

Irritable bowel syndrome in obstructive sleep apnea: a preliminary Egyptian study

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Background Sleep disturbances represent a common extra-intestinal manifestation of functional gastrointestinal disorders. This study aimed to determine the prevalence of irritable bowel syndrome (IBS) among some Egyptian patients with obstructive sleep apnea (OSA) and to further assess the correlation between the prevalence of IBS and the severity of OSA.

Patients and methods Patients referred to the Sleep Disorders Clinic with polysomnographically (PSG) confirmed OSA were included. A second group that included 15 patients with OSA-free IBS was enrolled as controls. For all patients, the Epworth Sleepiness Scale and the Berlin Questionnaire were used to assess subjective sleep quality and overnight PSG was performed to assess objective sleep quality.

Results A total of 256 patients with OSA were included; 225 (87.9%) were men and 31 (12.1%) were women. The mean (SD) age of the patients was 49.84 (11.41) years, with a range of 24–81 years. In terms of the severity of OSA, 40 (15.6%) patients had mild OSA, 33 (12.9%) patients had moderate OSA, and the remaining 183 (71.5%) patients had severe OSA. Among the study participants with OSA, IBS was found in 93 patients (80 men and 13 women); the prevalence of IBS was 36.3%. The severity of OSA among OSA patients with IBS was as follows: 23 had mild OSA, 11 had moderate OSA,

and 59 had severe OSA. There were nonsignificant differences between OSA patient subgroups for both Epworth Sleepiness Scale and the Berlin questionnaire ($P > 0.05$); yet, two objective PSG parameters differed significantly: apnea–hypopnea index ($P = 0.005$) and sleep latency ($P = 0.01$). Neither subjective nor objective sleep disturbances were found among the IBS controls. In the OSA group, IBS correlated significantly and inversely with apnea–hypopnea index ($r = -0.171$, $P = 0.006$), and OSA grading of severity ($r = -0.173$, $P = 0.005$).

Conclusion IBS is prevalent in OSA patients and is correlated inversely with the severity grading of OSA.

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Introduction

Functional bowel disorder (FBD) of the gastrointestinal tract (GIT) represents a group of diseases that manifest clinically with symptoms related to the mid or the lower parts of GIT [1].

Irritable bowel syndrome (IBS), being the most common FBD, accounts for 25–50% of medical referrals to gastroenterologists, [2] with an estimated prevalence of 3–20% [3]. The main presenting features of IBS include chronic abdominal pain and altered bowel habits in the absence of any organic disease process [4]. IBS, despite being a functional disorder, it causes significant morbidity and places a considerable burden on health care resources [5].

Interestingly, an association between sleep disturbances and FBD particularly IBS has been reported by several investigators [6–8]; sleep apnea was observed in IBS patients who underwent sleep studies [6]. Moreover, women with IBS showed increased tendency for pharyngeal collapse during sleep compared with healthy female control participants [9]. Possible assumptions for this relationship included difficulty in initiating and maintaining sleep secondary to abdominal pain. Also, a state of improper brain–gut interaction

because of altered autonomic nervous system in patients with functional gastrointestinal complaints can occur because of increased arousal during sleep [6,10].

Most of the published studies have focused on the prevalence of sleep disturbances among patients with IBS, but none of these studies assessed the prevalence of IBS among patients with obstructive sleep apnea (OSA). To explore this relationship, we investigated the prevalence of IBS among some Egyptian patients with OSA and we further assessed the correlation between the prevalence of IBS and the severity of OSA.

Patients and methods

This prospective study was carried out at Ain Shams University Hospital and a private sleep disorders center in Cairo city in the period between June 2013 and June 2017. Adult patients referred to the Sleep Disorders Clinic with a clinical suspicion of sleep-related breathing disorders and patients with polysomnographically

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(PSG) confirmed OSA were enrolled in the study. An additional group of IBS patients without OSA was included and served as a control group. This study was approved by the local institutional ethical committee of the Faculty of Medicine at Ain Shams University.

Subjective evaluation of sleep quality

Sleep consultation was performed by a physician specialized in sleep medicine. Patients underwent a comprehensive assessment of medical history and complete physical examination. All participants completed the Arabic versions of the Epworth Sleepiness Scale (ESS) and the Berlin questionnaire within a few days of the sleep study. The ESS is a self-administered questionnaire that asks participants to rate how likely it is for them to fall asleep in eight situations or activities commonly performed in daily life. The chance of falling asleep is rated on a scale of 0–3 (0=would never fall asleep, 1=slight chance of falling asleep, 2=moderate chance of falling asleep, and 3=high chance of falling asleep). The overall ESS score is the sum of the eight-item scores and can range between 0 and 24. The higher the score, the higher the individual's tendency toward daytime sleepiness. The cutoff for sleepiness in the ESS score is 11: <11→low risk for sleepiness and ≥11→high risk for sleepiness [11].

The Berlin questionnaire has 11 questions grouped into three categories. Questions 1–5 represent the first category. The second category is represented by questions 4–9. The third category is represented by questions 10–11. The first and second Categories are positive if there are at least two positive responses to each category, whereas the third category is considered positive with at least one positive response. High risk for OSA was considered with at least two positive categories. Low risk for OSA was considered with less than two positive categories [12].

Objective evaluation of sleep quality

Nocturnal full-night PSG in the sleep laboratory starting from 10 p.m. to 6 a.m. was performed for all patients using a computerized system (N4000 Embla; Somnologica, Reykjavik, Iceland) including the monitoring of electroencephalogram, electro-oculogram, submental and anterior tibial electromyogram, body position, oxygen saturation, ECG, inductance plethysmography of the chest and abdomen, a nasal pressure sensor, and an oronasal thermister. The recording was scored manually according to standard guidelines [13]. The apnea-hypopnea index (AHI) was calculated as the number of

apneas and hypopneas per hour of total sleep time (TST). The cutoff for the diagnosis of OSA was AHI of greater than or equal to 5 and the grading of severity of OSA was arbitrarily set at cutoff levels of AHI: greater than or equal to 5 to less than 15 episodes/TST for mild OSA, greater than or equal to 15 to less than 30 episodes/TST for moderate OSA, and greater than or equal to 30 episodes/TST for severe OSA [14].

Evaluation of irritable bowel syndrome

Only those IBS patients who were previously diagnosed with IBS and fulfilled the Rome III criteria [15] with no evidence of organic gastrointestinal disease were eligible for participation. Defined in accordance with Rome III criteria [15], IBS was recurrent abdominal pain or discomfort that was present for at least 3 months, with onset at least 6 months previously. In addition, two or more of the following symptoms had to be present: improvement with defecation; onset associated with a change in the frequency of defecation; and onset associated with a change in the form (appearance) of stool. Apart from a thorough physical examination, further diagnostic assessments were performed for some patients (those with the diarrhea-predominant IBS subtype) including complete blood picture, stool analysis, and stool culture.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences software (SPSS for Windows, version 17.0; SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were presented as mean±SD. A test for normality was carried out using the Shapiro–Wilk test. The χ^2 -test was used for comparison between qualitative variables. An independent-sample *t*-test was used for comparison between normally distributed quantitative variables. The Mann–Whitney test and the Kruskal–Wallis test were used for comparison between non-normally distributed quantitative variables. The Pearson correlation coefficient was used to assess the correlation between two variables. Statistical significance was set at *P* less than 0.05.

Results

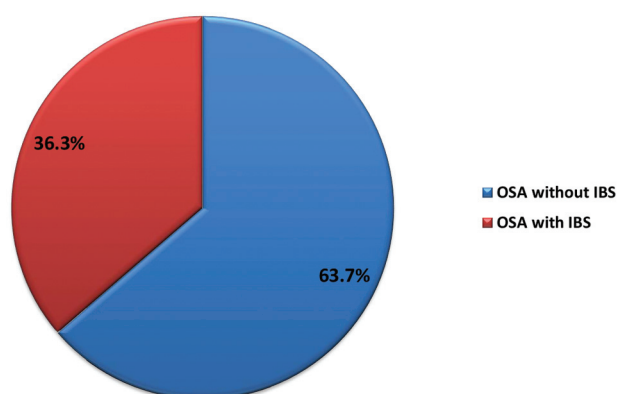
In all, 256 OSA patients fulfilled the inclusion criteria and were included in the study; 225 (87.9%) were men and 31 (12.1%) were women. The mean age (SD) of the patients was 49.84 (11.41) years, with a range of 24–81 years. In terms of the severity of OSA, 40 (15.6%) patients had mild OSA, 33 (12.9%) patients had moderate OSA, and the remaining 183 (71.5%) patients had severe OSA. Both OSA patient subgroups

(having IBS and free from IBS) were matched for age, sex, and BMI ($P>0.05$). Among the study participants with OSA, IBS was found in 93 patients (80 men and 13 women); the prevalence of IBS was 36.3% (Fig. 1). The severity of OSA among the 93 OSA patients with IBS was as follows: 23 had mild OSA, 11 had moderate OSA, and the remaining 59 patients had severe OSA (Fig. 2). The other group of patients with IBS, but without OSA, included 15 patients (13 men and two women) with a mean age (SD) of 44.33 (11.9) years, with a range of 25–67 years. There were no racial differences between any of the patients included.

Subjective sleep quality

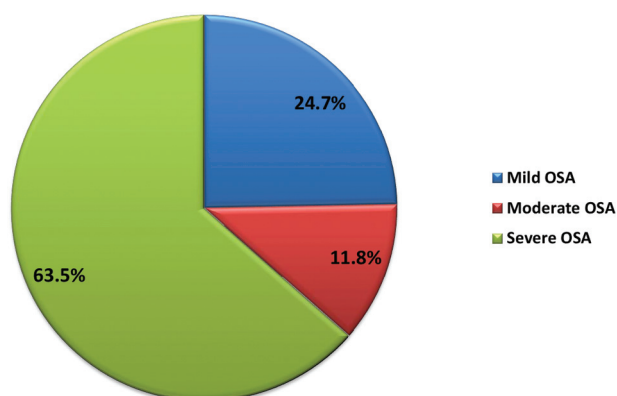
As shown in Table 1, OSA patient subgroups showed nonsignificant differences ($P>0.05$) in subjective sleep quality using either ESS or the Berlin questionnaire. On comparing the subjective sleep quality among the OSA-free IBS patients with both subgroups of OSA, all OSA patients (either free from or having IBS)

Figure 1



Frequency of IBS in patients with OSA. IBS, irritable bowel syndrome; OSA, obstructive sleep apnea

Figure 2



OSA severity in OSA patients with IBS. IBS, irritable bowel syndrome; OSA, obstructive sleep apnea

reported a significant increase in the tendency toward sleepiness in the ESS ($P=0.004$ and 0.009 , respectively, Table 3).

Comparison between polysomnographic parameters

In OSA patient subgroups, polysomnographic parameters showed significant differences in AHI ($P=0.005$) and sleep latency ($P=0.01$). Apart from these two parameters, all other sleep parameters did not differ significantly ($P>0.05$, Table 2).

On comparing each of the OSA patients' subgroups (with IBS and without IBS) with the control IBS patients, age was matched ($P>0.05$), but BMI differed significantly ($P=0.015$ and 0.005 , respectively). In addition, a number of sleep variables differed significantly: stages N1 and N2 sleep ($P=0.002$ and 0.001 , respectively), stages N3 ($P=0.004$ and 0.003 , respectively), AHI ($P=0.000$ and 0.000 , respectively), arousal index ($P=0.000$ and 0.000 , respectively). However, none of the other remaining parameters showed significant group differences, except for percentage of rapid eye movement (REM) sleep, which differed significantly only between the subgroup of OSA patients free from IBS ($P=0.018$), and REM latency, which differed significantly ($P=0.011$) only between the subgroup of OSA patients with IBS (Table 3).

Correlation between obstructive sleep apnea severity and irritable bowel syndrome

As shown in Table 4, IBS correlated significantly and inversely with both AHI ($r=-0.171$, $P=0.006$) and OSA grading of severity ($r=-0.173$, $P=0.005$) among the OSA group of patients.

Discussion

IBS remains a poorly understood chronic disorder despite recent advances in researches focused on its pathophysiology. It has long been recognized that sleep disturbances are a common extra-intestinal manifestation of some functional gastrointestinal disorders such as IBS. For this reason, IBS should be examined in terms of multiple physiological determinants rather than as a single disease entity, especially with IBS being considered one of the functional somatic syndromes nowadays [16,17].

Although not typically recognized as a presenting symptom, sleep complaints appear to be very common in the IBS population, resulting in poor sleep quality [7,8,18–23]. Yet, most studies have focused on the prevalence of sleep disturbances, either subjective or objective, among IBS patients.

Table 1 Questionnaires in obstructive sleep apnea patient subgroups

Variables	OSA without IBS (n=163)	OSA with IBS (n=93)	P
ESS (%)			
Total score (mean±SD)	13.85±6.4	13.51±6.28	
ESS<11	31.9	37.8	0.589
ESS≥11	68.1	62.2	0.603
Berlin (%)			
Positive category 1 (Q. 1–5)	96.9	95.7	0.727
Positive category 2 (Q. 6–9)	70.4	73.6	0.664
Positive category 3 (Q. 10–11)	92.6	90.2	0.636
Berlin Q % with ≥2 positive categories	95.6	93.4	1.000
Berlin Q % with <2 positive categories	4.4	6.6	

ESS, Epworth Sleepiness Scale; IBS, irritable bowel syndrome; OSA, obstructive sleep apnea.

Table 2 Demographic and polysomnographic parameters in obstructive sleep apnea patient subgroups

Variables	OSA without IBS (n=163) (mean±SD)	OSA with IBS (n=93) (mean±SD)	P
Age (years)	50.26±11.14	49.12±11.88	0.447
Sex (male/female)	145/18	80/13	0.649
BMI (kg/m ²)	39.18±8.83	38.23±10.24	0.287
TST (min)	357.89±87.79	365.65±81.9	0.456
% of N1 and N2 NREM sleep from TST	74±18.3	74.04±15.74	0.64
% of N3 NREM sleep from TST	12.09±17.43	10.15±11.13	0.675
% of REM sleep from TST	14.12±11.22	16.13±9.8	0.069
AHI (event/h of TST)	56.06±29.88	45.16±31.04	0.005
Arousal index (event/h of TST)	48.65±23.81	43.28±27.22	0.067
Sleep latency (min)	16.76±22.13	23.66±26.34	0.01
REM latency (min)	151.64±91.31	164.02±91.75	0.332
Sleep efficiency (TST/TIB)	78.11±17.55	77.85±16.62	0.701

AHI, apnea–hypopnea index; IBS, irritable bowel syndrome; N1, stage 1; N2, stage 2; N3, stage 3; NREM, nonrapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement; TIB, time in bed; TST, total sleep time.

Table 3 Demography, questionnaires, and polysomnographic parameters in obstructive sleep apnea patients and controls

Variables	OSA without IBS (n=163) (mean±SD)	OSA with IBS (n=93) (mean±SD)	IBS without OSA (n=15) (mean±SD)	P ₁	P ₂
Age (years)	50.26±11.14	49.12±11.88	44.33±11.9	0.052	0.151
Sex (male/female)	145/18	80/13	13/2	1.000	0.476
BMI (kg/m ²)	39.18±8.83	38.23±10.24	33.51±7.8	0.005	0.015
ESS	13.85±6.4	13.51±6.28	8.2±3.36	0.004	0.009
TIB (min)	456.57±44.86	469.24±33.95	468.2±30.74	0.121	0.74
TST (min)	357.89±87.79	365.65±81.9	364.81±90.93	0.531	0.752
% of N1 and N2 NREM sleep from TST	74±18.3	74.04±15.74	60.89±9.24	0.001	0.002
% of N3 NREM sleep from TST	12.09±17.43	10.15±11.13	17.61±9.56	0.003	0.004
% of REM sleep from TST	14.12±11.22	16.13±9.8	21.56±12.63	0.018	0.054
AHI (event/h of TST)	56.06±29.88	45.16±31.04	2.213±1.51	0.000	0.000
Arousal index (event/h of TST)	48.65±23.81	43.28±27.22	18.01±13.76	0.000	0.000
Sleep latency (min)	16.76±22.13	23.66±26.34	15.47±10.44	0.155	0.585
REM latency (min)	151.64±91.31	164.02±91.75	99.04±55	0.059	0.011
Sleep efficiency (TST/TIB)	78.11±17.55	77.85±16.62	77.57±17.99	0.819	0.94

AHI, apnea–hypopnea index; ESS, Epworth Sleepiness Scale; IBS, irritable bowel syndrome; N1, stage 1; N2, stage 2; N3, stage 3; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement; TIB, time in bed; TST, total sleep time. P₁: difference between OSA patients without IBS and IBS patients without OSA. P₂: difference between OSA patients with IBS and IBS patients without OSA.

To our knowledge, this study is unique because of the assessment of the prevalence of IBS among patients with OSA using both subjective and objective measures of sleep quality as several previous studies

have relied only on the subjective perception of sleep disorders among patients using different types of questionnaires. Moreover, this is the first Egyptian study to investigate this issue. The ESS and the

Table 4 Correlation between obstructive sleep apnea severity and irritable bowel syndrome

Variables	<i>r</i>	<i>P</i>
AHI	-0.171	0.006
Grade of severity of OSA	-0.173	0.005

AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.

Berlin questionnaire were used to assess subjective sleep quality, whereas PSG was performed to obtain objective measures of sleep quality. A clinical assessment for IBS combined with the Rome criteria was carried out in this study to substitute the use of invasive gastrointestinal monitoring, especially with the current acceptance of most gastroenterologists that IBS can simply be diagnosed by invasive procedures.

In our study, the prevalence of IBS among OSA patients was 36.3%. A study by Vege *et al.* [24] reported that the prevalence of IBS among patients with self-reported sleep disturbances was close to our results, being 33.3%. Yet, the sleep disturbance referred to in their study was insomnia rather than OSA. A deeper insight into the correlation between OSA and IBS present in this study has led us to an interesting finding; although all OSA patients were matched for age, sex, and BMI, yet, the severity of OSA differed significantly between the OSA subgroups, being lower among those with IBS. Moreover, the presence of IBS correlated significantly and inversely with AHI and OSA grading of severity in OSA patients. Thus, IBS was more common among OSA patients with a low grade of OSA severity rather than those with severe OSA.

A possible assumption for the correlation between sleep disturbances and FBD especially IBS suggests the involvement of the autonomic nervous system (ANS) as ANS represents the main link between the brain and the gut. Recently, Fass *et al.* [10] speculated that differences in autonomic balance during sleep can alter the gastrointestinal motility during sleep. A number of previous studies investigated the disturbances in autonomic function among IBS patients; Heitkemper *et al.* [25] have shown a significant decrease in vagal tone during sleep in patients with IBS. Orr *et al.* [26] reported a significant increase in sympatho-vagal balance exclusively during REM sleep in patients with IBS. Another study by Orr *et al.* [23] suggested intrinsic modulation of the ANS in IBS patients represented by an enhancement of REM sleep. In addition, over the past few years, it has been well accepted that ANS is strongly affected in OSA in the form of initial vagal

stimulation, followed by abrupt sympathetic activation that occurs secondary to the repetitive nocturnal upper airway collapse [27,28].

In terms of the subjective evaluation of sleep quality in our study, the control patients with IBS and without OSA did not manifest subjective sleepiness as assessed by ESS. Moreover, both subgroups of OSA patients showed subjective evidence of sleep disturbance as evidenced by both ESS and the overall score of the Berlin questionnaire as well as its individual three categories; yet, they did not differ significantly. Thus, the presence of IBS was not an additive factor for the subjective perception of daytime sleepiness and sleep disturbances. In a recent study, Goldsmith and Levin [8] suggested that IBS symptoms correlated with the quality of the previous night's sleep; yet, in their study, the methodology for the assessment of sleep quality was based on sleep diary and not on validated sleep questionnaires as in our study. Moreover, other studies suggested that self-reported poor sleep quality might pose a negative bias [29,30].

In our study, OSA patients with IBS tended to show a significant increase in sleep latency compared with OSA patients without IBS. Moreover, although in OSA patients with IBS some differences were observed in other objective sleep parameters such as a decrease in the arousal index, AHI, and percentage of deep sleep with an increase in the percentage of time spent in REM sleep and REM latency, these differences were nonsignificant between the two OSA subgroups. Accordingly, although frequent arousal is a common feature of OSA, the presence of IBS was not considered among the causes for these arousals. When testing both subjective and objective sleep quality in IBS controls, we observed that all variables were in the normal range, and yet, this was not surprising as other studies reported that minimal expression of IBS patients' symptoms or small intestinal motor abnormalities during sleep and that the perception of IBS necessitates an arousal state of the central nervous system [6,31,32]. Thus, no change is expected in their sleep. The study of Elsenbruch *et al.* [18] compared self-reported sleep quality with objective sleep assessment in IBS patients and found that the objective measures of sleep quality were not related to the subjective assessment. Accordingly, we assumed that IBS itself might not be a cause for sleep disturbances; instead, the presence of OSA might be the triggering factor for the occurrence of IBS possibly because of the hypoxia

and frequent nocturnal arousals with sleep fragmentation characteristic for OSA.

The comparison between age-matched and sex-matched IBS-free OSA and IBS controls aimed to facilitate, both subjectively and objectively, a comparison between OSA and IBS; these two groups were not matched for BMI on the basis of the fact that obesity is an important risk factor for OSA and not IBS. Subjective sleep quality as well as several objective sleep parameters, particularly those parameters with well-known OSA-related changes such as the percentage of time spent in light sleep (stages N1 and N2 non-REM sleep) as well as deep sleep (stage N3 non-REM sleep), REM sleep, the arousal index, and certainly AHI, differed significantly between the two groups. The difference in the percentage of time spent in both light sleep and deep sleep between the two groups was attributed to the recurrent nocturnal arousals in OSA patients, which results in sleep fragmentation and predomination of light sleep. Whereas the difference in the percentage of time spent in REM stage, being much more decreased in OSA, is attributable to the fact that OSA patients are REM deprived, with increased latency to REM sleep. The percentage of REM sleep in IBS controls in the present study was in agreement with that reported in a study by Orr *et al.* [23]. An additional important observation was the further increase in REM sleep in the OSA patients with IBS compared with the IBS-free OSA patients; yet, this could be explained on the basis of our findings that IBS was more prevalent in those OSA patients with low grading of severity in whom REM stage is less affected compared with those patients with more severe OSA. It is worth mentioning that in contrast to our results, two previous studies reported that IBS patients were characterized by increased REM sleep compared with healthy controls [6,23]. Yet, the limited number of patients in their studies might pose a bias.

Conclusion

The results of this study provide evidence that IBS is prevalent among OSA patients and correlated inversely with the severity grading of OSA. IBS alone or in association with OSA did not further affect subjective sleep quality. The presence of IBS in OSA patients affected some objective measures of sleep; yet, this was mostly attributed to OSA rather than IBS.

Finally, the prevalence of IBS in OSA should not be overlooked for a better understanding and deeper insight into the etiology of these disorders.

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Conflicts of interest

There are no conflicts of interest.

References

- 1 Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; **45**(Suppl II):II43-II47.
- 2 Everhart JE, Renault PF. Irritable bowel syndrome in office based practice in the United States. *Gastroenterol* 1991; **100**: 998-1005.
- 3 Foux-Orenstein A. IBS - review and what's new. *MedGenMed* 2006; **8**:20.
- 4 Drossman DA. Irritable bowel syndrome. *Gastroenterol* 1994; **2**:315-326.
- 5 Locke GR III. The epidemiology of functional gastrointestinal disorders in North America. *Gastroenterol Clin North Am* 1996; **25**:1-19.
- 6 Kumar D, Thompson PD, Wingate DL, Vesselinova-Jenkins CK, Libby G. Abnormal REM sleep in the irritable bowel syndrome. *Gastroenterology* 1992; **103**:12-17.
- 7 Jarrett M, Heitkemper M, Cain KC, Burr RL, Hertig V. Sleep disturbance influences gastrointestinal symptoms in women with irritable bowel syndrome. *Dig Dis Sci* 2000; **45**:952-959.
- 8 Goldsmith G, Levin JS. Effect of sleep quality on symptoms of irritable bowel syndrome. *Dig Dis Sci* 1993; **38**:1809-1814.
- 9 Gold AR, Broderick JE, Amin MM, Gold MS. Inspiratory airflow dynamics during sleep in irritable bowel syndrome: a pilot study. *Sleep Breath* 2009; **13**:397-407.
- 10 Fass R, Fullerton S, Tung S, Mayer EA. Sleep disturbances in clinic patients with functional bowel disorders. *Am J Gastroenterol* 2000; **95**:1195-1200.
- 11 Johns MW. Sleepiness in different situations measured by the Epworth Sleepiness Scale. *Sleep* 1994; **17**:703-710.
- 12 Mahboub B, Safaraini B, Alhariri H, Vats M. Reprinting of the Berlin questionnaire. *Sleep Breath* 2000; **4**:187-192.
- 13 Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, *et al.* *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 2.3.* Darien, IL: American Academy of Sleep Medicine; 2016.
- 14 Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research: The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; **22**:667-689.
- 15 Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterol* 2006; **130**:1480-1491.
- 16 Barsky AJ, Borus JF. Functional somatic syndromes. *Ann Intern Med* 1999; **130**:910-921.
- 17 Aaron L, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 2001; **134**:868-881.
- 18 Eisenbruch S, Harnish MJ, Orr WC. Subjective and objective sleep quality in irritable bowel syndrome. *Am J Gastroenterol* 1999; **94**:2447-2452.
- 19 Heitkemper M, Jarrett M, Burr R, Cain KC, Landis C, Lentz M, *et al.* Subjective and objective sleep indices in women with irritable bowel syndrome. *Neurogastroenterol Motil* 2005; **17**:523-530.
- 20 Whorwell PJ, McCallum M, Creed FH, Roberts CT. Non-colonic features of irritable bowel syndrome. *Gut* 1986; **27**:37-40.
- 21 Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EA, Lowman BC, *et al.* Psychosocial factors in the irritable bowel syndrome. *Gastroenterology* 1988; **95**:701-708.
- 22 Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with irritable bowel syndrome. *J Psychosom Res* 1991; **34**:483-491.
- 23 Orr WC, Crowell MD, Lin B, Harnish M, Chen J. Sleep and gastric function in irritable bowel syndrome (IBS): derailing the brain gut axis. *Gut* 1997; **41**:390-393.
- 24 Vege SS, Locke GR 3rd, Weaver AL, Farmer SA, Melton LJ 3rd, Talley NJ. Functional gastrointestinal disorders among people with sleep disturbances: a population-based study. *Mayo Clin Proc* 2004; **79**:1501-1506.

- 25 Heitkemper M, Burr RL, Jarrett M, Hertig V, Lustyk MK, Bond EF. Evidence for autonomic nervous system imbalance in women with irritable bowel syndrome. *Dig Dis Sci* 1998; **43**:2093–2098.
- 26 Orr WC, Elsenbruch S, Harnish MJ. Regulation of cardiac function in patients with irritable bowel syndrome. *Gastroenterology* 1999; **116**: A1054.
- 27 Roche F, Gaspoz JM, Court-Fortune I, Minini P, Pichot V, Duverney D, et al. Screening of obstructive sleep apnea syndrome by heart rate variability. *Circulation* 1999; **100**:1411–1415.
- 28 Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998; **98**:1071–1077.
- 29 Naliboff BD, Munakata J, Fullerton S, Gracely RH, Kodner A, Harraf F, et al. Evidence for two distinct perceptual alterations in irritable bowel syndrome. *Gut* 1997; **41**:505–512.
- 30 Gomborone J, Dewsnap P, Libby G, Farthing M. Abnormal illness attitudes in patients with irritable bowel syndrome. *J Psychosom Res* 1996; **39**:227–230.
- 31 Thompson DG, Laidlaw JM, Wingate DL. Abnormal small bowel motility demonstrated by radiotelemetry in a patient with irritable colon. *Lancet* 1979; **2**:1321–1323.
- 32 Kellow JE, Gill RC, Wingate DL. Prolonged ambulant manometry of small bowel motility demonstrates abnormalities in irritable bowel syndrome. *Gastroenterology* 1990; **98**:1208–1218.