

Re: 32848

Stress and sleep quality in doctors working on-call shifts are associated with functional gastrointestinal disorders

Thank you very much for giving us an opportunity for revision.

For the reviewers' convenience, the alterations were marked with red font instead of black to indicate the revised manuscript.

We hope that the revised version will fulfill the requirements for publication in **World Journal of Gastroenterology** and give you satisfaction.

We appreciate the reviewers' comments and the opportunity to improve the manuscript.

Thank you very much.

Sincerely,

Seong-Joon Koh, M.D., Ph.D.

Division of Gastroenterology, Department of Internal Medicine,

Seoul National University College of medicine, Seoul National University Boramae Hospital,

5 Gil 20, Boramae-Road, Dongjak-Gu, Seoul, 156-707, Korea

TEL: + 82 2 870 2234, FAX: + 82 2 870 3863

E-mail: jel1206@snu.ac.kr

Reviewer #1:

This paper studied about Stress and sleep quality in doctors working on-call shifts with functional gastrointestinal disorders. This paper is well designed and is good to publish in WJG.

Reply) We really appreciate your kind comments.

Reviewer #2

In this paper, authors evaluated the prevalence of irritable bowel syndrome and functional dyspepsia in 170 doctors who had experienced 24 hour-on-call shifts in the last 6 months. Rome III criteria and a validated Korean version of Bowel Disease Questionnaire were used for the assessment of FD and IBS. It is a well designed study and, to my knowledge, the first one assessing the impact of 24 hour-on-call shifts in the prevalence of functional gastrointestinal disorders (FGID) in this specific population. Interestingly and according to some previous studies authors also found that sleep impairment and psychological stress are associated to a higher prevalence of FGID in this specific population, after adjusting for multiple confounding factors.

Question 1) I would like to know if authors have any explanation to the finding that poor quality sleep was associated with IBS but was not associated with FD.

Reply) Thank you for the pointing this out. In accordance with the reviewer's suggestion, we added sentences and references about reviewer's question.

(Discussion section, Page 18 line 20-23 to Page 19 line 1-8)

FD and IBS are considered as different aspects of a unifying spectrum of disease, as they often appear together as overlapping syndromes^[28,29]. In addition, IBS and FD belong to the same categorical concept as FGIDs, and may share common pathophysiology such as visceral hypersensitivity^[30]. However, they are somewhat different in aspects of risk factors^[31]. In **the present** study, marital status, alcohol drinking, and serious psychosocial alarm were risk factors of FD, and female gender,

occupational position of resident, and poor sleep quality were risk factors of IBS. Furthermore, poor sleep quality was associated with IBS but not associated with FD. A previous study also has demonstrated that sleep disturbance was independently associated with the prevalence of IBS, but not FD^[32]. Our previous study showed that IBS had a relationship with poor sleep quality rather than psychosocial stress, and FD showed an association with psychosocial stress^[9]. Unfortunately, the effect of sleep disturbance in IBS and FD remains still obscure. Recently, there are major advances in our understandings with the identification of subtype of FGIDs. There exist the differences in genetics, microbiota, brain-gut axis, and stress susceptibility between FD and IBS^[33,34]. The interplay among these factors may contribute to the development of different gastrointestinal symptoms. This is a plausible explanation that sleep disturbance has a different role in FD and IBS. Further mechanistic studies are needed to elucidate the role of sleep disturbance in the development of FGIDs.

We believe that this study is valuable to readers for the following reasons.

(Reference section, Page 26 line 20-23 to Page 27 line 1-6)

32 **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;**12**:1501-1506. [PMID: 15595333 DOI: 10.4065/79.12.1501]

33 **Talley NJ**, Holtmann G, Walker MM. *J Gastroenterol.* 2015;**50**:601-613. Therapeutic strategies for functional dyspepsia and irritable bowel syndrome based on pathophysiology. [PMID: 25917563 DOI: 10.1007/s00535-015-1076-x]

34 **Khanijow V**, Prakash P, Emsellem HA, Borum ML, Doman DB. Sleep dysfunction and gastrointestinal diseases. *Gastroenterol Hepatol*. 2015;**12**:817-825. [PMID: 27134599]

Reviewer#3

This work examined factors contributing to the patterns of FGID in doctors in Korea.

Comments 1) One assumes that the subjects were all junior doctors? (rather than individuals who have completed their training - and are now consultants or specialists)

Reply)

Thank you for your valuable comment. As we mentioned in Study subjects section, our subjects were all junior doctors who underwent 24-hour-on-call shifts during last 6 months from research period and they filled in questionnaire during training in our hospital.

Comments 2) Some of the text (such as in the Introduction) could be referenced more clearly

Reply) Thank you for bringing this to our notice. We have matched text with reference and revised text adding related new references according to the reviewer's recommendation.

(Introduction section, Page 8 line 9-17)

Although psychosocial factors are not required for diagnosis of FGIDs, they influence physiological functioning of the GI tract via the brain-gut axis^[3,4].

Psychosocial stress and physical stress, such as infection, trauma, and excessive work, may contribute to symptoms and development of FGIDs^[5,6]. It is well known that altered sleep patterns are also linked to the FGIDs and altered intestinal sensitivity. A report demonstrated that poor sleep quality is associated with functional gastrointestinal symptoms in the general population^[7]. Interestingly, insufficient sleep with reduced sleep quality could be a severe stress factor and results in emotional, cognitive, and somatic effects^[8].

(References section, Page 22 line 21-25)

3 **Wilhelmsen I.** Brain-gut axis as an example of the bio-psychosocial model. *Gut* 2000; **47 Suppl 4**: iv5-7; discussion iv 10. [PMID: 11076893]

4 **Van Oudenhove L, Demyttenaere K, Tack J, Aziz Q,** Central nervous system involvement in functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004; **18**: 663-680. [PMID: 15324706 DOI: 10.1016/j.bpg.2004.04.010]

Comments 3) Would it have been helpful to include a group of young doctors at a similar level of training who do not have night shifts?

Reply)

Thank you for nice comment. It would be a great idea to enroll subjects without night shifts for comparing with subjects with night shifts and for identifying the role of disturbance of sleep and stress in development of FGIDs. We considered this point before conducting study. However, we could not enroll the doctors because the majority of trainees has night shift in our hospital. We have revised and mentioned about your recommendation as limitation of this study in Discussion section. Consideration about this point would be helpful in our future studies.

(Discussion section, Page 19 line 19-23)

Additionally, problem of discerning organic gastrointestinal disease can also be raised, as the presence or absence could not be verified via endoscopy. **Moreover, because our present study enrolled only doctors with 24 hour-on-call shift, it would be helpful to include doctors without 24 hour-on-call shift as future study subjects**

for identifying the role of on-call shift work in development of FGIDs by comparing with doctors who experienced 24 hour-on-call shift.

In conclusion, our study targeting doctors working 24 hour-on-call shifts showed a higher prevalence of sleep impairment and psychological stress in this population.

Comments 4) The title of Table 1 is inadequate and should be expanded

Reply) Thank you for your comment. We have revised Table 1 according to the reviewer's recommendation.

Table 1. Prevalence of IBS and FD according to the subsets of Functional Gastrointestinal Disorders

Subsets of IBS and FD

IBS	28/170 (16.5%)
IBS-C	1/28 (3.6%)
IBS-D	10/28 (35.7%)
IBS-M	16/28 (57.1%)
IBS-U	1/28 (3.6%)
FD	29/170 (17.1%)
EPS	7/29 (24.1%)
PDS	10/29 (34.5%)
Both EPS and PDS	12/29 (41.4%)

IBS, irritable bowel syndrome; IBS-C, constipation predominant IBS;

IBS-D, diarrhea predominant IBS; IBS-M, mixed IBS;

IBS-U, un-subtyped IBS; FD, functional dyspepsia.

EPS, epigastric pain syndromes; PDS, postprandial distress syndromes

Comments 5) The titles and legends for the other tables (other than #2) are also inadequate

Reply)

Thank you for your comment. We have revised Table 3, 4, 5, and 6 according to the reviewer's recommendation.

Table 3. Prevalence of IBS and FD according to the sleep quality

	PSQI < 6 (Non-poor sleeper) [n (%)] (n=46)	PSQI ≥ 6 (Poor sleeper) [n (%)] (n=124)	<i>p</i> -value
IBS	3/46 (6.5%)	25/124 (20.2%)	0.033
FD	2/46 (4.3%)	27/124 (21.8%)	0.007

IBS, irritable bowel syndrome; FD, functional dyspepsia; PSQI, Pittsburgh Sleep Quality Index.

Table 4. Prevalence of Functional Gastrointestinal Disorder According to the Psychosocial Alarm

	Alarm absent [n (%)] (n=37)	Alarm present [n (%)] (n=24)	Alarm serious [n (%)] (n=109)	<i>p</i> -value
IBS	4/37 (10.8%)	3/24 (12.5%)	21/109 (19.3%)	0.416
FD	2/37 (5.4%)	1/24 (4.2%)	26/109 (23.9%)	0.007

IBS, irritable bowel syndrome; FD, functional dyspepsia

Table 5. Risk factors for Functional Dyspepsia in Univariate and Multivariate analysis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value
Age (year)	0.91	0.79-1.03	0.136	1.166	0.96-1.42	0.131
Sex(female)	2.35	1.02-5.42	0.045	2.07	0.77-5.58	0.151
BMI (kg/m ²)	1.00	0.96-1.02	0.686			
Occupational position						
Intern	Reference			Reference		
Resident	0.37	0.16-0.85	0.019	0.28	0.12-0.68	0.005
Fellow	0.48	0.05-4.28	0.511	1.42	0.12-17.58	0.783
Marriage	2.18	1.05-3.36	0.001	2.73	1.08-6.39	0.039
Smoking	0.33	0.15-2.33	0.099	3.07	0.610-15.45	0.174
Drinking (≥1day/week)	2.38	1.02-3.60	<0.0001	5.96	1.08-10.22	0.025
Duration of recent on-call work (month)	0.32	0.28-0.67	0.001	0.64	0.31-2.94	0.076
Psychosocial alarm						
None	Reference			Reference		
present	0.76	0.07-8.88	0.827	0.69	0.05-9.11	0.780
serious	5.48	1.23-24.36	0.025	5.47	1.06-28.15	0.042
Length of sleep (hour)	0.88	0.56-1.43	0.453			
Poor sleep quality (PSQI ≥ 6)	0.28	0.04-0.72	<0.0001	1.10	0.47-1.36	0.076
Working period (year)	0.94	0.69-1.28	0.690			

BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; OR, Odds ratio; 95% CI, 95% Confidential interval.

For the occupational position, the intern is the reference group.

For the psychosocial alarm, the absence of psychosocial alarm is the reference group.

Table 6. Risk factors for Irritable Bowel Syndrome in Univariate and Multivariate analysis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value
Age (year)	0.92	0.81-1.06	0.239	1.03	0.88-1.20	0.696
Sex(female)	0.54	0.23-1.25	0.151	2.33	1.25-14.00	0.020
BMI (kg/m ²)	1.00	0.97-1.01	0.206			
Occupational position						
Intern	Reference			Reference		
Resident	0.99	0.43-2.29	0.977	4.29	1.25-14.73	0.021
Fellow	0.87	0.09-7.63	0.872	2.29	0.95-3.90	0.460
Marriage	1.19	0.45-2.94	0.778			
Smoking	0.42	0.05-3.38	0.411			
Drinking (≥1day/week)	0.79	0.58-3.14	0.478			
Duration of recent on-call work (month)	0.92	0.88-2.78	0.125	1.45	0.40-5.26	0.576
Psychosocial alarm						
None	Reference			Reference		
present	1.18	0.24-5.80	0.840	1.81	0.44-4.62	0.817
serious	1.97	0.63-6.17	0.245	1.53	0.42-5.64	0.523
Length of sleep (hour)	1.11	0.45-1.17	0.934			
Poor sleep quality (PSQI≥ 6)	3.16	1.04-12.63	0.002	4.17	1.92-19.02	0.016
Working period (year)	0.72	0.51-1.02	0.601			

BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; OR, Odds ratio; 95% CI, 95% Confidential interval.

For the occupational position, the intern is the reference group.

For the psychosocial alarm, the absence of psychosocial alarm is the reference group.

Comments 6) There are a number of errors of English language (grammatical errors) that all must be corrected

Reply)

Thank you for pointing this out. I have edited this manuscript by English editing specialist and received certificate about English editing of this manuscript. I will attach this certificate to WJG manuscript editing site.