Menstrual Status Is Associated with the Prevalence of Irritable Bowel Syndrome in a Japanese Young Population: A Cross-Sectional Study

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Abstract

Introduction: There is evidence regarding the association between dysmenorrhea and irritable bowel syndrome (IBS), although it is lacking in the Asian population. Therefore, the purpose of this study was to investigate the association between menstrual status and IBS in a young Japanese. ***Methods:*** Overall, 4,693 female college students were included in the analysis of this study. Information regarding lifestyle habits, menstrual status (irregularity, pain severity, and medication), and IBS (Rome III criteria) was obtained using a self-reported questionnaire. Age, body mass index, exercise habits, smoking, drinking habits, and anemia were analyzed as potential confounders. ***Results:*** The prevalence of IBS was 6.1%. Moderate {adjusted odds ratio (OR): 1.89 (95% confidence interval [CI]: 1.27–2.91)} and heavy (adjusted OR: 2.14 [95% CI: 1.42–3.45]) menstrual pain were independently positively associated with IBS (*p* for trend = 0.001). Using medication sometimes (adjusted OR: 1.41 [95% CI: 1.09–1.84]) and often (adjusted OR: 1.60 [95% CI: 1.13–2.24]) was independently positively associated with IBS. There was no association between menstrual cycle and IBS. In subjects without functional dyspepsia, irregular menstrual cycle was independently positively associated with IBS. ***Conclusion:*** In the young Japanese population, menstrual pain and medications for menstrual pain may have a significant positive association with IBS.

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Introduction

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders and also reduces the quality of life of patients [1–3]. The etiology of IBS is still poorly understood, however. Dysmenorrhea is a serious medical issue for numerous young women. In about 30% of women with reproductive age, their quality of life is impaired by dysmenorrhea [4, 5].

Evidence regarding the association between dysmenorrhea and IBS has been reported. Icelandic, US, and Iranian studies suggested a positive association between dysmenorrhea and IBS [6–10]. The prevalence of IBS is generally higher in women than in men [2]. Thus, further research regarding the association between female-specific symptoms, including menstrual status, and IBS is warranted.

A meta-analysis showed that although the prevalence of IBS differs among geographic locations, it is not increasing worldwide [2]. There is no evidence of an association between menstrual status and IBS in Asian female populations, including the Japanese. Therefore, the purpose of this study was to explore the relationship between menstrual status and the prevalence of IBS in young Japanese population.

Methods

Study Design
This study was a cross-sectional study.

Study Population
In this study, 4,951 female students who underwent medical checkups conducted at Ehime University (Ehime, Japan) from 2015 to 2017 were included. These were routine medical checkups. A web-based questionnaire on IBS (the Rome III criteria classification) was sent to all students during the health screening interview. Information on organic gastrointestinal diseases and physical signs to complement the Rome III criteria was also obtained using a self-administrated questionnaire. The exclusion criteria for this study were treatment for gastrointestinal diseases within the last 6 months, and history of gastrointestinal disease (e.g., gastroesophageal reflux disease, gastritis, *Helicobacter pylori* infection and/or its eradication therapy, ulcers, and cancer), liver, biliary, and pancreatic diseases, and the presence of physical symptoms related to gastrointestinal disease, such as weight loss and recurrent vomiting. Thus, 258 subjects were excluded, and 4,693 subjects who responded to the questionnaire on menstrual status and IBS were included in the final analysis of this study (Fig. 1). This research protocol was developed in compliance with the ethical guidelines of the Declaration of Helsinki. Opt-out informed consent protocol was used for this study. This consent procedure and research protocol were reviewed and approved by the Institutional Review Board of Ehime University School of Medicine, approval number (No. 1610012 and 2208007).

Questionnaires and Measurements
Lifestyle habits such as smoking, drinking, and exercise habits, as well as medical history were surveyed by means of a web-based self-administered questionnaire. Height and weight were measured at the time of the checkup in light clothing, and BMI was calculated by dividing your weight (in kilograms) by your height (in meters) squared. Current smokers were defined as those who reported that they smoked, regardless of frequency. Current drinkers were defined as subjects who reported drinking alcohol, regardless of frequency or quantity. Subjects were defined as having an exercise habit if they reported exercising at least once a week.

Assessment of Menstrual Status
A self-administered web-based questionnaire was used to obtain the data on menstrual status using the following multiple choice questions: (1) menstrual cycle irregularity: "Which of the following best describes your menstrual cycle?" (no cycle for 3 months or more, irregular, and mainly regular), (2) menstrual pain: "How strong is your menstrual pain, if any?" (none, light, sometimes heavy, and heavy), and (3) medication for menstrual pain: "How often do you use medication for menstrual pain?" (never, sometimes, and often).

Definition of IBS and Functional Dyspepsia
IBS and functional dyspepsia (FD) were defined according to the Rome III criteria (outline of the Japanese version of the Rome III Research Diagnostic Questionnaire translated by the Japanese Society of Neurogastroenterology) [11]. The definition was symptom onset more than 6 months prior to diagnosis, recurrent abdominal pain or discomfort more than 3 days per month for the past 3 months, and at least 2 of the following: improvement of symptoms with defecation, change in frequency of defecation with onset of abdominal symptoms, or change in stool shape with onset of abdominal symptoms. FD was defined as positive if participants experienced postprandial fullness, early satiation, and/or epigastric pain or burning for the last 3 months, with symptom onset at least 6 months before diagnosis.

Statistical Analysis
Menstrual irregularity was divided into three groups: amenorrhea (no cycle for 3 months or more), irregular, and mainly regular (reference). Menstrual pain severity was divided into four groups: none (reference), light, moderate, and heavy. Medication for menstrual pain was divided into three groups: never (reference), sometimes, and often.

Logistic regression analysis was used to estimate crude odds ratios (ORs) and their 95% confidence intervals (CIs) between menstrual cycle irregularity, severity of menstrual pain, and treatment of menstrual pain and IBS. Multiple logistic regression analysis was also used to adjust for age, body mass index, alcohol consumption, smoking, exercise habits, and anemia as potential confounders. Statistical analysis was performed with SAS software package version 9.4 (SAS Institute Inc., Cary, NC, USA), and statistical tests of all probability values were two-sided, and $p < 0.05$ was considered statistically significant.
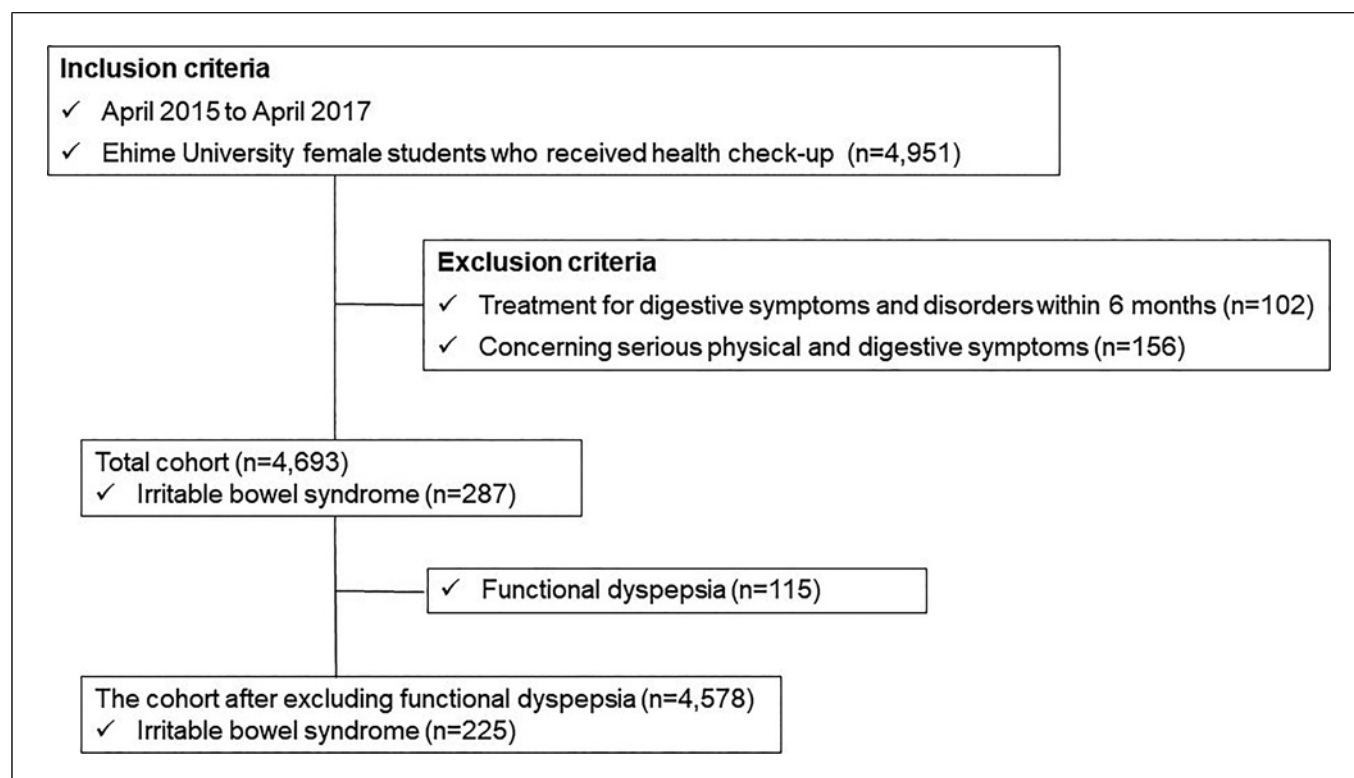
Fig. 1. Flowchart of the study population.

Results

Characteristics and Prevalence of IBS in This Cohort

The prevalence of IBS and the characteristics of this cohort are shown (Table 1). The prevalence of IBS in subjects with no pain, light, moderate, and heavy pain was 3.8%, 5.3%, 7.0%, and 8.0%, respectively. Regarding menstruation, the IBS group was more likely to have severe menstrual pain and to use medication for menstrual pain more often. The prevalence of FD was 2.5% in total cohort. The prevalence of FD in subjects with IBS (21.6%) was significantly higher than without IBS (1.2%).

Association between Menstruation and the Prevalence of IBS

Table 2 shows the association between menstrual status and IBS. The prevalence of IBS among subjects with amenorrhea, an irregular cycle, and a mostly regular cycle were 3.9%, 7.9%, and 5.9%, respectively. Menstrual cycle irregularity was not associated with IBS in this cohort (Fig. 2).

Moderate pain (moderate adjusted OR: 1.89 [95% CI: 1.27–2.91]) and heavy pain (heavy adjusted OR: 2.14 [95% CI: 1.36–3.45]) were independently positively associated with the prevalence of IBS after adjustment for confounding factors (p for trend = 0.001). Using medication for menstrual pain sometimes (adjusted OR: 1.41 [95% CI: 1.09–1.84]) and often (adjusted OR: 1.60 [95% CI: 1.13–2.24]) was independently positively associated with IBS.

Association between Menstruation and the Prevalence of IBS in Subjects without FD

After excluding FD, the analysis sample consisted of 4,578 female students (Fig. 1). The association between menstrual status and IBS in subjects without FD is shown in Table 3. Irregular menstrual cycle was independently positively associated with IBS (adjusted OR: 1.49 [95% CI: 1.04–2.10]).

Moderate (adjusted OR: 1.91 [95% CI: 1.23–3.08]) and heavy menstrual pain (adjusted OR: 1.16 [95% CI: 1.16–3.31]) were independently positively associated with IBS (p for trend = 0.002). "Sometimes medication" for menstrual pain was independently positively associated with IBS (adjusted OR: 1.55 [95% CI: 1.16–2.07], p for trend = 0.002). The association between "often medication" and IBS was marginally significant (p = 0.07).

**Table 1.** Clinical characteristics of 4,693 study participants

	Total (*n* = 4,693)	IBS (*n* = 287)	Non-IBS (*n* = 4,406)	*p* value
Age, years, mean±SD	19.9±3.2	19.7±3.2	19.9±3.2	0.23
BMI	20.89±2.73	21.09±3.07	20.86±2.71	0.22
Smoking, *n* (%)	41 (0.9)	3 (1.1)	38 (0.9)	1.00
Drinking, *n* (%)	279 (6.0)	18 (6.3)	261 (5.9)	0.91
Regular exercise, *n* (%)	1,453 (31.0)	83 (28.9)	1,370 (31.1)	0.48
Medical history				
ECG abnormality, *n* (%)	47 (1.0)	2 (0.7)	45 (1.0)	0.81
Anemia, *n* (%)	261 (5.6)	23 (8.0)	238 (5.4)	0.08
Sport injury, *n* (%)	90 (1.9)	3 (3.3)	87 (2.0)	0.37
Menstrual regularity				0.18
Mainly regular, *n* (%)	4,018 (85.6)	236 (82.2)	3,782 (85.8)	
Irregular, *n* (%)	624 (13.3)	49 (17.1)	575 (13.1)	
Amenorrhea, *n* (%)	51 (1.1)	2 (0.7)	49 (1.1)	
Menstrual pain severity				0.001
None, *n* (%)	774 (16.5)	29 (10.1)	745 (16.9)	
Light, *n* (%)	1,391 (29.6)	74 (25.8)	1,317 (29.9)	
Moderate, *n* (%)	1,828 (39.0)	128 (44.6)	1,700 (38.6)	
Heavy, *n* (%)	700 (14.9)	56 (19.5)	644 (14.6)	
Medication for menstrual pain				0.005
Never, *n* (%)	2,450 (52.2)	124 (43.1)	2,326 (52.8)	
Sometimes, *n* (%)	1,615 (34.4)	113 (39.4)	1,502 (34.1)	
Often, *n* (%)	628 (13.4)	50 (17.4)	578 (13.1)	
Irritable bowel syndrome, *n* (%)	287 (6.1)			
Functional dyspepsia, *n* (%)	112 (2.5)	62 (21.6)	53 (1.2)	0.001

IBS, irritable bowel syndrome; BMI, body mass index; ECG, electrocardiogram; SD, standard deviation.

Table 2. Association between menstruation and IBS

Variable	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)
IBS			
Menstrual cycle			
Mainly regular, *n* (%)	236/4,018 (5.9)	1.00	1.00
Irregular, *n* (%)	49/624 (7.9)	1.37 (0.98–1.86)	1.37 (0.98–1.87)
Amenorrhea, *n* (%)	2/51 (3.9)	0.65 (0.11–2.13)	0.72 (0.12–2.34)
Menstrual pain severity			
No, *n* (%)	29/774 (3.8)	1.00	1.00
Light, *n* (%)	74/1,391 (5.3)	1.44 (0.94–2.27)	1.43 (0.93–2.26)
Moderate, *n* (%)	128/1,828 (7.0)	1.93 (1.30–2.97)	1.89 (1.27–2.91)
Heavy, *n* (%)	56/700 (8.0)	2.23 (1.42–3.58)	2.14 (1.36–3.45)
p for trend			0.001
Medication for menstrual pain			
Never, *n* (%)	124/2,450 (5.1)	1.00	1.00
Sometimes, *n* (%)	113/1,615 (7.0)	1.41 (1.08–1.84)	1.41 (1.09–1.84)
Often, *n* (%)	50/628 (8.0)	1.62 (1.15–2.27)	1.60 (1.13–2.24)
p for trend			0.003

Odds ratios were adjusted for age, body mass index, drinking, smoking, exercise habit, and anemia. IBS, irritable bowel syndrome; OR, odds ratio; CI, confidence interval.

Furukawa et al.
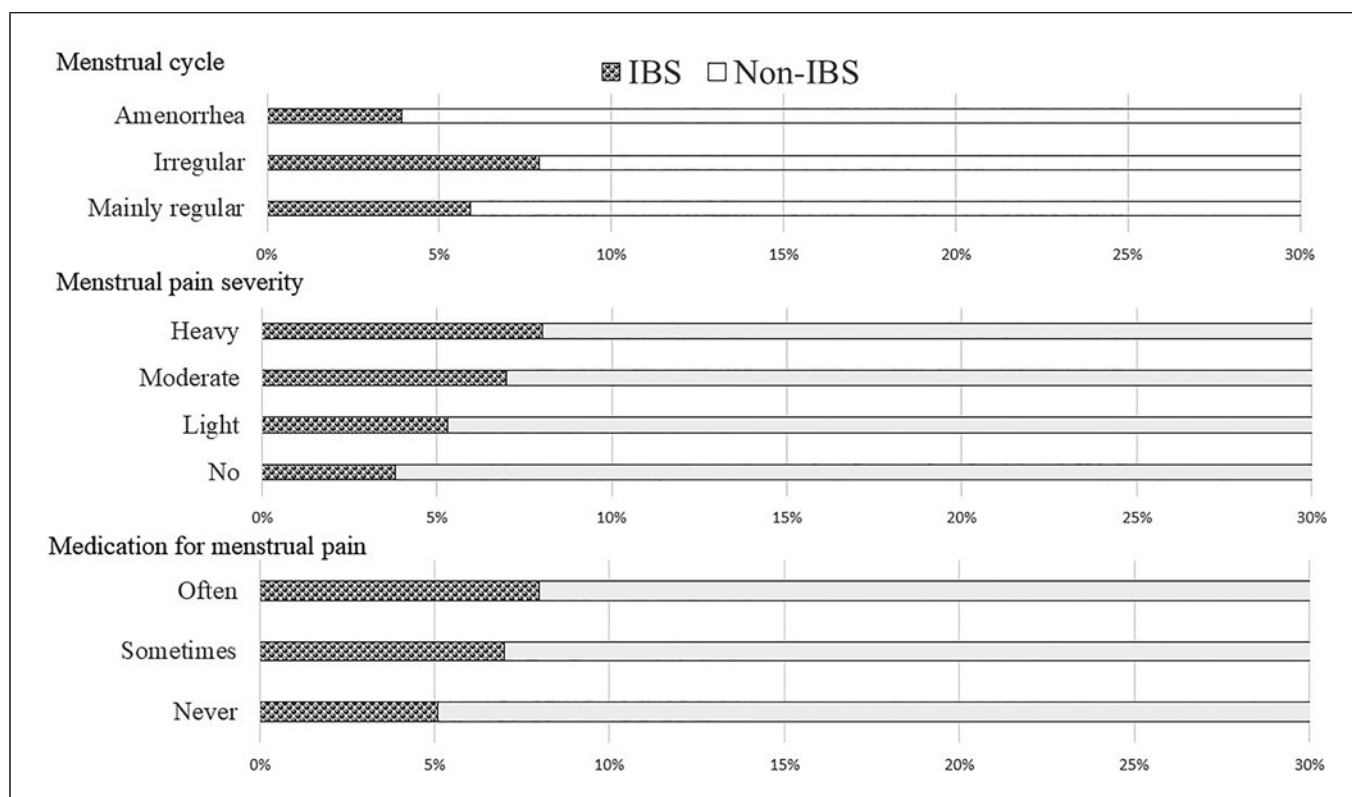
Fig. 2. Association between menstrual status and IBS in total cohort.

Table 3. Association between menstruation and IBS in students without FD

Variable	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)
IBS			
Menstrual cycle			
Mainly regular, *n* (%)	183/3,923 (4.7)	1.00	1.00
Irregular, *n* (%)	41/605 (6.8)	1.49 (1.03–2.10)	1.49 (1.04–2.10)
Amenorrhea, *n* (%)	1/50 (2.0)	0.42 (0.02–1.92)	0.43 (0.02–2.01)
Menstrual pain severity			
No, *n* (%)	24/764 (3.1)	1.00	1.00
Light, *n* (%)	57/1,366 (4.2)	1.34 (0.84–2.22)	1.35 (0.84–2.23)
Moderate, *n* (%)	104/1,780 (5.8)	1.91 (1.24–3.07)	1.91 (1.23–3.08)
Heavy, *n* (%)	40/668 (6.0)	1.96 (1.18–3.34)	1.94 (1.16–3.31)
p for trend			0.002
Medication for menstrual pain			
Never, *n* (%)	96/2,403 (4.0)	1.00	1.00
Sometimes, *n* (%)	95/1,578 (6.0)	1.53 (1.15–2.06)	1.55 (1.16–2.07)
Often, *n* (%)	34/597 (5.7)	1.45 (0.96–2.15)	1.45 (0.96–2.15)
p for trend			0.011

Odds ratios were adjusted for age, body mass index, drinking, smoking, exercise habit, and anemia. IBS, irritable bowel syndrome; FD, functional dyspepsia; OR, odds ratio; CI, confidence interval.

Discussion

In this study, the severity of menstrual pain and the use of menstrual pain medication were independently positively associated with IBS; in subjects without FD, the positive association between menstrual irregularity and IBS was also significant. This first study is to reveal a positive association between dysmenorrhea and IBS as defined by Rome III criteria in an Asian population.

Several studies have showed the positive association between dysmenorrhea and functional gastrointestinal disorder, including IBS. In three combined US studies of 266 women aged 18–45 with IBS, the prevalence of dysmenorrhea and/or premenstrual syndrome was 49.6% [7]. In a population-based study of Icelandic women (aged 18–75 years), dysmenorrhea was positively correlated with the prevalence of IBS as defined by the Rome III criteria [6]. In another Icelandic population-based postal study, women with IBS based on the Manning criteria had more severe dysmenorrhea than women without IBS [8]. In an Iranian study of 448 adolescent girls, IBS as defined by the Rome III questionnaire was associated with dysmenorrhea, while premenstrual syndrome alone, both premenstrual syndrome and dysmenorrhea, and normal were not associated with IBS [9]. In another Iranian study of 182 female university students aged 18–25 years, IBS was positively associated with duration of menstrual bleeding and pain during menstruation [10]. Regarding the association between menstrual status and IBS, these previous evidences and the findings of this study are similar and consistent regardless of geography.

In subjects without FD, "sometimes medication" but not "often medication" was independently positively associated with IBS. The low prevalence of IBS may be the reason why the difference did not reach statistical significance. Medication for menstrual pain itself might cause IBS. Previous epidemiological studies have shown that pill and NSAID use may themselves cause IBS [12–14]. Medication for menstrual pain may mask the relationship between drug use frequency and IBS.

The mechanism of the relationship between dysmenorrhea and IBS remains unclear. Female sex hormones are known to induce changes in gastric motility [15–17]. In addition, sex hormones have been shown to affect visceral nociception in women [18–20]. Women with IBS have also shown a tendency to have more severe menstrual symptoms [21]. Dysmenorrhea might induce IBS by triggering changes in sex hormone levels that delay gastrointestinal motility and induce dysregulation of the pain pathways. Further study on the mechanisms underlying the association between dysmenorrhea and IBS is warranted in the future.

There are several limitations to this study. First, being a cross-sectional study, we were not able to show a causal relationship between dysmenorrhea and IBS. Second, the study did not include medical records including endoscopy, *Helicobacter pylori* infection, or other history (although subjects with severe physical symptoms, self-reported gastrointestinal diseases, and subjects undergoing treatment for gastrointestinal diseases were excluded). Third, the information regarding menstrual cycle regularity, menstrual pain severity, and medication for pain was obtained using a self-reported questionnaire. Additionally, patients with gynecological or urinary disorders cannot be completely excluded. Fourth, in this cohort, the data regarding hormones, nervous system function, and gut microbiota are lacking. Fifth, the data regarding information on medication for menstrual pain was lacking in this cohort. Sixth, as psychological diseases can affect both menstrual status and IBS, data on psychological factors are lacking in this cohort. Finally, the prevalence of IBS in this cohort appears to be lower than in previous studies on IBS. The study population included only university students. Additionally, the study could not perform endoscopy and excluded students with a history of previous gastrointestinal disease or physical symptoms such as weight loss, which may have resulted in a lower prevalence of IBS. Of the 258 excluded students, the prevalence of IBS was 26.7% (69/258) (data not shown), and the prevalence of IBS was high despite the possibility of receiving treatment. It is unclear whether similar results will be seen in the entire young population of Japan.

In conclusion, menstrual pain and medication for pain may be independently associated with IBS in the young Japanese population. In subjects with IBS but not FD, menstrual pain, use of medication, and irregular menstrual cycle might be independently positively associated with IBS. Further studies assessing the association between dysmenorrhea and IBS are needed in the future.

Statement of Ethics

This research protocol was developed in compliance with the ethical guidelines of the Declaration of Helsinki. Opt-out informed consent protocol was used for this study. This consent procedure

and research protocol were reviewed and approved by the Institutional Review Board of Ehime University School of Medicine, approval number (No. 1610012 and 2208007).

Conflict of Interest Statement

All authors have no conflicts of interest for this article.

Funding Sources

Author Contributions

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical reasons but are available from the corresponding author upon reasonable request.

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