variables	Suicidal Ideation		P value	
	No (N=4746)	Yes (N=860)		
Age, years, mean ± SD	33.69 ± 11.12	31.63 ± 11.68		<.001
Menstrual cycle irregularity, N (%)				
Regular	4098 (86.35)	590 (80.47)		<.001
Irregular	648 (13.65)	148 (19.53)		
Education level, N(%)				
under high school graduated	915 (19.28)	241 (28.02)		<.001
≥ high school graduated	3831 (80.72)	619 (71.98)		
Household income(year), N (%)				
Q1	1278 (26.93)	318 (36.98)		<.001
Q2	1047 (22.06)	195 (22.67)		
Q3	1199 (25.26)	183 (21.28)		
Q4	1222 (25.75)	164 (19.07)		
Job, N(%)				
No	2428 (51.16)	453 (52.67)		0.435
Yes	2318 (48.84)	407 (47.33)		
Marital status, N(%)				
Not married	1656 (34.90)	386 (45.04)		<.001
Married-living together	2929 (61.73)	423 (49.36)		
Married-separate	13 (0.27)	7 (0.82)		
Divorce&Bereavement	147 (3.10)	41 (4.78)		
Age at menarche, mean ± SD	13.60 ± 1.74	13.52 ± 1.84		<.001
Comorbidity, N(%)				
0	4317 (90.96)	776 (90.23)		0.091
1	361 (7.61)	63 (7.33)		
2+	68 (1.43)	21 (2.44)		
Current smoking status, N(%)				
Non-smoker	4243 (89.40)	677 (78.72)		<.001
Former smoker	244 (5.14)	103 (11.98)		
Current smoker	259 (5.46)	80 (9.30)		
Current drinking status, N(%)				
Non-drinker	780 (16.43)	126 (14.65)		0.209
Current drinker	3966 (83.57)	734 (85.35)		
Moderate physical activity, N (%)				
No	4419 (93.15)	782 (91.04)		0.033
Yes	325 (6.85)	77 (8.96)		
Severe physical activity, N(%)				
No	4152 (87.48)	721 (83.93)		0.005
Yes	594 (12.52)	138 (16.07)		

**Table 2**

Association between menstrual cycle irregularity and suicidal ideation adjusted in 4 models by age and age at menarche in KNHANES, 2010-2012 (N=5,606).

Variables	Case N (%)	Suicidal Ideation Model 1 <sup>1)</sup>		Model 2 <sup>2)</sup>		Model 3 <sup>3)</sup>		Model 4 <sup>4)</sup>	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Menstrual cycle irregularity									
Irregular vs Regular	816 (14.56) vs 4790 (85.44)	<b>1.53</b>	<b>(1.22-1.91)</b>	<b>1.49</b>	<b>(1.19-1.87)</b>	<b>1.48</b>	<b>(1.18-1.87)</b>	<b>1.44</b>	<b>(1.14-1.82)</b>
<b>Stratified by age</b>									
T1 (12≤age<29)	1976 (35.25)	<b>1.47</b>	<b>(1.06-2.04)</b>	<b>1.49</b>	<b>(1.07-2.06)</b>	<b>1.51</b>	<b>(1.09-2.09)</b>	<b>1.45</b>	<b>(1.04-2.03)</b>
T2 (30≤age<40)	1928 (34.39)	<b>1.88</b>	<b>(1.19-2.96)</b>	<b>1.68</b>	<b>(1.04-2.70)</b>	<b>1.68</b>	<b>(1.05-2.69)</b>	<b>1.55</b>	<b>(0.96-2.51)</b>
T3 (41≤age<65)	1702 (30.36)	1.24	(0.83-1.85)	1.16	(0.75-1.79)	1.18	(0.76-1.84)	1.21	(0.77-1.90)
<b>Stratified by age at menarche</b>									
T1 (8≤age<13)	2822 (50.34)	<b>1.74</b>	<b>(1.27-2.38)</b>	<b>1.67</b>	<b>(1.21-2.30)</b>	<b>1.67</b>	<b>(1.21-2.31)</b>	<b>1.60</b>	<b>(1.15-2.23)</b>
T2 (age=14)	1234 (22.01)	1.29	(0.78-2.13)	1.21	(0.69-2.13)	1.23	(0.69-2.16)	1.16	(0.67-2.03)
T3 (15≤age<21)	1550 (27.65)	1.34	(0.90-2.00)	1.31	(0.87-1.97)	1.31	(0.87-1.98)	1.32	(0.86-2.01)
<b>Currently working status<sup>5)</sup></b>									
NO	2295(46.32)	<b>1.46</b>	<b>(1.06-2.00)</b>	<b>1.40</b>	<b>(1.01-1.94)</b>	<b>1.39</b>	<b>(1.01-1.93)</b>	<b>1.40</b>	<b>(1.01-1.95)</b>
YES	2660(53.68)	<b>1.60</b>	<b>(1.17-2.19)</b>	<b>1.50</b>	<b>(1.08-2.09)</b>	<b>1.50</b>	<b>(1.08-2.09)</b>	<b>1.46</b>	<b>(1.05-2.04)</b>

- 1) Model 1 : Adjusted age.
- 2) Model 2 : Model1+Adjusted SES(education, income, marital status, currently working status).
- 3) Model 3 : Model2+Adjusted age at menarche, comorbidity.
- 4) Model 4 : Model3+Adjusted smoking status, drinking status, physical activity status.
- 5) Currently working status did not adjust.

smoking status, drinking status, and physical activity.

After stratification by age tertiles (T1: 12–29 years, T2: 30–40 years, and T3: 41–65 years), the OR for suicidal ideation was 1.45 (95% CI = 1.04–2.03), 1.55 (95% CI = 0.96–2.51), and 1.21 (95% CI = 0.77–1.90), respectively, after adjusting for age, education level, household income, marital status, occupational status, age at menarche, comorbidities, smoking status, drinking status, and physical activity. Likewise, when age at menarche was stratified by tertile (T1: 8–13 years, T2: 14 years, and T3: 15–21 years), the OR for suicidal ideation was 1.60 (95% CI = 1.15–2.23), 1.16 (95% CI = 0.67–2.03), and 1.32 (95% CI = 0.86–2.01), respectively, after full adjustments. In women who were employed, the OR for suicidal ideation among those with menstrual cycle irregularity compared to women with regular cycles was 1.46 (95% CI = 1.05–2.04), after full adjustments. The p-interaction of menstrual cycle irregularity and occupational status was 0.8119, with no interaction term.

Supplementary table 1 shows the association between menstrual cycle irregularity and suicide attempts among people who reported suicidal ideation, stratified by age, age at menarche, and occupation status. The OR for suicide attempt among women with irregular menstrual cycles, compared with regular cycles, was 2.54(95%CI = 1.14-5.67) after full adjustment. Compared with an OR of 1.44(95%CI 1.14-1.82) for suicidal ideation, we observed a much stronger association when the outcome was limited to a stronger definition representing suicidality.

**4. Discussion**

To our knowledge, this is the first study of suicidal ideation in relation to menstrual cycle irregularity in Korean women. Overall, our research indicated that women with menstrual cycle irregularity were about 1.5 times more likely to have suicidal ideation than women with regular cycles. Women aged 33 to 41 with menstrual cycle irregularity were about twice as vulnerable to suicidal ideation compared with women of the same age range with regular cycles. In addition, when stratified by age of menarche, women with irregular menstrual cycles who had the earliest menarche (aged 8–13 years) had the highest increased likelihood of suicidal ideation (OR 1.60, 95% CI = 1.15–2.23). These findings are consistent with the hypothesis that menstrual cycle irregularity is associated with the determinants of suicidal ideation.

This study found an association between menstrual cycle irregularity and suicidal ideation in the general female community population. Our results are in line with findings from a cross-sectional study conducted in the U.S. on in-patients with chronic mental illnesses such as bipolar mood disorder and schizophrenia, which suggests that the postovulatory

phase of the menstrual cycle may be a time of increased risk for schizophrenia (Lande and Karamchandani, 2002). Another case-control study of 164 U.S. women whose menstrual cycle phase was assessed at the time of emergency psychiatric admission, had a higher proportion of admission (47%), compared with that of controls. In the same study, 33.3% of admissions occurred within 4 d of the onset of menses (Targum et al., 1991). It appears that the menstrual cycle, especially related to the late luteal phase, may biologically affect the onset of psychiatric symptoms in vulnerable patients. The previous studies show, therefore, that menstrual cycle may be closely related to psychiatric vulnerability and even suicidal ideation. A cross-sectional study of 1,482 college students at a U.S. university evaluated the cyclic variation in hormone levels (including progesterone and prolactin) and increased feelings of burdensomeness and loneliness (Smith et al., 2015). In this study, women aged 12 to 29 years were shown to have more suicidal ideation associated with menstrual cycle irregularity than the other groups. Pilver et al. (2013) found that premenstrual dysphoric disorder was positively associated with suicidal ideation among women aged 18–40 years. Our results are comparable to the findings of this study.

Our study examined the irregularity of the menstrual cycle based on self-reporting. Women’s self-definitions of their menstrual regularity and irregularity may lack a certain level of reliability (Weller and W. eller, 2002), and there is no clear consensus on standard measurement of menstrual cycle irregularity yet. We reviewed one study using the same menstrual irregularity question among 808 female adolescents, and the authors therein noted a positive association between mental health issues, including depression and high stress, and menstrual cycle irregularity (Yu et al., 2017). One study suggested a high negative predictive value, compared with a positive predictive value, in the assessment of true case menstrual irregularity. Meanwhile, another study found that only 44% of women who defined themselves as irregular were likewise defined by objective criteria, whereas 82% of women who defined themselves as regular were also deemed so by objective criteria (Weller and W. eller, 1998). If the findings from this study are indeed applicable to the real world, we might have underestimated the true cases of menstrual irregularity, which could have led to underestimation of a true association. Notwithstanding, one cross-sectional study suggested that the overall validity of a single-item question on the regularity of menstrual status is relatively robust. Therein, the validity of self-reports was compared with data from ovulation monitoring with ultrasound in Brazilian women. Among 199 women who reported regular menstruation, ultrasound monitoring confirmed actual regular menstruation in 133, and 24 of 29 women who reported having irregular menstrual cycle were confirmed by ultrasound monitoring. Therefore, we suggest that



questionnaires surveying regularity of the menstrual cycle would be accurate (Sasaki et al., 2016). Suicidal ideation was also investigated with self-reports. One study compared two assessment methods (self-reports and face-to-face interviews) for determining suicidal ideation. In 80% of cases, responses were in agreement between the two assessment methods. (Yigletu et al. 2004). Therefore, in our study, sensitivity analysis was performed by analyzing the association between menstrual cycle irregularity and suicide attempt, which showed a stronger association. Therefore, we suspect that the true association between menstrual irregularity and suicidal ideation might be stronger than that indicated in our results.

Our study considered many variables associated with menstrual cycle irregularity, as reported in previous studies. Menstrual cycle irregularity was associated with age and age at menarche. However, the limited number of evidence in the literature has been inconsistent. In our previous study, we observed a heterogeneous relationship between women grouped according to menarche age and likelihood of physician-diagnosed depression, which is a strong factor for predicting the suicidality (Jung et al., 2015). In one of the few studies on suicidal ideation, girls who were younger at menarche reported a higher prevalence of past-year suicidal ideation than girls with normative age at menarche (Lee et al., 2020). In a cross-sectional study of Chinese adolescents, earlier menarche and irregular menstrual cycle were associated with suicidal behavior among female adolescents (Chen et al., 2017). Additionally, hormonal fluctuations starting around menarche have been linked to increases in negative affect and depressive symptoms (Martel et al., 2009); therefore, we assumed that the age of menarche could be an effect modifier.

A cross-sectional study conducted to determine the association between occupational status and menstrual irregularity in Korean women using KNHANES data showed that the prevalence of menstrual cycle irregularity was higher in working women, which included service/sales and manual workers, temporary workers, and workers with non-daytime working patterns (Kwak and Kim, 2018). The results of that study demonstrated a greater association between employment and suicidal ideation than unemployment and suicide ideation, which is consistent with our study results. In a follow-up study, the association between menstrual cycle irregularity and suicidal ideation according to the type of occupation should also be assessed. These studies provide evidence for the association between menstrual cycle irregularity and suicidal ideation, even after adjustment for a number of variables. Therefore, menstrual cycle irregularity could be a risk factor for suicidal ideation.

#### Strength

One strength of this study was the use of large, representative datasets compiled by national institutions. This nationally representative cross-sectional survey includes approximately 10,000 individuals each year as a survey sample and collects information on socioeconomic status, health-related behaviors, quality of life, healthcare utilization, anthropometric measures, biochemical and clinical profiles for non-communicable diseases, and dietary intake with three component surveys: health interview, health examination, and nutrition survey. The health interview and health examination were conducted by trained staff members, including physicians, medical technicians, and health interviewers at a mobile examination center, and dietitians performed follow-up visits at the homes of the study participants (Kweon et al., 2014). Furthermore, this study considered various confounding variables that may have affected both menstrual cycle irregularity and suicidal ideation.

#### Limitations

Several limitations should be considered when interpreting the results of this study. First, it was a cross-sectional study; therefore, a causal relationship could not be drawn. Second, as we utilized self-reported data on menstrual regularity, this exposure variable may be underestimated. Therefore, further studies with more accurate measurements, such as simultaneous assessments with structured questionnaires and

biomarkers, are needed to clarify associated mechanisms and to confirm the association between menstrual cycle irregularity and suicidal ideation. However, these retrospective, clearly operationalized self-reports in adults have been demonstrated to be sufficiently valid to warrant their use in research. Finally, there may be residual confounding because we did not consider all possible covariates, such as type of occupation, working hours, and types of work (Dendup et al., 2014). However, we adjusted for several potential confounders related with SES, including marital status, household income, education level, and occupational status. While further investigation accounting for other SES factors would be beneficial, we believe a significant amount of the effects from SES was covered in our model.

#### Conclusion

Our study assessed whether menstrual cycle irregularity was associated with suicidal ideation. Results of controlled covariates indicated an association between menstrual cycle irregularity and suicidal ideation. This association was particularly noticeable in women aged 12–29 years and in those who had menarche at a relatively early age (aged 8 to 13 years). In addition, an association between menstrual cycle irregularity and suicidal ideation was found in employed women, but not in women who were not employed.

#### Authors' contributions

Dr. Jung had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Study design and concept: Jung SJ, Park MS; acquisition, analysis, and interpretation of data: Jung SJ, Park MS; drafting of the manuscript: Park MS; critical revision of the manuscript for important intellectual content: Jung S-J; statistical analysis: Park MS; obtaining funding: Jung SJ; administrative, technical, or material support: Park MS; and study supervision: Jung SJ.

#### Declaration of Competing Interest

We declare no competing interests.

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#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.06.052.

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