



# The assessment of the correlation between sleep quality and irritable bowel syndrome among medical students

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Received 16 Mar. 2021

Accepted 12 May 2021

Published online 20 May 2021

**Keywords:** Sleep, Medical student, Gastrointestinal disorders, Irritable bowel syndrome

## Abstract

**Introduction:** Remarkable high rates of functional gastrointestinal disorders, irritable bowel syndrome (IBS) in particular, is prevalent among medical students. On the other hand, nature of studying medicine leads to sleep disorders in this population. Increased innate immunity in the intestinal mucosa and lamina propria, particularly mast cells and monocytes along elevated numbers of T cells along with antibody production suggest a role for the adaptive immune response.

**Objectives:** The current study aims to assess the prevalence and association between IBS and sleep quality in medical students.

**Patients and Methods:** This is a cross-sectional study on 100 medical students to assess the correlation between sleep disorders and IBS. ROME IV criteria were utilized to determine the diagnosis of IBS and The Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep disorders. The students' length of sleep, age, gender and residence were recorded.

**Results:** According to ROME-IV criteria, 24 medical students, including 18 females (75%) were diagnosed with IBS. As measured by the PSQI, 66% of the students reported disturbed sleep quality. The mean length of sleep of the participants was 6.02 ( $\pm$ 1.29 hours). The IBS incidence was not associated with age ( $P=0.56$ ), gender ( $P=0.49$ ) or residence ( $P=0.66$ ). The logistic regression assessment revealed that impaired sleep quality was an independent risk factor for IBS diagnosis among the medical students ( $P<0.001$ , OR: 10, 95% CI: 4.3-23.3).

**Conclusion:** Based on the current study, IBS was diagnosed in 24% of the medical students in Isfahan. The length of sleep was significantly associated with IBS; however, age and gender and also sleep quality did not have any significant association with it

**Citation:** Maghsoudi S, Amra B, Teimouri A. The assessment of the correlation between sleep quality and irritable bowel syndrome among medical students. *Immunopathol Persa*. 2022;8(1):e07. DOI:10.34172/ipp.2022.07.

## Introduction

Irritable bowel syndrome (IBS) is one of the prevalent forms of functional gastrointestinal disorders characterized by recurrent abdominal pain, discomfort, and stool habit changes in the absence of any organic disorders (1). This functional disorder has turned into a significant medical challenge of the 21<sup>st</sup> century as IBS affects the quality of life negatively, while no unified therapeutic approach has been proposed and poor responses have been achieved to the administered treatments, as well (2). Considering several factors, the worldwide prevalence of IBS ranges from 3%-22% in different communities (3).

There is no confirmative investigation or biomarker for IBS diagnosis; however, genetics, environmental factors, gut microbiota, visceral hypersensitivity, gut-brain axis disorders, and psychological factors

## Key point

The prevalence of IBS is high in medical students which is directly associated with their sleep quality. Therefore, the ultimate preventive efforts should be made to minimize this bothering syndrome, as inappropriate length of sleep with poor quality is an inevitable fact of studying medicine. In a cross-sectional study on 100 medical students to assess the correlation between sleep disorders and IBS; we found, the length of sleep was significantly associated with IBS.

are related to IBS incidence (4). Molecular and histopathological investigations have shown traces of inflammation among IBS patients. Increased innate immunity in the intestinal mucosa and lamina propria, particularly mast cells and monocytes along elevated numbers of T cells along with antibody production suggest a role for the

adaptive immune response (5, 6).

Medical students experience higher levels of physical and psychological stress than the other similar age groups of the population. They are involved in a stressful academic environment, struggle with physical stress, sleeplessness, and inappropriate eating habits. In addition to the physical disturbances, psychological stresses such as demanding responsibilities are the other aspects that affect medical students' lifestyle negatively. The mentioned factors seem to be associated with the high prevalence of IBS in this group of people (7).

Sleep disorders are among the prevalent complaints of patients with IBS and seem to be correlated with the symptoms' severity (8). It is assumed that 7.9%-73% of the IBS patients have presented sleep disturbances (9).

### Objectives

Although the association of sleep disturbances with IBS is relatively proved, and studies in the literature have shown higher levels of sleep disturbances among this group (9-11), there is no study assessing the quality of life among medical students and its correlation with the diagnosis of IBS in medical students. To the best of our knowledge, the current study is the first one assessing the prevalence of IBS, sleep quality, and impact of sleep quality on IBS among medical students in Iran.

### Patients and Methods

#### Study design

The current report is a cross-sectional study conducted on 100 medical students studying at Isfahan university of medical sciences from January 2018 to March 2019.

The medical students studying at any grade of medicine at this university were included. The student's reluctance to participate in the study and presence of the alarm signs (including dysphagia, odynophagia, anorexia, weight loss, and gastrointestinal bleeding), university dropout, and family history of gastric cancer were considered as unmet criteria. Over 20% defect in the filled questionnaires was considered as the exclusion criterion.

The study population was selected using block sampling in a way that each grade was considered as a block, and the included students of each block were selected through convenience sampling.

#### Means of assessment

The participants' demographic information, including age, gender, residence (native versus non-native), were recorded in the study checklist.

#### Irritable bowel syndrome diagnosis

The Rome IV criteria were utilized to determine the diagnosis of IBS among the studied population. The Rome IV criteria for the diagnosis of IBS include recurrent abdominal pain on average at least once a week during the previous three months that is associated with two or more

of the following; the pain is

- Related to defecation (may be increased or unchanged by defecation)
- Associated with alteration in stool frequency
- Associated with alteration in stool form or appearance(12).

Furthermore, IBS was categorized into four subtypes, including constipation dominant (IBS-C), diarrhea dominant (IBS-D), mixed type (IBS-M), and unspecified (IBS-U)(13).

#### The Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a valuable means for assessing sleep in seven entities, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. This questionnaire contains 19 items score based on a four-scale Likert from zero to three. Questions number 1 and 3 are not scored in the same pattern as the others, but their score should be added to the other questions. In question number 2, the alternatives are scored as zero (less than 15 minutes), one (16-30 minutes), two (31-60 minutes), and three (more than 60 minutes). Question number 4 is scored as zero (more than 7 hours), one (6-7 hours), two (5-6 hours), and three (less than 5 hours). The remained questions are scored from zero to three, interpreted as never, once a week, twice a week, and three times or more per week. Eventually, the scores attributed to each of the seven entities are measured, and the score of each entity is interpreted as zero (no sleep problem), one (moderate), two (severe), and three (very severe). A total score higher than five for the questionnaire means poor sleep quality. The questionnaire was primarily raised by Buysse et al in 1989 with Cronbach's alpha of 0.83, the validity of 0.86, and reliability of 0.89 (14). The Persian version of this questionnaire has been validated by Ebrahimi et al in 2008 (15).

#### Data analysis

Data were analyzed using IBM SPSS (IBM Crop. 2019. IBM SPSS Statistics for Windows, version 26.0. NY, EUA). First, the frequency distribution of socio-demographics and sleep disturbances of students was presented by the number of cases (percentage). The association between the categorical variables was evaluated by the chi-square, Fisher's exact, Gamma, and likelihood ratio tests. The mean value ( $\pm$ SD) of the length of sleep was reported. After checking the normality of the distribution by the Shapiro-Wilks test, the student's t-test was used to investigate the differences between independent samples in the length of sleep. Then, the multivariate logistic regression models were fitted to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of sleep disturbances (no versus yes) with relation to IBS (healthy versus patient). The logistic regression analysis was run three times: Model I; unadjusted model, Model II; adjusted for the length of

sleep, and Model III; adjusted for gender, age category, residence, and the length of sleep. A level of 5% was considered as the significance level.

## Results

A total of 106 Students were approached and 100 responded and attempted the questionnaire. The final respondents (n=100) had the mean age of 23.2 ( $\pm 4.8$  SD years) (range: 18-28 years) consisted of 68 females (68%). Most of the students were not Isfahan city inhabitants (non-native: n=78, 78%).

According to Rome IV criteria, 24 medical students, including 18 females (75%) were diagnosed with IBS. The most common complaint of the patients was decrease in abdominal pain following defecation (91%) followed by change in the appearance of stool (84%), change in the frequency of stool defecation (76%) and urgency in defecation (68%).

As measured by the PSQI, 66% of the students reported disturbed sleep quality. The mean length of sleep of the participants was 6.02 ( $\pm 1.29$  hours). **Table 1** demonstrates the characteristics of sleep quality among the studied medical students.

**Table 2** shows the association of IBS with diverse characteristics of the studied population. Based on this table, age, gender, residence and sleep disturbances based on PSQI was not associated with IBS, while shorter length of sleep was significantly in association with IBS among the medical students.

The logistic regression assessment revealed that impaired sleep quality was an independent risk factor for IBS diagnosis among the medical students ( $P < 0.001$ , OR: 10, 95% CI: (4.3, 23.3), while these statistically significant associations were eliminated by the adjustments for gender, age category, residence, and length of sleep ( $P > 0.05$ ; **Table 3**).

## Discussion

In the current study, we diagnosed IBS in 24% of the medical students; however, it was not associated with age, gender, residence, and poor sleep quality. Length of sleep was the only factor inversely associated with IBS. Surfing the literature has shown IBS prevalence of 15%-24% in the general population in Western countries (16), while the rate of 5%-10% for the Asian communities is considerably lower (17). A possible logic behind this phenomenon seems to be related to more developed primary health care in Western countries (7) and the higher diagnosis rate in these communities.

Studies on medical students of different communities in Asia have shown an IBS rate of 25-32% (1,7). Although our data are compatible with the previous Asian studies, the studies on this group in Iran have reported considerably lower rates (18). We assume the impact of genetics and race on this difference between IBS rates in Iran and the other societies. However, the higher incidence of IBS in

**Table 1.** The frequency of responses to different sleep quality-related characteristics

The Pittsburgh Sleep Quality Index	Percent	
Subjective sleep quality	Good	38
	Fairly good	27
	Bad	31
	Very bad	4
Day time function	Normal	23
	Mild problem	49
	Moderate problem	23
	Severe problem	5
Sleep duration	More than 7 hours	9
	6-7 hours	26
	5-6 hours	42
	Less than 5 hours	23
Sleep latency	Normal	11
	Mild problem	36
	Moderate problem	33
	Severe problem	20
Sleep efficiency	More than 85%	57
	75-84%	26
	65-74%	12
	Less than 65%	5
Night awakenings	Normal	16
	Mild problem	79
	Moderate problem	3
	Sever problem	2
Sleep medication	Never	62
	Once a week	35
	Twice a week	2
	Triple a week	1

the current study may reflect the role of administered means for IBS diagnosis, the selected age- or course-group of the study, and the sample population's size.

In the current study, consistent with the previous reports (1,19,20), females were dominantly affected by IBS. However, this predominance did not lead to a significant difference in our research. On the other hand, a Korean study (21) stated inverse results regarding the predominance of male involvement.

Sleep disturbances are one of the probable aspects associated with IBS. In the current study, we have evaluated sleep processes from two perspectives; primarily, PSQI as the determinant of sleep quality and secondarily, daily length of sleep, which was an independent factor inversely associated with IBS incidence.

Sleep disturbances seem to have turned into an unavoidable problem among medical students. The previous studies have represented sleep disturbances among 30%-60% of the medical students, which was associated with female gender, lower length of daily sleep, increased sleep onset latency, and increased frequency of self-reported sleep disturbances (11, 22). Similar outcomes

**Table 2.** The association of IBS diagnosis with the demographic and sleep-related characteristics among the studied population

Variables	IBS			P value
	All (n = 100)	Healthy (n = 76)	Patient (n = 24)	
Gender, n (%)				
Female	69 (69)	51 (~67.4)	18 (75.0)	0.498 <sup>a</sup>
Male	31 (31)	25 (~32.6)	6 (25.0)	
Age category, n (%)				
18 – 20 years	21 (21)	18 (~23.9)	3 (12.5)	0.661 <sup>b</sup>
21-24 years	64 (64)	46 (~59.8)	18 (75.0)	
25-28 years	15 (15)	12 (~16.3)	3 (12.5)	
Residence, n (%)				
Native	22 (22)	16 (~21.7)	6 (25.0)	0.562 <sup>a</sup>
Non-native	78 (78)	60 (~78.3)	18 (75.0)	
Sleep dysfunction, <sup>d</sup> n (%)				
No	34 (34)	26(~34.8)	6 (25.0)	0.447 <sup>a</sup>
Yes	66 (66)	48 (~65.2)	18 (75.0)	
Length of sleep (h), mean ± SD	6.02 ± 1.29	6.10 ± 1.25	5.00 ± 1.34	0.019 <sup>*c</sup>

The results are presented as n (%) & the mean value ± standard deviation (SD).

<sup>a</sup> Fisher's exact test; <sup>b</sup> The likelihood ratio test; <sup>c</sup> The student's *t*-test; <sup>d</sup> Measured according to the Pittsburg Sleep Quality Index (PSQI).

\*Significant at the level of 5%.

**Table 3.** The logistic regression assessment for irritable bowel syndrome

	Model I		Model II		Model III	
	OR (95% CI)	P value	AOR (95% CI)	P value	AOR (95% CI)	P value
Sleep dysfunction (yes versus no)	10.0 (4.3, 23.3)	<0.001*	1.1 (0.2, 4.7)	0.923	1.3 (0.2, 10.3)	0.802

The model I: Unadjusted logistic regression model; Model II: Adjusted for the length of sleep; Model III: Adjusted for gender, age category, residence, and length of sleep. OR: Odds ratio; 95% CI: 95% confidence interval. AOR: Adjusted odds ratio.

\*Significant at the level of 5%.

were detected in our study in which 66% of the studied medical students had sleep disorders.

A remarkable point about the daily sleep time in Iran versus the other studies is the shorter length of sleep in our study than the studies performed in the United States (23) as a developed and Brazil (24) as a developing community. Therefore, short daily sleep time as a strong predictor of poor sleep quality has a worse condition among students in Iran.

Although the etiology is unknown, reviewing the literature shows that circadian disturbance may play a causative role in functional gastrointestinal disorders as nurses with rotating shifts had a higher prevalence of IBS than those with fixed shifts. Similar patterns were noted among medical students and those on-call specialists whose nocturnal sleep duration was undetermined (19, 25,26). Schey and colleagues proposed a theory about visceral hypersensitivity for the higher incidence of functional gastrointestinal disorders among those with sleep deprivation (27).

An increase in the cortisol level and suppression of the parasympathetic system that is well-established in people with sleep disturbances are the other aspects probably in association with gastrointestinal disorders (28). Short sleep length, on a hand, and the stressful nature of studying

medicine, on the other hand, are the factors affecting the autonomic system in medical students that may be related to the high incidence rate of IBS.

Several other factors have been demonstrated as relevant to visceral hypersensitivity in IBS, including alterations in neurotransmitters (e.g., serotonin), intestinal permeability, microinflammation, and the bacterial milieu. It seems that IBS patients are more susceptible to visceral hypersensitivity and the alterations in gut-based derangements due to sleep disturbances (29).

### Conclusion

In this study we found, IBS was diagnosed in 24% of the medical students in Isfahan. The length of sleep was significantly associated with IBS; however, age and gender and also sleep quality did not have any significant association with it

### Limitations of the study

The small sample population was the most remarkable limitation of this study. In addition, we have not evaluated the course of study as a potential risk factor for sleep dysfunction among the studied population. Further studies by consideration of more detailed confounders affecting sleep quality are recommended.

### Acknowledgments

We are grateful to Dr. Ali Safaei for his efforts in the preparation of the current manuscript.

### Authors' contribution

SM, BA and AT were the principal investigators of the study. SM, BA and AT were included in preparing the concept and design. SM, BA and AT revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols (IR.MUI.MED.REC.1399.1091). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D thesis of Dr. Samin Maghsoudi at this university. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

### Funding/Support

The current paper has been sponsored by Isfahan University of Medical Sciences. No further sponsorship has been administered (grant#3991028).

### References

- Ibrahim NK. A systematic review of the prevalence and risk factors of irritable bowel syndrome among medical students. *Turk J Gastroenterol.* 2016;27(1):10-6. doi: 10.5152/tjg.2015.150333.
- Black CJ, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. *Nat Rev Gastroenterol Hepatol.* 2020;17(8):473-486. doi: 10.1038/s41575-020-0286-8.
- Brown RJ. Introduction to the special issue on medically unexplained symptoms: background and future directions. *Clin Psychol Rev.* 2007;27(7):769-80. doi: 10.1016/j.cpr.2007.07.003.
- Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. *N Engl J Med.* 2017 Jun 29;376(26):2566-2578. doi: 10.1056/NEJMr1607547.
- Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol.* 2010;7(3):163-73. doi: 10.1038/nrgastro.2010.4.
- Ng QX, Soh AYS, Loke W, Lim DY, Yeo WS. The role of inflammation in irritable bowel syndrome (IBS). *J Inflamm Res.* 2018 Sep 21;11:345-349. doi: 10.2147/JIR.S174982.
- Qureshi SR, Abdelaal AM, Janjua ZA, Alasmari HA, Obad AS, Alamodi A, Shareef MA. Irritable Bowel Syndrome: A Global Challenge Among Medical Students. *Cureus.* 2016 Aug 1;8(8):e721. doi: 10.7759/cureus.721.
- Wang B, Duan R, Duan L. Prevalence of sleep disorder in irritable bowel syndrome: A systematic review with meta-analysis. *Saudi J Gastroenterol.* 2018;24(3):141-150. doi: 10.4103/sjg.SJG\_603\_17.
- Patel A, Hasak S, Cassell B, Ciorba MA, Vivio EE, Kumar M, et al. Effects of disturbed sleep on gastrointestinal and somatic pain symptoms in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2016 Aug;44(3):246-58. doi: 10.1111/apt.13677.
- Liu Y, Liu L, Yang Y, He Y, Zhang Y, Wang M, et al. A school-based study of irritable bowel syndrome in medical students in Beijing, China: prevalence and some related factors. *Gastroenterol Res Pract.* 2014;2014:124261. doi: 10.1155/2014/124261.
- Azad MC, Fraser K, Rumana N, Abdullah AF, Shahana N, Hanly PJ, et al. Sleep disturbances among medical students: a global perspective. *J Clin Sleep Med.* 2015 Jan 15;11(1):69-74. doi: 10.5664/jcsm.4370.
- Schmulson MJ, Drossman DA. What Is New in Rome IV. *J Neurogastroenterol Motil.* 2017 Apr 30;23(2):151-163. doi: 10.5056/jnm16214.
- Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology.* 2016;150(6):1257-61. doi: 10.1053/j.gastro.2016.03.035.
- Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4.
- Ebrahimi Afkham A, Ghalebani M, Salehi M, Kafian Tafti A, Vakili Y, Akhlaghi Farsi E. Study of sleep parameters and factors effecting on sleep quality of outpatients clients of selected Rasol-E-Akram hospital clinics. *J Iran Univ Med Sci.* 2008;58(15):31-7.
- Dong YY, Zuo XL, Li CQ, Yu YB, Zhao QJ, Li YQ. Prevalence of irritable bowel syndrome in Chinese college and university students assessed using Rome III criteria. *World J Gastroenterol.* 2010 Sep 7;16(33):4221-6. doi: 10.3748/wjg.v16.i33.4221.
- Gwee KA, Ghoshal UC, Chen M. Irritable bowel syndrome in Asia: Pathogenesis, natural history, epidemiology, and management. *J Gastroenterol Hepatol.* 2018;33(1):99-110. doi: 10.1111/jgh.13987.
- Mansouri A, Rarani MA, Fallahi M, Alvandi I. Irritable bowel syndrome is concentrated in people with higher educations in Iran: an inequality analysis. *Epidemiol Health.* 2017 Feb 1;39:e2017005. doi: 10.4178/epih.e2017005.
- Okami Y, Kato T, Nin G, Harada K, Aoi W, Wada S, et al. Lifestyle and psychological factors related to irritable bowel syndrome in nursing and medical school students. *J Gastroenterol.* 2011;46(12):1403-10. doi: 10.1007/s00535-011-0454-2.
- Kim YS, Kim N. Sex-Gender Differences in Irritable Bowel Syndrome. *J Neurogastroenterol Motil.* 2018 Oct 1;24(4):544-558. doi: 10.5056/jnm18082.
- Jung HJ, Park MI, Moon W, Park SJ, Kim HH, Noh EJ, et al. Are Food Constituents Relevant to the Irritable Bowel Syndrome in Young Adults? - A Rome III Based Prevalence Study of the Korean Medical Students. *J Neurogastroenterol Motil.* 2011;17(3):294-9. doi: 10.5056/jnm.2011.17.3.294.
- Seoane HA, Moschetto L, Orliacq F, Orliacq J, Serrano E, Cazenave MI, et al. Sleep disruption in medicine students and its relationship with impaired academic performance: A systematic review and meta-analysis. *Sleep Med Rev.* 2020;53:101333. doi: 10.1016/j.smrv.2020.101333.
- Ayala EE, Berry R, Winseman JS, Mason HR. A Cross-Sectional Snapshot of Sleep Quality and Quantity Among US Medical Students. *Acad Psychiatry.* 2017;41(5):664-668. doi: 10.1007/s40596-016-0653-5.
- Corrêa CC, Oliveira FK, Pizzamiglio DS, Ortolan EVP, Weber SAT. Sleep quality in medical students: a comparison across the various phases of the medical course. *J Bras Pneumol.* 2017;43(4):285-289. doi: 10.1590/S1806-37562016000000178.
- Nojkov B, Rubenstein JH, Chey WD, Hoogerwerf WA. The impact of rotating shift work on the prevalence of irritable bowel syndrome in nurses. *Am J Gastroenterol.* 2010;105(4):842-7. doi: 10.1038/ajg.2010.48.

26. Wells MM, Roth L, Chande N. Sleep disruption secondary to overnight call shifts is associated with irritable bowel syndrome in residents: a cross-sectional study. *Am J Gastroenterol.* 2012;107(8):1151-6. doi: 10.1038/ajg.2011.486.
27. Schey R, Dickman R, Parthasarathy S, Quan SF, Wendel C, Merchant J, et al. Sleep deprivation is hyperalgesic in patients with gastroesophageal reflux disease. *Gastroenterology.* 2007;133(6):1787-95. doi: 10.1053/j.gastro.2007.09.039.
28. van Langenberg DR, Papandony MC, Gibson PR. Sleep and physical activity measured by accelerometry in Crohn's disease. *Aliment Pharmacol Ther.* 2015;41(10):991-1004. doi: 10.1111/apt.13160.
29. Mertz H. Review article: visceral hypersensitivity. *Aliment Pharmacol Ther.* 2003 Mar 1;17(5):623-33. doi: 10.1046/j.1365-2036.2003.01447.x.