The High Frequency Component of Heart Rate Variability and Delta EEG Power during Sleep in Healthy Women and Women with Irritable Bowel Syndrome

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Abstract

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Background Sleep disturbances are well-documented among persons with irritable bowel syndrome (IBS). Imbalanced autonomic nervous system (ANS) has been proposed to be one of the pathophysiology for IBS. Polysomnography (PSG) is a gold measure for sleep quality and heart rate variability (HRV) is a non-invasive measure of ANS activity. Correlations between HRV parameters and electroencephalogram (EEG) power band have been reported in healthy participants and the correlations are weaker among some patient population, e.g., insomnia.

Objective A systematic review was conducted to evaluate the evidence of sleep disturbances in adults with IBS and their relationship with GI symptoms. A secondary data analysis was conducted to investigate the relationship between the high frequency (HF) power of HRV and EEG delta band power in women with IBS compared to healthy control women.

Methods A literature search was conducted in PubMed, CINAHL, and PsycINFO using keyword 'irritable bowel syndrome' and 'sleep'. In the second study, HRV and EEG data were recorded using PSG in 20 women with IBS and 20 healthy control women in a sleep laboratory for three consecutive nights. Data from the second night were used for this analysis. The traditional coherence analysis was used to determine the coherence, gain, and phase shift between normalized high frequency (HF) power of HRV and normalized delta band power of EEG in the first four NREM-REM sleep cycles.

Results The systematic review showed that sleep disturbances are common in adults with IBS. Sleep discrepancy is found between objective and subjective sleep measures. Some evidence supports the positive association between increased sleep disturbances and exacerbated GI symptoms. In the second study, women with IBS had slightly lower coherence between normalized HF and normalized EEG delta band power but it was not statistically significant; had longer phase shift between HF and delta band power than controls (11.6±4.8 min vs. 6.3±3.0 min).

Conclusion Sleep disturbances are common in adults with IBS, which also related to exacerbation of GI symptoms. Based on the coherence analysis, there is evidence of dysfunction in the communication between ANS and CNS in women with IBS.

Keywords Autonomic nervous system; coherence analysis; electroencephalogram; delta band power; heart rate variability; irritable bowel syndrome; sleep; sleep disturbances, sleep misperception.

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DEDICATION

This dissertation work is dedicated to my passed grandmother, Xueping Weng, who brought me up and made me good person.

Chapter 1. INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder (FGID). It is characterized by abdominal pain associated with alterations in defecation or stool frequency and consistency. (1) In two systematic reviews of the prevalence of IBS in the general population, it ranges from 3% to 20% in North America and 7% to 19% globally. In addition, the prevalence of IBS is more common in women than in men. (2, 3) IBS is associated with high costs in terms of health care consumption and productivity loss. (4, 5) In the U.S., the annual direct cost of IBS management per patient was $5049 in 200 (6), and the estimated annual indirect costs (productivity lost) of IBS was $205 billion in the US in 1998. (7)

1.1 GI Symptoms

Alteration in defecation is a symptom that is the defining characteristic of IBS. The categories are constipation, diarrhea, and alternating between constipation and diarrhea. Women report constipation more often than men, whereas men report diarrhea more frequently.(8) Constipation can be prolonged and be accompanied by severe pain and bloating. In several qualitative studies, diarrhea-predominate IBS patients report less pain but often more problems with bowel urgency, which can lead to the embarrassment and sense of loss of dignity.(8-11)

Other highly prevalent symptoms of IBS are abdominal pain and bloating. A 15-year prospective study in Pakistan showed that 97.6% (285/292) of the IBS patients had abdominal pain and 93.8% (274/292) of the patients had bloating during the study.(12) In addition, Khokhar et al. (12) found that the IBS symptoms fluctuated during the 15 years follow-up, and the symptoms were exacerbated by sleep disturbance, stress, and food sensitivities. Another longitudinal study examined the natural history of IBS symptoms over 12 weeks in 122 patients. (13) The researchers reported that the majority of patients had at least one symptom during the 50% of the reporting period, and the duration of the symptoms were relatively short with an average of five days. Pain and bloating were also the most frequent symptoms reported by these patients. The findings are further supported by a population-based study. In the telephone survey study in eight European countries (United Kingdom, France, Germany, Italy, Holland, Belgium, Spain and Switzerland) among 41,984 people from community, the chief symptoms experienced by the IBS responders (N=1838) were abdominal pain (88%) and bloating (80%). (14)

The results from qualitative studies involving participants with IBS line up with the findings from the aforementioned quantitative studies.(9, 11, 15-17) In these studies, abdominal pain is frequently listed as the worst aspect of IBS to deal with, and it significantly affects the patients' ability to carry on their daily life activities.(9, 11) Abdominal pain results in various adverse consequences, including difficulty in concentrating, sleep disturbance, vomiting, and being depressed, which can contribute to impaired quality of life. (9, 11)

1.2 Sleep Disturbance

In addition to GI symptoms, extra-intestinal symptoms frequently accompany IBS. These symptoms include urinary urgency, headaches, backaches, musculoskeletal pain, and sleep disturbances. Among these, sleep disturbances is the most frequent complaint in IBS patients.(18)

Sleep disturbances, such as having difficulties falling asleep, shorter sleep time, frequent arousals and awakenings, feeling less refreshed after waking up, are well documented among IBS patients.(19-24) Poor self-reported sleep quality is related to both of the IBS prevalence and IBS symptoms.(19, 22, 23, 25-27) Several independent studies (conducted in US, South Korea, and Singapore, respectively) in rotating shift nurses, primarily women (>90%), indicate that the shift work is associated with an increased report of IBS and/or IBS-like symptoms.(26-28) These findings imply that the disturbance of circadian rhythm may be part of the pathogenesis for some individuals with IBS.

Research of people with IBS that implemented objective sleep measures (polysomnography [PSG] and/or actigraphy) provides mixed results. (29, 30) In a study by Rotem et al, 18 IBS patients and 20 controls, the investigators utilized both PSG and actigraphy to measure sleep and sleep/activity, respectively. They found that the IBS group had significant sleep fragmentation with higher arousal and awakening index (2-folds greater), a longer wake period after sleep onset, and more shifts to lighter sleep stages during the night as indicated by single-night PSG indices. These findings were also supported by the 4-night actigraphy data and self-reported daytime sleepiness. (29) However, Elsenbruch et al. (31) reported that sleep stage distribution, sleep efficiency and numbers of awakening and arousals in IBS group in their sample of 31 women with IBS were within normal range and did not differ from the control group (n=23). Heitkemper et al. (30) also did not find any major differences in electroencephalograph (EEG) sleep time measures between IBS group and control group in their study with 36 IBS women and 38 age-matched controls. There were more subjective 'poor' sleepers in the IBS group compared to control group, as measured by Pittsburgh Sleep Quality Index (PSQI) using a Global PSQI score ≥ 6 as a cutoff. Therefore, sleep misperception was proposed based on the mismatched objective and subjective sleep measures.(30) However, the differences in study sample and different measurements made it hard to compare the results from these three studies and draw a solid conclusion.

Although visual sleep EEG scoring is useful for characterizing sleep architecture and continuity, power spectral analysis (PSA) of whole-night sleep EEG provides quantitative and more refined information on the continuous fluctuations of sleep patterns overnight. (32, 33) Power spectral software is used to evaluate EEG power in different power spectra, usually including delta, theta, alpha, sigma, and beta. Alpha and beta frequency bands are considered indicators of awakening. Delta frequency band corresponds to deep sleep. The theta frequency band usually occurs in the transition from a lighter sleep stage to deeper sleep stage.(34, 35) There are many studies in insomnia and depression using PSA of sleep EEG. One study in psychophysiological and paradoxical insomnia patients (N=26 psychophysiological insomnia, 20 paradoxical insomnia, and 21 good sleepers) used PSA to assess their rapid eye movement (REM) sleep and (non-rapid eye movement (NREM) sleep over two consecutive nights in a sleep laboratory.(36) The study showed more absolute delta activity in paradoxical insomnia patients than psychophysiological insomnia patients, and further analyses revealed that the majority of the differences between the two groups were in NREM sleep. Also, paradoxical insomnia group had lower relative activity in slower frequency band (0-1 Hz) compared with good sleepers, while psychophysiological insomnia group had less relative theta activity compared with good sleepers, indicating higher activation in both groups with insomnia during REM sleep. There were no group differences in macrostructure of sleep. All groups were similar in sleep duration and time spent in each sleep stages. Bader et al. (37) also used PSA of EEG to study the relationship between childhood maltreatment experience (MAL) and the high frequency EEG activity during sleep in 45 adults with primary insomnia. The MAL group had more absolute and relative beta 1 and beta 2 activity in NREM, and more absolute beta 1 and beta 2 activity in REM, but there were no statistically significant differences in the macrostructure parameters of sleep, except for microarousal index (the MAL group had higher microarousal index compared with non-MAL group). The findings from these studies imply that PSA may be a better measure to detect subtle differences of sleep structure in insomnia patients.

PSA has also been employed in studies of other patients groups when poor sleep is reported. A PSA study in inpatients with depression (38) showed that PSA was able to detect the first-night effect, characterized by a reduced delta and theta power spectral activity in NREM sleep of the first night compared with the second and third nights. These differences were not found on macrostructure sleep EEG analysis. The researchers also reported that these differences were limited to the early stage of the sleep period (NREM sleep). Similar to patients with insomnia, there were no significant differences in spectral parameters across the three nights in REM sleep. This finding is opposite to the one from healthy subjects, in whom the main changes in sleep across night were seen in REM sleep.(39)

There is a high prevalence of comorbidity of both depression and insomnia/sleep disturbance in IBS patients. Therefore, it will be meaningful to find out the characteristics of PSA during sleep in patients with IBS. To the best of my knowledge, there is only one study in IBS population using PSA and the study did not measure nocturnal EEG. In the study (40), 10 IBS patients and 11 healthy controls (both men and women) were recruited to study the brain-gut interaction by measuring the pressure changes of colon and small intestine in response to a mental stress and cholinergic stimulation. This study was done over three daytime hours and the focus was on the GI response to mental stimulation. Thus, the characteristics of EEG power spectra during the relatively uninterrupted status (sleep time) have not been studied yet and further study is needed.

1.3 Psychological Factors

Psychological factors, including but not limited to psychological distress, psychopathology, and stress, might trigger or worsen GI symptoms in IBS patients. (41) Anxiety and depression are the two most commonly reported psychological symptoms by IBS patients. (42-45) One population-based study surveyed among 900 patients aged between 20 to 70 year from 18 family medicine clinics in Croatia (12 in urban area and 6 in rural area). (46) Among the 703 patients who returned the survey, the prevalence of anxiety and depression in IBS patients (n=205) were 26.3% and 25.9%, respectively. They did not report the data from the patients without IBS. Usually, anxiety is more prominent in the early course of IBS, while depression is more common in patients suffering from IBS for a long time.(47, 48)

The comorbidity rate of psychiatric disorders in IBS population is high, ranging from 50% to 90% depending on the criteria for the psychiatric diseases.(42, 48-50) IBS is also more prevalent in psychiatric patients than in the general population.(51) Psychological factors are associated with sleep disturbances in IBS population.(52) Heitkemper et al. (53) studied the effects of anticipation of public speaking on sleep in women with IBS, and found that the acute stress of public speaking reduced sleep efficiency and increased serum cortisol levels early in the night in women with IBS (n=43) compared to age-matched controls (n=24). The 'first night' effect (poorer sleep efficiency and increased arousals on the first night of PSG monitoring in a sleep laboratory compared with the following nights) in IBS patients provides further evidence that acute stress impacts sleep quality in this patient population.(30)

In addition, other psychological factors, such as early adverse life events(54), personality characteristics (48, 55) are also revealed to play roles in the pathogenesis of IBS. Other investigators proposed that psychological factors, such as catastrophic thinking and somatization, may increase IBS patients' awareness of their symptoms.(56-58) Therefore, psychological factors should be included when analyzing the role of ANS and sleep in IBS and their relationship with GI symptoms.

1.4 Autonomic Nervous System (ANS)

Knowledge regarding the pathophysiology of IBS continues to evolve, beginning with disturbances in motility to visceral hypersensitivity, and now to the more integrated model of brain-gut bidirectional interaction.(59-62) Increasingly, studies are focusing on brain-gut interaction, especially the information relay center between the brain and gut: ANS.(63-66)

The ANS is the part of the peripheral nervous system. It acts as a control system, which functions primarily below consciousness to control visceral function, including heart beat and digestion. The ANS can be divided into two branches, sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS). These branches work collaboratively to regulate the functions of the targeted organs. Usually, the SNS is predominant during the daytime, while PSNS is predominant during the night. Under particular circumstances, one branch can override the other, e.g., SNS becomes the dominant branch under fighting even during nighttime. There is also evidence that in some pathological condition, such as rheumatoid arthritis, where reduced PSNS and increased SNS is consistently found.(67)

Studies about ANS function of IBS patients are well documented, but the results are not consistent.(68-70) Some researchers reported that IBS patients have reduced vagal tone (or reduced PSNS activity) during sleep and in response to rectal distention experiment (71, 72), while other researchers failed to find any difference in ANS function measured by heart rate variability (HRV) between IBS patients and controls. However, some differences in HRV parameters were found in IBS subgroups, categorized by bowel pattern characteristics, comorbidity of anxiety or depression, history of childhood abuse, or abdominal pain severity.(52, 54, 64, 73-76)

ANS activities in different sleep stages in persons with IBS are reported. Orr et al. (77) found that IBS patients exhibited SNS dominance during REM sleep. In another study with 75 IBS women by this research group, diarrhea predominant IBS patients (IBS-D) showed evidence of significant vagal withdrawal (resulting in SNS dominance) compared to IBS with alternative stool patterns (IBS-A) during both REM and non-REM sleep. IBS-D patients had higher SNS dominance compared to IBS-A during non-REM sleep.(78) However, Jarrett et al. (74) found opposite results in their study of women with IBS (N=35) and healthy controls (N=38). Women with IBS-D demonstrated significantly increased PSNS activity and lower SNS and PSNS balance in all NREM and REM cycles compared to both IBS-C and IBS-A. A study by another research group did not find differences in the measured ANS parameters during sleep. (52) The possible reason for the mixed results may be differences in sample characteristics. Specifically, there were differences in terms of mean age, percentages of different types of IBS, and when women were studied relative to menstrual cycle phase. These heterogeneous characteristics of studies make it difficult to compare the study findings. Meanwhile, ANS imbalance is also frequently seen in patients with insomnia (79), a common complaint in individuals with IBS. Thus, additional investigation is needed to explore the ANS function during sleep in IBS patients and to clarity whether the sleep disturbance is the cause or the results of ANS imbalance.

Some evidence supports an association between the central nervous system (CNS) arousal as measured by PSA of EEG as well as ANS arousal as measured by heart rate changes, blood pressure (BP) changes, and HRV in healthy participants.(80-82) In a noise-induced awakening study with nine young, healthy female shift workers, Carter et al. (34) found that the alpha band responses to noises were related to BP increase. Spectral analysis of BP variability revealed increased sympathetic vascular tone due to noise, suggesting that CNS arousal and ANS arousal are interrelated. An early study in healthy adults found heart rate increased at least10 beats ahead of the EEG arousal, namely, the sympathetic activity preceded and might play a role in arousals during sleep.(83) In a study about pain response during sleep in healthy adults, Chouchou et al. (84) concluded that the nociceptive stimuli induced cardiac activation (measured by HRV) that is regulated by cortical activation and not by sleep itself. Based on the current literature, the relationship of sleep with ANS activity is still unclear and further studies are required.

To date, there is little attention to PSA of EEG data and its relationship to ANS activity and balance in IBS patients. The only study that used PSA in IBS participants had small sample size (10 IBS and 11Control). In this study, PSA of EEG data was used to measure the mental response to stimuli.(40) Fukudo et al. found that an increased colonic motility, reduced EEG alpha power, and increased beta and theta power after mental stress and cholinergic stimulation. It will be interesting to find out whether a relationship between EEG and ANS measures exists in IBS patients and how this might potentially contribute to the pathogenesis of IBS.

In summary, IBS is a chronic functional GI disorder with a high prevalence and health care costs. Besides bowel function changes, people with IBS frequently suffer from abdominal pain and bloating, poor sleep, and psychological comorbidities, which severely impairs their quality of life. Self-reported poor sleep usually correlates to their IBS symptoms, however, the studies that employed objective sleep measures provide inconsistent results. Most of the IBS research published used EEG macrostructure analysis. A more refined EEG analysis method PSA, has not been commonly employed. PSA of EEG has proved to be a better method to detect subtle differences in sleep in people with insomnia and depression. Given the high comorbidity of depression and sleep problems in IBS patients, it will be meaningful to apply this method to IBS studies as well. So far, the etiology of IBS is still not clear, and the imbalance of ANS function is a potential pathogenesis for it. HRV is a commonly used noninvasive method to indirectly measure ANS function in studies involving human subjects. The interrelationship between central arousal (indicated by EEG parameters) and ANS arousal in healthy subjects allows us to explore the relationship between these two aspects in IBS patients and also their relations to IBS symptoms. This effort might lead to greater understanding of the etiology of IBS.

Chapter 2. SLEEP DISTURBANCES IN IRRITABLE BOWEL SYNDROME: A SYSTEMATIC REVIEW

2.1 INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder (FGID) characterized by abdominal pain associated with alterations in defecation or stool frequency and consistency.(1, 2) The prevalence of IBS in the general population is 3-20% in western countries, and the prevalence is two to three times more in women than in men.(3, 4) IBS is associated with significantly higher costs in terms of health care consumption and work and school productivity loss.(5, 6)

Besides gastrointestinal (GI) symptoms, sleep disturbances are well documented in the IBS population. The broad concept of sleep disturbance may refer to various alterations in sleep, including poor perceived quality of sleep; symptoms of insomnia (difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, and non-restorative sleep); or alterations of sleep quality and stages on objective measurement.(7-9) Sleep quality is assessed by two approaches, i.e., subjective or self- report sleep measures and objective sleep measures. Subjective measures most commonly used in research include questionnaires and diaries. Questionnaires, such as the Pittsburgh Sleep Quality Index or Insomnia Severity Index, retrospectively assess the individual's perception of sleep quality over a period of time (usually one week to one month). Objective measures include polysomnography (PSG), which is also considered as the gold standard for sleep measurement, and actigraphy, which is a wrist-worn device that measures movement as an indicator of wake-sleep behavior. PSG is a comprehensive biophysiological monitoring system that provides quantification of whole-night sleep parameters (e.g., total sleep time, latency to sleep onset, wake time after sleep onset) as well as sleep stages.

PSG-defined sleep stages progress throughout the night in 90-120 minute cycles of non-rapid-eye-movement (non-REM) sleep, with each stage represented "deeper" sleep from which the individual is more difficult to around, and REM sleep, which is characterized by muscle atonia but active neurological patterns on electroencephalography (EEG).

Adults with IBS usually report difficulty in falling asleep, shorter sleep time, frequent arousal and awakenings, or nonrestorative sleep.(8, 10-14) Poor sleep is reported to relate to the prevalence and symptoms in IBS.(10, 12, 13, 15-17) In a population-based study with 2269 participants, Vege et al.(18) reported that the prevalence of IBS was 33% among the participants with sleep disturbances. The risk of having IBS was 1.6 times greater in people with sleep disturbances as compared to those who did not have sleep disturbances, even after adjusting for age, sex, and somatization scores.(18)

Several researchers have found evidence of a positive association between poorer subjective sleep quality and greater IBS symptoms in terms of frequency and severity.(8, 10, 12, 13) Visceral hyperalgesia, increased sensitivity to visceral stimuli, has been proposed to contribute to the GI symptoms amongst people with FGIDs.(19) There is some evidence that sleep disturbances are associated with heightened visceral sensitivity.(19, 20) However, findings from IBS studies using objective sleep measures are less conclusive. Some researchers suggest that the sleep perception of IBS patients, in terms of overall sleep quality, sleep length, and sleep continuity, is different from non-IBS individuals. Catastrophic thinking and somatization, which are frequently present in persons with IBS, may affect the subjective perception of sleep, thus at least partially explaining the differences between subjective and objective sleep measures.(14, 21-23)

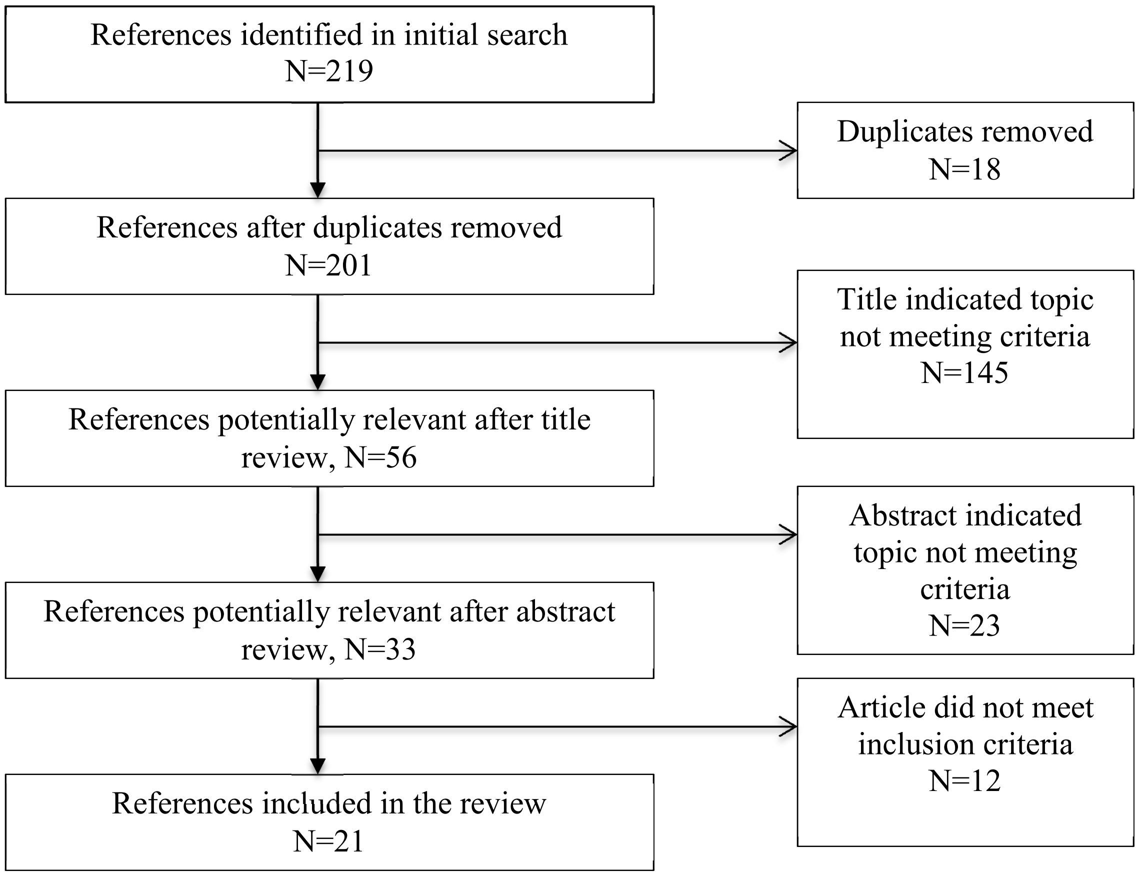
In the current review, we evaluated the evidence of sleep disturbances in adults with IBS and relationship of sleep disturbances and exacerbation of GI symptoms. This paper synthesizes the most recent literature on sleep disturbance in IBS to evaluate the current state of knowledge and identify areas for future research.

2.2 METHODS

For the purpose of this systematic review, the eligibility criteria for studies included: (1) subjects aged 18 years or older; (2) diagnosis of IBS made based on established diagnosis criteria at the time of study; (3) observational studies that described sleep characteristics in IBS participants and/or compared sleep between IBS and a healthy control (control) group; (4) the outcome measures included at least one sleep measure (subjective and/or objective); (5) published between 1990 and 2015 in peer-reviewed journals (unpublished papers, dissertations, book chapters, and conference abstracts were excluded); and (6) published in English. We excluded studies examining shiftwork and IBS because we were interested in sleep disturbance as a symptom rather than extrinsic and/or behavioral influences on sleep.

A literature search was performed in three academic databases: PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO. The key words were “irritable bowel syndrome” and “sleep”, with limits to English language and published between 1990 and 2015. This search resulted in 219 articles of which 18 were redundant. After reviewing the title and abstract of the 201 articles, 33 articles were reviewed in full text. Finally, 21 studies were included in the review after excluding 12 articles (including two repeated reports from the same dataset) (Figure 2.1).

Figure 2.1 Flowchart of literature search



2.3 RESULTS

The majority of the studies included (17/21) were done in US. Study characteristics and main findings are listed in Table 2.1. The total sample size of these studies was 1,169 with IBS and 578 as controls; 92% of the IBS participants and 90% of controls were women. One study(8) was excluded from the gender calculation because no exact number of women participants was reported. Most studies (17/21) were case-control studies with at least one control group.

The most frequently used subjective sleep measure was Pittsburgh Sleep Quality Index (PSQI), followed by sleep diaries (diary days ranged from 2 weeks(15) to 8 weeks(13)). The most common objective sleep measure among these studies (15/16) was PSG, and only two studies employed actigraphy. Five studies used only subjective sleep measures,(8, 10, 12-14) three studies used only PSG,(24-26) and the remaining 13 studies(11, 15, 27-37) used at least one subjective and one objective sleep measure.

2.3.1 *Subjective Measures of Sleep in IBS*

Subjective sleep disturbances in people with IBS have been reported across the studies despite differences in the subjective sleep measures used. Among all the studies with subjective sleep measures, a total of 1,145 persons with IBS were enrolled. Poor sleep quality, prolonged sleep latency, frequent nighttime awakenings, and daytime dysfunction were common complaints from participants in the studies. The IBS group had significantly greater sleep disturbances in at least one variable (e.g., difficulty getting to sleep, awakening during the night) compared to controls.

In addition to providing evidence of general sleep disturbance, certain studies showed differences between persons with IBS and controls on the reasons for awakening and medication use. In a survey study of 505 patients with FGIDs (IBS, functional dyspepsia [FD], and with both IBS and FD [IBS-FD]) at a large tertiary GI clinic,(8) 50% to 71% of patients with FGIDs reported sleep disturbances, compared to 55% of controls. The most common sleep disturbances in all patient groups were frequently waking up during the night and feeling unrefreshed in the morning. Fass et al.(8) also reported greater use of sleep medications by patients with IBS and IBS-FD (14.4% and 12.4%, respectively) compared to 7.1% of controls. Abdominal ache, pain, or discomfort were reported as the reason for awakening by persons with IBS (50%) and IBS-FD (64%).(8)

Frequent awakening was also an important concern for patients with IBS in a study by Ranjbaran and colleagues.(14) In this study, repeated awakenings more than once or twice per week were reported by 88% of participants with IBS compared to 40% of controls. IBS patients most frequently attributed awakenings to the need to use bathroom (87%, among which 58% indicated having a bowel movement) and abdominal pain (71%). The main reason for awakenings among controls was also the need to use the bathroom, but most frequently the need to urinate (57%). Other reasons for awakening were more common among persons with IBS than controls, including feeling too hot or cold (IBS, 61%; controls, 7%); having a nightmare (IBS, 67%; controls, 7%); or breathing problems (IBS, 50%; controls, 0%). None of the controls reported awakening from abdominal pain. The differences in percentages of all the waking up reasons abovementioned between IBS and controls were statistically significantly ($P < .001$). A higher percentage (54%) of patients with IBS, compared to Fass's study, needed sleeping pills for their sleep disturbances.

Several of the studies explored factors hypothesized to contribute to sleep disturbances in persons with IBS, including IBS defecation patterns, gender, childhood abuse and neglect, and psychological factors such as depression and anxiety. Sleep disturbance differences are not obvious among subgroups of IBS patients based on the predominant defecation patterns. Robert et al.(29) recruited 22 diarrhea-predominant (IBS-D), 33 constipation-predominant (IBS-C), and 20 IBS with alternating pattern (IBS-A) participants based on Rome II criteria and found no differences in PSQI items.

Whether gender plays a role in sleep disturbances in IBS is not clear yet. In a cohort of 142 GI clinic outpatients with IBS (110 women, Rome III criteria), Bellini et al.(10) found that, based on the PSQI, men had worse sleep than women. However, this finding did not agree with the report from the study by Fass.(8). Fass et al. found that sleep disturbances were equally common in both men (57%) and women (58.4%) in all patient groups (IBS, FD, and IBS-FD) and in controls. This may be related to age differences in the samples studied, i.e., Bellini's sample was primarily young (median age 38), menstruating women as compared to older (mean age 47) women in the Fass study.

Childhood abuse and neglect seems to influence the sleep quality in women with IBS; whereas little is known about men with IBS. Heitkemper et al.(36) found that 81% of women with IBS who had a history of childhood abuse and/or neglect were poor sleepers (PSQI >5) compared to 26% of the IBS women without such history or 12% of control women after controlling for age. Also, women with IBS and a history of childhood abuse and neglect reported greater psychological distress.

It is well established that psychological factors such as anxiety and depression negatively impact sleep.(38-40) Some researchers also suggest that psychological factors may be partially responsible for sleep misperception, which is a mismatch of subjective and objective sleep measures, in patients with IBS.(32) However, in this review inconsistent findings on the relationship of psychological factors to subjective sleep were found. For example, researchers(8, 14, 15, 27, 31-33, 35-37) reported that psychological factors (e.g., anxiety, depression, or stress) influenced the degree of subjective report differences between IBS and the control group. Fass et al.(8) reported that IBS patients with sleep disturbances had significantly higher mean anxiety and depression T-scores than their controls without sleep problems. However, researchers in two studies reported no impact of psychological factors on reported sleep differences in IBS versus controls.(13, 28)

2.3.2 *Objective Measures of Sleep in IBS*

Compared to subjective sleep results which tended to consistently report evidence of poor sleep quality, group difference findings using objective sleep measures were mixed. The majority of the selected studies used PSG as their objective sleep measure, and only two studies(28, 34) employed actigraphy. Most of the studies (10/15) that utilized PSG only used a single night recording.

Among the studies with at least one objective sleep measure and with a control group, 71.4% (10/14) of the studies demonstrated that the IBS group had poorer sleep compared to the control group on varied measures, including prolonged sleep onset latency SOL), increased percentage of Stage 2 sleep (stage 2%), increased REM sleep (percentage, length), increased latency to first REM onset (REM latency), increased arousals and awakenings and wake time after sleep onset, and decreased total sleep time and sleep efficiency (percentage of time in bed spent asleep). Only three studies (28, 33, 35) reported reduced sleep length in IBS patients compared to controls. In two studies(33, 35), poorer PSG sleep measures (i.e., lower sleep efficiency, less total sleep time, more awake percentage) corresponded to the subjective sleep complaints.

Differences in REM sleep were the most common finding across the studies. In an early study by Kumar et al.,(24) a significant increase of percentage of REM sleep (REM%) was found in IBS patients (36.5%) compared to controls (18.2%). Orr et al.(26) reported both increased percentage and duration of REM in their studies with 10 women with IBS and 10 control women. However, the difference in REM% was smaller than in Kumar's study (21.5% vs. 15.2%). Increased REM% was also reported in some IBS subgroups, i.e., IBS with severe GI symptoms (32) and IBS with a history of childhood abuse and neglect.(36) Contrary to the findings of Orr's findings, Heitkemper and colleagues(35) reported reduced REM% in IBS patients versus controls (17.5% vs 21.2%, respectively; p=.015). However, the protocol of this study included an indwelling intravenous line for blood sampling throughout the night, which was different from other studies.

In addition to alterations in REM sleep, there is some evidence that persons with IBS spend increased time in light sleep (Stages 1 and 2).(35) Given that arousal/awakenings occur more easily in light sleep, this alteration might explain the increased frequency of arousal/awakenings in persons with IBS. In a study of 18 IBS patients and 20 controls using both PSG and actigraphy, Rotem et al.(28) found that sleep fragmentation was significantly greater in the IBS group compared to the control group using both approaches. Compared to the controls, persons with IBS had more than 2 times the arousal and awakening index on PSG, and close to 2 times the sleep fragmentation index on actigraphy.

However, four studies (11, 25, 27, 30) showed no differences in any of the PSG-measured sleep variables between the IBS group and age- and gender-matched control group. Furthermore, two studies presented contradictory evidence on PSG-measured sleep variables among IBS subgroups (IBS-A, IBS-C, and IBS-D), with one study reporting no significant difference between the groups,(29) but another reporting differences in stage 2% among these subgroups (IBS-A, IBS-C, and IBS-D).(37) In the latter study, IBS-D had the highest stage 2% (48.8%) and IBS-C had the lowest stage 2% (40.8%).

2.3.3 *Discrepancy between Subjective and Objective Reports of Sleep Disturbances*

In spite of the common subjective sleep complaints among people with IBS compared to controls, objective sleep measures have not always shown differences. In the selected literature using both subjective and objective sleep measures with a control group, nearly half of these (5/11) demonstrated some degree of discordance between subjective and objective sleep measures of sleep in persons with IBS, with persons reporting greater severity of sleep disturbance than was evident objectively.(11, 15, 27, 30, 35) Researchers in some studies showed differences in subjective sleep measures between IBS and control group, but no differences in objective sleep measures.(11, 27, 30, 35) In one study, Heitkemper et al.(15) found that there were some differences in both subjective and objective sleep between IBS and controls. Of interest is that while there was no correlation between the self-reported and PSG-measured sleep variables in the IBS group; there was a significant positive correlations between self-reported and PSG-measured SOL and awakenings in control group.(15)

2.3.4 *Relationship between Sleep Disturbances and GI Symptoms*

Poor sleep has been linked to GI symptoms in people with GI diseases, such as gastroesophageal reflux disease or FD,(41) and there is some evidence in the IBS population as well. Among the selected literature exploring the link between sleep and GI symptoms, most of the studies (7/9) showed some degree of positive correlation. Fass et al.(8) observed a trend of positive relationship between greater subjective sleep disturbance and greater perceived severity of GI symptoms in IBS group, but this was not statistically significant (p=.138). It is worth noting that most researchers established the link between sleep and GI symptoms based on self-reported measures; thus, both sleep and GI symptoms may be due to a self-report bias (i.e., the tendency to rate all symptoms high or low).

There was only one group that employed both subjective and objective sleep measures and explored their relationship to GI symptoms in female IBS participants.(34) In this study, researchers used symptom/sleep diaries and actigraphy concurrently for seven consecutive days. They found that there was a within-subject relationship between sleep quality and IBS symptoms. Specifically, reduced self-reported sleep quality predicted next-day abdominal pain, anxiety, and fatigue. In addition, actigraphy-measured sleep efficiency negatively related to next-day fatigue (within-subject), and the self-reported sleep quality correlated with actigraphy-measured sleep efficiency.

2.4 DISCUSSION

2.4.1 *Summary of Evidence*

Based on this systematic review of sleep disturbances in patients with IBS, there is consistent evidence to support the subjective sleep disturbances, but less conclusive evidence of objective sleep disturbances. Discrepancies between subjective and objective sleep variables were reported in a few studies.(11, 15, 27, 30) There is some evidence of positive correlation between sleep disturbances and GI symptoms among people with IBS; however, the evidence is mostly based on self-report/subjective measures in cross-sectional or case-controlled studies. Therefore, it is not currently possible to determine the cause-effect relationship between sleep disturbances and GI symptoms.

2.4.2 *Characteristics of Sleep Disturbances in IBS*

Sleep disturbances in people with IBS appear to primarily include the following aspects of sleep: latency, length, depth, sleep stages, and sleep fragmentation, which all contribute to the sleep quality. Having a hard time falling asleep (prolonged latency) is common among people with IBS. Elsenbruch et al.(11, 27) found that women with IBS had longer SOL based on the PSQI item. Only one group found increased PSG-measured SOL in women with mild to moderate IBS compared to controls.(32) In addition, longer latency to REM sleep is reported in women with IBS.(15) A few researchers reported shorter sleep length among people with IBS, both in subjective sleep(14, 27, 33) and objective sleep.(28, 33, 35) However, most studies(11, 24-27, 30-32, 36) found no difference in total sleep hours between IBS and control groups. In regard to sleep stages, study results from PSG-measured sleep variables showed that patients with IBS had more stage 2%(33) and REM%(23, 25) than controls.

Sleep fragmentation is a major complaint for patients with IBS. Although the need to use bathroom was also the main reason for both persons with IBS and controls to wake up in the night,(12) most of controls woke up to urinate whereas more than half of people with IBS had a bowel movement. Fass et al.(9) also reported that abdominal discomfort woke people with IBS up during the night. These findings indicated that the GI symptoms were partially responsible for the sleep disturbances amongst adults with IBS. However, the data from two PSG studies showed that there was no difference in the frequency of arousal and awakening during the night between people with IBS and controls.(21, 29)

Sleep disturbances are a common complaint in people with IBS, but few objective sleep data support these sleep complaints in this review. Some researchers suggested (8, 28) sleep misperception might be the reason for the frequent subjective sleep complaints in people with IBS. Sleep misperception is also a concept frequently cited in patients with insomnia and fibromyalgia, which are common comorbidities among people with IBS.(39-45) Maes et al. (42) reported that sleep misperception, as evaluated in sleep onset latency, in patients with primary insomnia associated with increased EEG activity. They also found that the hyper-arousal status was correlated with a lower parasympathetic nervous system activity.

2.4.3 *Association between Sleep Disturbances and GI Symptoms in IBS*

Based on the limited evidence, there is some association between sleep disturbances and GI symptoms in people with IBS. Visceral hyperalgesia could be a mechanism link sleep disturbance and GI symptoms.(43) Schey et al. (19) found that sleep deprivation had a adverse effect on visceral sensation in adults with gastro-esophageal reflux disease in terms of symptom report lag time, symptom severity ratings, and symptom severity scores after esophageal acid perfusion. These phenomena were not in controls, although a trend of increased esophageal sensation was noticed. No such study has been done in IBS population yet. Chen et al. (44) found a lower threshold volume for urge and anal sphincter pressure for maximal squeeze in IBS with sleep disturbance compared to IBS without sleep disturbance. In this study, Chen et al. used PSQI score > 5 as an indicator of having sleep disturbance. The PSQI score is an average assessment for the sleep quality in the previous month, therefore, this study revealed a effect of chronic sleep disturbance in the rectal hyperalgesia in IBS patients.

It is important to note that most of the participants (77%) in the studies reviewed were women. There is an increasing body of evidence, both from human and animal studies, that sex and gender may influence the expression of IBS.(53-55) However, many studies in IBS either recruited women participants only or had a very small number of men, and this resulted in inadequate power for subgroup analyses based on gender. More studies with larger sample size, participants of both genders, longitudinal design, and both subjective and objective sleep measures are needed in order to determine the casual relationship between sleep and GI symptoms. This effort will give clinicians a better understanding of the disease and targeted method of treatment.

2.4.4 *Central and Peripheral Mechanisms Involved in Sleep*

In persons with insomnia, physiological mechanisms that influence sleep, particularly cortical arousal and autonomic nervous system (ANS) activity, have been suggested as potential mechanisms for both sleep disturbance and for the discrepancy between subjective and objective measures.(45, 46) Regarding the latter, it has been hypothesized that persistent arousal cortical may permit sensory processing during sleep, leading to the misperception of being awake during sleep. (45, 46) Exploration of these mechanisms may provide data for understanding sleep disturbance in persons with IBS.

Autonomic nervous system (ANS) activity impacts both GI function and sleep, and may be a factor contributing to sleep disturbance in persons with IBS. Five studies examined ANS activity, quantified by heart rate variability (HRV) during overnight sleep,(26, 27, 30, 31, 34) but many of the findings are contradictory. Jarrett and colleagues generally found IBS-D significantly increased parasympathetic modulation across NREM and REM cycles compared to IBS-C and IBS-A.(31) However, no difference in HRV was found between the IBS and control groups. On the other hand, a study by Orr, Robert, and colleagues(30) found that the IBS-D group had significant parasympathetic withdrawal during NREM and REM sleep, and significantly higher sympathetic dominance during NREM sleep compared to IBS-A. Additionally, this group reported that female IBS patients with a history of childhood abuse or neglect had lower HRV compared to those patients without such a history (34), but the presence of depressive symptoms did not affect ANS activity during sleep.(27) Another research study reported substantial vagal withdrawal or higher sympathetic dominance during REM sleep was also documented in IBS-only patients compared to IBS patients with dyspeptic symptoms and controls in one study.(26) In this overall body of literature, sample characteristics may have contributed to the mixed results. Specifically, differences existed in sample size, mean age, types of IBS bowel predominance, and menstrual cycle phase when menstruating patients were involved. These heterogeneous characteristics of studies make it difficult to compare the study findings.

Whereas HRV provides information on peripheral physiological regulation, analysis of EEG microstructure provides central nervous system (CNS) data on the depth of sleep and physiological arousal that is not readily available from the analysis of sleep macrostructure (i.e., whole- night sleep variables and sleep stages). PSA uses power spectral software to evaluate EEG power in different frequency bands. There are a number of studies in insomnia and depression using PSA of sleep EEG that show associations between these conditions and variation from the sleep microstructure of healthy adults (e.g., increased high frequency EEG in persons with insomnia).(46-48) To date, there is only one study with only 10 IBS patients and 11 controls (52) that utilized PSA, and they found a significant positive correlation between colonic motility and power spectral changes in IBS patients. Each of these methods of analyzing EEG may provide useful information to the literature on understanding of sleep disturbances in persons with IBS.

Some evidence supports an association between the central nervous system arousal as measured by PSA of EEG and ANS arousal as measured by heart rate changes, blood pressure (BP) changes, and HRV in healthy participants.(56-58) In a noise-induced awakening study with nine young, healthy female shift workers, Carter et al. (59) found that the alpha band responses to noises were related to BP increase. Spectral analysis of BP variability revealed increased sympathetic vascular tone due to noise, suggesting that CNS arousal and ANS arousal are interrelated. An early study in healthy adults found heart rate increased at least 10 beats ahead of the EEG arousal, namely, the sympathetic activity preceded and might play a role in arousals during sleep.(60) In a study about pain response during sleep in healthy adults, Chouchou et al. (61) concluded that the nociceptive stimuli induced cardiac activation (measured by HRV) that is regulated by cortical activation and not by sleep itself. Therefore, the relationship between sleep EEG and ANS activity is still unclear. To date, there has been little research on sleep EEG and its relationship to ANS activity in IBS patients.

2.5 LIMITATIONS

Several limitations of this systematic review are acknowledged. First, the literature search was done with three literature databases (PubMed, CINAHL, and PsycINFO) and may not have captured all of the available literature on this topic. However, since these are the major health literature databases, our search is likely to have covered the most available literature. Second, due to the limited number of research papers on this topic, we set broad selection criteria to include studies that did not have a control group, or had subjects with other comorbidities (e.g., depression, dyspepsia) or the main study population was not restricted to persons with IBS. This enabled us to shed a light on the possible influences of the common comorbidities on sleep disturbances amongst adults with IBS. Third, we only included peer-reviewed published literature, therefore, publication bias could be a concern.

2.6 SUGGESTION FOR FUTURE RESEARCH

Lack of a unified definition of sleep disturbance and standardized sleep measurement were noticed among the selected studies. Various indicators of sleep disturbance were used in the literature included poor self-rated sleep quality, ratings on standardized questionnaires beyond a threshold indicating sleep disturbance (e.g., PSQI >5), and sleep diary, PSG, or actigraphy sleep measures that differ from the range considered normal (e.g., sleep latency >30 minutes). These differences may partially account for the inconsistent findings among the studies reviewed.

Differences in sleep measurement were evident on both subjective and objective sleep measures. Sleep assessments varied in the period of assessment, type of measures, and circumstances of measurement (retrospective or prospective). In the selected literature, the assessment period of retrospective subjective sleep measures ranged from one day(10, 11) to one month.(7, 12) Sleep questionnaires were retrospective, whereas sleep diaries were prospective; therefore, these types of measures may have yielded different results and may have been differentially affected by recall bias. The PSQI assesses sleep quality and disturbances over a month long time frame(62) and therefore reflects the average sleep quality and not the daily fluctuation of sleep quality. Instead, diaries may be a better tool to capture the daily variations of sleep quality and symptoms, however, reporting fatigue can occur when using in a long period of time.(63)

The most common concern for using PSG is the "first night effect" (FNE), which is characterized by more arousals and poorer sleep efficiency on the first night sleeping in a controlled condition with PSG compared to subsequent days of monitoring. The FNE phenomenon has been reported in both healthy and various patient populations (including IBS population), and is likely due to the novelty of the laboratory setting and intrusiveness of PSG sensors.(28, 47, 64-74(32)) Heitkemper et al.(28) reported FNE in their study in both IBS group and control group. Some researchers suggested that at least two nights of recording is needed and the first night can serve as the adaptation and the second night's data can be used for data analysis.(75) However, two thirds (10/15) of the PSG studies in this systematic review used recordings from a signal night.

Environment or under what circumstance the measurement is taken also an important factor. A new environment can cause stress to participants, which may influence their sleep quality and structure. In one study(33), there was no difference in the PSQI score at baseline (measure the average sleep quality over previous month in participants' home setting) between IBS group and healthy control group, yet, overall the IBS group rated their sleep significantly poorer the morning after having their sleep recorded in a sleep laboratory. This finding demonstrated the influence of environment.(74)

In summary, using a unified definition of sleep disturbances and standardized sleep measurement protocol in future studies will be beneficial to compare and generalize research findings.

2.7 CONCLUSION

In conclusion, our systematic review suggests that sleep disturbances are common in people with IBS. However, study findings do not consistently support the prevalence of specific types of sleep disturbances, especially when measured objectively, and there is a discrepancy between subjective and objective sleep measurements. Whether this discordance is due to misperception of sleep, insufficiently sensitive measures or methods, or other undetermined factors needs to be determined. A positive relationship between sleep disturbances and GI symptoms is also found. ANS function may be interrelated with sleep and may be an underlying mechanism for IBS in a subset of patients. Gender may play a pivotal role in modulating IBS, and more male participants should be involved in further studies. For future studies, standardized definition of sleep disturbances, proper sleep measurement, and sensitive data analysis methods may help understand the interrelationship among sleep, ANS function, and GI symptoms better. Solving these puzzles may benefit the development of a multi-component treatment plan for patients with IBS.

Table 2.1 Summary of literature addressing sleep disturbance in Adults with IBS

Author, Year, Country	IBS Criteria Used	Subjects (Age)	Outcome Measures	Main Findings[a]		
				Subjective[b] Sleep Measures	Objective Sleep[b] Measures	Links between Sleep Disturbance and GI Symptoms in IBS
Kumar, 1992, UK	Manning	6 IBS: 3F (21-46) 6 Control: 0F[c] (18-25)	1 night PSG	n/a	↑ %REM sleep	n/a
Goldsmith, 1993, USA	Manning	23 IBS: 18F (M=41.0±14.9)	28 days symptom diary	74% reported being "poor sleepers"	n/a	Poorer sleep quality the prior night correlated with worse morning IBS symptoms
Gorard, 1995, UK	Rome I	8 IBS: 4F (24-53) 10 Control: 4F (19-32)	1 night PSG	n/a	n.s.	n/a
Orr, 1997, USA	Rome I	All F 10 IBS (M=38.6) 10 Controls (age matched, mean n.r.)	1 night PSG	n/a	↑ REM time, ↑ %REM	n/a
Heitkemper, 1998, USA	Rome I	All F 16 IBS (M=44.8±5.2) 16 Control (M=43.8±5.8)	• Sleep questionnaire • 2 nights PSG (night 2)[d]	↑ awakenings ↑ restless & disturbed sleep (n.s. trend)	↑ REM latency ↑ SE (n.s. trend)	Self-report SOL, morning drowsiness, & morning tiredness correlated with GI symptoms in IBS
Elsenbruch,	Rome I	15 IBS: 13F	• PSQI	↑ global PSQI ↓	n.s.	n/a

1999, USA		(M=34.9±2.1) 15 Control: 13F (M=36.2±2.3)	• 1 night PSG	sleep quality, ↑ SOL, ↓SE, ↑ daytime dysfunction		
Fass, 2000, USA	Manning	305 IBS[e] 125 IBS+FD (M=47.4) 247 Control (M=42.6)	Sleep questionnaire	Sleep disturbance reported by 50% IBS, 55% control (sig n.r.). Controls reported more difficulty falling asleep. IBS reported more problems with waking up repeatedly, waking up feeling tired, needing medication to sleep(sig n.r.).	n/a	Worsening of bowel symptoms with sleep problems (sig n.r.)
Jarrett, 2000, USA	Rome I	All F 82 IBS (M=31.9±8.1) 35 Control (M=31.8±8.2)	• Symptom diary (1 menstrual cycle + 5 days after the following menses) • BDQ, 1 sleep item • SCL-90, 3 sleep items	Diary: ↑ difficulty falling asleep, waking during the night, waking too early, fatigue; ↓ rested on waking, TST SCL-90: ↑ restless/disturbed sleep, awakening in early morning	n/a	Greater sleep disturbance predicted worse next-day GI symptoms. GI symptoms did not predict next-night sleep disturbance.

	Rome I	All F 31 IBS (15 IBS only, 16 IBS+Dyspepsia) (M=34.0±8.5) 23 Control (M=36.4±10)	• PSQI • SSS • Insomnia questionnaire • 1 night PSG	PSQI: ↑ score on global PSQI and all subscales Questionnaire: ↓ satisfaction with sleep SSS: ↑ sleepiness	n.s.	n/a
Thompson, 2002, USA	Rome I	All F 16 IBS[f] (M=37±2) 21 Control (M=38±2)	1 night PSG	n/a	n.s.	n/a
Rotem, 2003, Israel	Rome I	18 IBS: 13F (M=43.1±12.6) 20 Control: 11 F (M=43.4±10.0)	• Sleep history questionnaire • ESS • 1 night PSG • 4 nights actigraphy	Sleep history: ↑ difficulty falling asleep (n.s. trend). ESS: ↑ daytime sleepiness	PSG: ↓ TST, ↓ SE, ↑ arousal & awakening indexes, ↑ WASO, ↑ %NREM1, ↑ %NREM2, ↓ %SWS ↓ SOL (n.s. trend). Actigraphy: ↑ sleep fragmentation index ↓ SE, ↑ SOL, ↑ %WASO (n.s. trend)	n/a
Robert, 2004, USA	Rome II	All F 44 IBS+Depressive Symptoms (DS) (M=40.1±2.6) 26 IBS	• PSQI • 1 night PSG	global PSQI score: IBS+DS > IBS and C, IBS > C	REM latency: IBS+DS > C, IBS > C (n.s. trend)	n/a

		(M=33.0±1.1) 21 Control (M=34.7±1.9)				
Heitkemper, 2005, USA	Rome II	All F 18 mild-to-moderate IBS (IBS-M) (M=30±9), 18 severe (IBS-S) IBS (M=32±7), 38 Control (M=32±7)	• PSQI • Morning sleep quality assessment • 2 nights PSG	↑ global PSQI score ↓ sleep quality, ↓ SE, ↑ sleep disturbance; ↑ SOL (n.s. trend). PSQI worst in IBS-S.	IBS-M vs IBS-S: ↑ SOL. IBS-M & IBS-S vs C: ↑ REM latency (n.s. trend). IBS-S vs. IBS-M & C: ↑ % REM.	n/a
Keefer, 2006, USA	Rome II	9 IBS: 7F (M=52.67±12.12) 7 Control: 3F (M=34.29±9.39)	• PSQI • ESS • Questionnaire on perceived link between sleep and GI symptoms • 1 night PSG	↑ global PSQI score, ↓ sleep quality, ↓ sleep duration, SE, ↑ sleep disturbances	↓ TST, SE	75% perceived GI symptoms made them wake up & difficult to sleep; 50% believed that poor sleep increased GI symptoms the next day.
Robert, 2006, USA	Rome II	All F 22 IBS-Diarrhea (M=39±2) 33 IBS-Constipation (M=37±2) 20 IBS-Alternating (M=36±2)	• PSQI • 1 night PSG	n.s.	n.s.	n/a
Ranjbaran, 2007, USA	Rome II	24 IBS: 21F[g] (M=56±2) 15 Control: 8F (M=48±4)	Modified PSQI (added 4 questions re: subjects' perception of the links between sleep and GI)	↑ SOL, ↑ % of group who reported - taking >30 min to fall asleep ≥1	n/a	52% believed that sleep affected GI symptoms.

				night/wk, repeated awakenings, using medication to sleep; ↓ % with good sleep quality		
Jarrett, 2008, USA	Rome II	All F 35 IBS (M=31.06±7.96) 38 Control (M=32.16±6.72)	• PSQI • 2 nights PSG	↑ % with PSQI scores >5	↑ REM latency	n/a
Bellini, 2011, Italy	Rome III	142 IBS: 110F (Median=38)	• PSQI • IBS-SSS	PSQI: 42% scored >5.	n/a	Weak positive correlation between PSQI and IBS-SSS
Heitkemper, 2011, USA	Rome II	All F 21 IBS with childhood abuse/neglect (A/N) (M=34.6±7.9) 19 IBS without A/N (M=28.4± 7.2) 32 Control (M=NR)	• PSQI • 3 night PSG (night 2)[d]	IBS+ A/N vs. IBS- A/N: ↑ global score, ↑ % with scores >5	IBS+ A/N vs. IBS- A/N: ↑ % REM	n/a
Heitkemper, 2012, USA	Rome III	All F 43 IBS 24 Control (combined sample, M=28±6)	• PSQI • Symptom diary (one menstrual cycle) • 3 nights PSG (night 3)[d]	n.s.	↓ TST, ↓ SE, ↑ %wake, ↑ %NREM2, ↑ %REM.	n/a
Buchanan, 2014, USA	Rome II	24 IBS, all F (M=32±8)	• PSQI • Symptom diary (menstrual cycle) • Actigraphy	PSQI: 58% with scores >5.		Worse sleep quality in diary predicted higher abdominal, anxiety, and

						fatigue the next day. Lower actigraphy SE predicted higher fatigue the next day. Symptoms were not related to next-night sleep on diary or actigraphy.

BDQ, Bowel Disease Questionnaire; C, control group; ESS, Epworth Sleepiness Scale; F, female; IBS-SSS, IBS Symptom Severity Score; M, mean age; n.r., not reported; NREM, non-rapid eye movement sleep; n.s., no significant difference; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement sleep; SE, sleep efficiency; SOL, sleep onset latency; SSS, Stanford Sleepiness Scale; TST, total sleep time; wk, week.

[a] Findings were statistically significant unless otherwise stated.

[b] Findings were for IBS group if there was no control group, or comparison between IBS group and control group unless otherwise stated.

[c]Demographics of controls obtained from Kumar et al (1990)[1].

[d] Only data from the night in parentheses were analyzed.

[e]This study included persons with functional dyspepsia (FD) and with both FD and IBS; results not reported here. Gender representation was 70.5% female in the entire patient group (FD, IBS, IBS+FD) and 61.9% in the control group.

[f]These studies included persons with IBS plus dyspepsia; results not reported here.

[g]This study also included a group with inflammatory bowel disease, not reported here.

[1]Kumar D, Idzikowski C, Wingate DL, Soffer EE, Thompson P, Siderfin C Relationship between enteric migrating motor complex and the sleep cycle. *The American journal of physiology* 1990;259:G983-90.

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Chapter 3. THE HIGH FREQUENCY COMPONENT OF HEART RATE VARIABILITY AND DELTA EEG POWER DURING SLEEP IN HEALTHY WOMEN AND WOMEN WITH IRRITABLE BOWEL SYNDROME

3.1 INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder (FGID). It is characterized by abdominal pain associated with alterations in defecation or stool frequency and consistency. (1) The prevalence of IBS in the general population ranges from 7% to 19% globally, and the prevalence of IBS is more common in women than in men.(2, 3) IBS is associated with high costs in terms of health care consumption and productivity loss.(4, 5)

The etiology of IBS is likely multifactorial.(6-8) Dysfunction or imbalanced autonomic nervous system (ANS) has been proposed to be one of the potential mechanisms involved in the pathophysiology of IBS.(9-13) The ANS consists of sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS). Increases in SNS activity can shunt blood from GI system and delay peristalsis, increased PSNS produces the opposite effects. These changes in ANS balance can result in clinical symptoms of constipation and diarrhea, two main manifestations of IBS.

Research in IBS and the ANS has frequently assessed SNS and PSNS through measurement of heart rate variability (HRV, changes in the length of time between each heart beat). HRV is based on the premise that vagal (parasympathetic) inputs result in rapid changes in the inter-beat interval (i.e., time in between the R wave of adjacent heart beats) whereas sympathetic inputs, mostly catecholamines (CAs) and adrenal cortical hormones, result in reduced variability of the inter-beat interval. Because heart rate can be heavily influenced by daily activity, many researchers have used nighttime or during sleep ANS assessments.(11, 13-15) To date, comparisons of HRV parameters between adults with and without IBS have yielded conflicting results. Some researchers (16, 17) found significant differences, e.g., reduced vagal activity in IBS group compared to a healthy control group, but others have did not find any differences in ANS activities.(9, 18) A few researchers found no difference in ANS function between IBS group and controls, however, they found significant differences between subgroups based on clinical phenotype (e.g., IBS bowel pattern subtypes (9, 11), history of depression and/or anxiety (12, 13, 19), symptoms severity (10, 18), or experience of early adverse life event (14)). The heterogeneity of participants, such as severity of IBS symptoms, psychological factors, other comorbidities, may contribute to the discrepancy in the study findings.

Sleep disturbance is one of the most common complaints amongst people with IBS.(14, 20-24) Difficulty in falling asleep, shorter sleep time, frequent arousal and awakenings, or nonrestorative sleep are the common complaints.(25-27) Increasingly, interest has focused on studying the relationship between peripheral ANS activity (measured by HRV) and central sleep mechanisms that may be altered in IBS (quantified by spectral analysis of electroencephalographic [EEG] waveforms). Researchers suspect that there is some common, underlying pathway coordinating these two oscillating systems functioning.(28-30)

Power in the various spectral bands of sleep EEG recordings are thought to correspond to certain characteristics of sleep; for example, increased power in the high frequencies indicates increased cortical arousal that should not be present in consolidated sleep, whereas increased low frequency power indicates predominance of deeper sleep. Fukudo et al.(31) used power spectral analysis (PSA) to assess EEG power band in response to specific stimuli (mental stress, cholinergic stimulation) found reduced EEG alpha power, and increased beta and theta power in IBS participants after stimulation. At the same time, they also noted increased colonic motility in the IBS participants. However, to date, PSA of EEG has not been used in sleep studies comparing IBS and healthy controls.

Studies in healthy humans have shown a correlation between HRV parameters and EEG power bands, especially between high frequency HRV (indicating greater PSNS activity) and delta band of EEG (indicating deep sleep).(29) However, studies in patient groups, such as those with insomnia or sleep apnea-hypopnea syndrome, have revealed a weaker association between HRV and EEG parameters.(28, 32-35) There is also evidence that this impaired link may be reversible. For example, a long-term continuous positive airway pressure (CPAP) treatment was reported to partially improve the coherence between cardiac vagal influence and delta sleep with little to no change in sleep quality (all sleep parameters were similar among untreated patients, CPAP treated patients, and controls at baseline though).(36)

To date, no studies have investigated the relationship between HRV and EEG parameters during sleep in IBS population. The investigation of dynamic interaction between HRV and EEG parameters could give us a better understanding of the physiological mechanisms underlying the interactions between sleep and ANS function. In our previous studies(37, 38), we found that abdominal pain was the most important factor that influenced the quality of life and work and daily activity of patient with IBS. Also, abdominal pain has a negative impact on sleep in people with IBS. Therefore, our aim of the study is to investigate the relationship of high frequency (HF) band of HRV with the delta band power of sleep EEG in women with IBS with moderate to severe abdominal pain compared to healthy control women.

3.2 METHODS

3.2.1 *Sample*

The sample for the current study came from a larger study (R01NR001094) and the detailed criteria of the original inclusion and exclusion criteria were previously published.(9) In brief, women with IBS and healthy control women, aged 18 to 46 years, were recruited from community advertisement between 2001 and 2005. To be enrolled, the women in IBS group needed to have a medical diagnosis of IBS and currently experiencing symptoms compatible with the Rome-II criteria for IBS. Women in control group were free of any symptoms of a functional GI disorder. Women were excluded from both groups if they had (a) a history of GI pathology (e.g., inflammatory bowel disease), (b) GI surgery, renal, or gynecological pathology that might result in IBS-like symptoms (e.g., bowel resection, endometriosis), (c) a significant comorbidity (excluding treated hypothyroidism, mild asthma), (d) a known cardiac dysrhythmia, (e) a sleep disorder, (f) taking medications that could interfere with sleep, cortisol, CAs, or HRV, such as beta blockers, antihistamines, serotonin reuptake inhibitors, or taking GI prokinetic or serotonergic agents. Women who used hormonal contraceptives were also excluded.

To be included in the current study, participants in IBS group had to report moderate to severe abdominal pain on Rome II questionnaire and also report moderate to severe abdominal pain on the daily symptom diaries at least 20% of all the days that they kept the diaries. Participants in healthy control group were randomly selected from the healthy control group from the larger study who did not report any moderate to severe adbominal pain on Rome II questionnaire. Approval was obtained from the University of Washington Human Subjects Board prior to the recruitment. All participants gave written informed consent before participating in this study.

3.2.2 *Procedures*

The purpose of the parent study was to compare women with medically diagnosed IBS to healthy control women on parameters of sleep and psychophysiological arousal. All the participants in the study kept symptom diaries for one menstrual cycle and spent three consecutive nights in a university sleep laboratory with polysomnography (PSG) monitoring. The first night was for adaptation, the second night served as 'baseline' sleep, and the third night examined the women's responses to a stressful stimulus (anticipation of public speaking the next morning) and blood levels of ACTH and cortisol measured. Data from the third night were previously published.(39) All participants completed a demographic form and a Brief Symptom Inventory (BSI-53). BSI-53 was used to evaluate participants' psychological factors and detailed description was previously published.(39) All participants were financially compensated for their participation in the study. For the purpose of this study, only the data from the second night were analyzed.

Prior to coming to the sleep laboratory, all participants were instructed to refrain from drinking caffeinated beverages, taking acetaminophen or aspirin within 6 hours of bedtime, drinking any alcohol, or napping. For the first two nights, the participants came 2 hours before their habitual sleep time and had electrodes placed for a standard PSG monitoring. Once the electrode placement was done, participants read or watched television in the bed until their routine bedtime and then the lights were turned off. The participants woke up spontaneously in the morning.

All participants were screened for two common sleep disorders, apnea/hypopnea and periodic leg movements, on the first night. Details of the screening were previously published.(9) On the second night, only essential recordings were performed to avoid disturbance to sleep, which included two EEGs (C3-A2 and C4-A1), two electrooculograms (EOG), one electromyogram (EMG), and one electrocardiogram (ECG). All recordings were recorded using the Embla Recording System with Somnologica software (Embla, Broomfield, CO). All channels were sampled at 500 Hz. Before analysis, EEG recordings from C3-A2 and C4-A1 were screened for epochs with movement, breathing or muscle artifact using RemLogic software. Either recordings from C3-A2 or C4-A1 were chosen for further processing based on which of these showed lower artifact levels. The chosen sleep recordings were visually scored in 30-s epochs as wake, stage 1, 2, 3, 4 and 5 (REM) by an experienced technician according to the standard criteria in place at the time of the study.(40)

3.2.3 *Data Processing*

Heart Rate Variability

ECG was measured within the PSG montage using a modified lead II electrode placement and was digitized with a sampling rate of 500 Hz. Sleep EEG and ECG data were synchronized on the same time base. The R-R intervals between adjacent QRS complexes were calculated by the signal processing algorithm implemented within the Somnologica software. PSA was performed with a fast Fourier transform (FFT) non-parametric algorithm in consecutive 5-min epochs. The power bands were extracted and grouped in the following frequency ranges: low frequency (LF) band (0.04-0.15 Hz) and high frequency (HF) band (0.15-0.4 Hz). The normalized values of HF, HF_{nu} were calculated based on formula HF_{nu}=HF/(LF+HF). Several researchers (41) have suggested that the LF band is predominantly reflective of sympathetic influence, but others suggest it is a measure of both SNS and PSNS balance.(42, 43) HF has been used to reflect PSNS activity.(42) The LF/HF ratio is usually used as an index of sympathetic and parasympathetic balance.(42)

EEG Power Spectral Analysis

Somnologia data acquisition system was used to calculate spectral power of the EEG recording in five frequency bands by the fast FFT algorithm. Frequency bands were defined as follows: delta (0.50-3.99 Hz), theta (4.00-7.99 Hz), alpha (8.00-11.99 Hz), sigma (12.00-15.99 Hz), and beta (16.00-39.99 Hz). The epoch length was 6 seconds, and Hamming windows were applied to reduce truncating error. Then, the mean values of each power band (44) within 30-second epochs (5 adjacent 6-second epochs) were calculated to synchronize with visual stage scoring. This study only reports delta power. The normalized value of delta power was calculated as the ratio between the power value of delta and the power of all frequency bands over the whole night.(29, 45)

3.2.4 *Data Analyses*

Coherence Analysis

A traditional coherency analysis was applied to analyze the relationship between HF_{nu} of HRV and $delta_{nu}$ of EEG. The methods assess the linear relationship between two consecutive frequency parameters x(f) and y(f).(29) In this study, x was the normalized HF of HRV and y was the normalized delta band power. In order to meet the stationarity requirement of coherence analysis(29) and also increase the time resolution, only data from the first four NREM-REM cycles were analyzed.

The frequency variable $f_{x,y}$ was the frequency at which the cross-spectrum between HF_{nu} and $delta_{nu}$ was maximum. The gain value is the ratio between amplitude of both signals. The phase shift is expressed in minutes, is the time lag between the change in HRV and EEG at that frequency. Positive result means that changes in HRV precede changes of EEG, and negative result means changes in EEG precede changes of HRV. The coherence between x and y is considered to be a measure of the relative strength of the linear relationship between two time series and it is similar to the squared correlation coefficient in a time domain. The value of coherence is 0 to 1, and high number means a stronger linear relationship between the two time series at the frequency of $f_{x,y}$.

Statistical Analysis

All the data analyses were computed by statistical software SPSS 22 (IBM SPSS Statistics, USA). The results were expressed as mean ± standard deviation. All the parameters, including demographics, sleep, HRV, and coherence analysis between HF_{nu} of HRV and $Delta_{nu}$ of EEG, were compared between women with IBS and healthy controls. A t-test was performed if the parameter had a normal distribution; otherwise, Mann–Whitney U test was performed. An analysis of variance (ANOVA) for repeated measures was used to compare the within group differences in HRV parameters across sleep stages. An alpha level was set as 0.05.

In order to control the potential effect of age, BMI, psychological factor and durations of the first four NREM-REM cycles on the HRV and EEG parameters, ANOVA was performed with age, BMI, BSI-53 score and the duration of the first four NREM-REM cycles as covariates and a second set of p values was listed in addition to the p values obtained by above mentioned statistical method.

3.3 RESULTS

3.3.1 *Demographic Characteristics*

There were 20 women with IBS and 20 age- and BMI-matched control women who initially met the inclusion criteria for this study. One subject in IBS group was excluded from final analysis due to missing HRV recordings. One subject in control group and three subjects in IBS group were excluded from final analysis because the data from these subjects greatly deviated from mean and were in opposite direction of literature. However, post hoc analysis showed that excluding these data from analysis did not change the direction of analysis results. There were 16 women with IBS and 19 control women in the final analysis. There were no differences in age or BMI between the two groups. The mean score of BSI-53 was significantly higher in IBS group compared to control group (p = .003). (Table 3.1)

Table 3.1 Demographics of Women with IBS and Healthy Controls

	IBS (n=16)	Control (n=19)	P
Age	28.5±7.0	28.6±6.9	.973
BMI	24.87±3.99	24.27±3.56	.647
BSI-53	23.6±19.4	9.7±12.4 [a]	.003[b]

BMI: body mass index; BSI-53: Brief Symptom Inventory.
[a]n=18 (one subject miss BSI-53 data); [b]Mann-Whitney U Test.

3.3.2 *Sleep Parameters*

The IBS group had a higher percentage of NREM sleep than controls in the first four NREM-REM cycles (p = .030). Other than that, all the sleep stage variables were similar between groups, both in the whole night and the first four NREM-REM cycles. The IBS group had less normalized delta power than the control group in the whole night (p = .039) and also the IBS group had less normalized delta power than the control group in the first four NREM sleep cycles (p= .020). (Table 3.2)

Table 3.2 Sleep Characteristics of Women with IBS and Healthy Controls

	IBS	Control	P1	P2
Variables for the entire night				
Time in bed (min)	478.7±33.5	491.7±36.1	.280	.165
Total sleep time (min)	427.8±28.8	426.4±36.9	.899	.660
Sleep Efficiency (%)	89.7±6.9	86.9±7.3	.593[a]	.332
Fragmentation index	6.5±1.7	7.2±2.7	.318[b]	.182
Sleep latency (min)	11.3±9.6	11.0±9.3	.509[a]	.738
REM latency (min)	84.3±34.3	96.2±55.7	.613[a]	.556

Wake (%)	10.3±6.9	12.6±7.0	.509[a]	.371
Stage 1 (%)	5.0±1.8	5.3±2.9	.726	.489
Stage 2 (%)	38.5±9.0	37.9±8.8	.850	.716
SWS (%)	23.4±10.4	20.3±6.6	.299	.056
NREM (%)	66.8±5.5	63.5±5.7	.089	0.074
REM (%)	22.8±4.5	23.5±7.0	.760	.588
$Delta_{nu}$	.76± .05	.77± .04	.231	.039
Variables for the first four NREM-REM cycles				
Mean sleep cycle duration (min)	402.1±52.9	405.6±53.2	.847	.949[c]
Wake (%)	9.2±5.4	12.3±7.3	.158	.191
Stage 1 (%)	4.7±1.6	5.0±2.9	.772	.666
Stage 2 (%)	36.5±8.7	35.8±8.6	.824	.738
SWS (%)	26.3±11.6	22.2±6.4	.219[b]	.050
NREM (%)	67.6±5.6	63.1±6.1	.030	.045
REM (%)	23.2±4.9	24.4±7.6	.607	.605
Wake $Delta_{nu}$	.62± .09	.64± .09	.523	.510
NREM $Delta_{nu}$	.80± .45	.83± .04	.129	.020
REM $Delta_{nu}$	.65± .09	.64± .09	.418	.064

NREM: non rapid eye movement sleep; REM: rapid eye movement sleep; SWS: slow wave sleep (stages 3 and 4); WASO: wake after sleep onset; P1: test results between IBS group and control group; P2: test results between IBS group and control group after controlling for age, BMI, BSI-53, first four NREM-REM sleep cycle duration.

[a]Mann-Whitney U Test; [b]Equal variances not assumed; [c] test results between IBS group and control group after controlling for age, BMI and BSI-53.

3.3.3 *Heart Rate Variability Parameters*

Surprisingly, the IBS group had higher HF_{nu}, lower LF_{nu}, and lower LF/HF ratio than the control group across during the first four NREM-REM cycles. No differences in length of R-R intervals, total power, absolute HF or absolute LF between groups across the first four NREM-REM cycles were observed (Table 3.3, upper panel). The IBS group also had higher HF_{nu} and lower LF_{nu} in NREM and REM sleep stages compared to the control group. In addition, REM LF/HF ratio was lower in IBS group (p=. 007). (Table 3.3, lower panel).

Table 3.3 Heart Rate Variability Parameters of Women with IBS and Healthy Controls

	IBS	Control	P1	P2
HRV parameters across the first four NREM-REM cycles				
RRI (ms)	947.4±179.3	941.3±143.8	.912	.946

TP (ms^2)	11085±3550	11429±3003	.758	.983
HF (ms^2)	2522±1195	1962±1064	.152	.218
LF (ms^2)	2972±980	3663±1537	.131	.131
HF_{nu}	46.36±11.41	35.63±10.14	.006	.012
LF_{nu}	53.65±11.41	64.39±10.14	.006	.012
LF/HF	1.66± .98	2.74±1.36	.012	.009
HRV parameters across sleep stages of the first four NREM-REM cycles				
NREM RRI (ms)	956.5±185.5	948.0±148.1	.882	.945
REM RRI (ms)	922.1±165.2	929.1±129.0	.890	.917
Awake RRI (ms)	920.2±166.5	923.8±119.9	.942	.843
NREM HF_{nu}	48.89±11.71	39.69±10.71	.021	.035
REM HF_{nu}	40.08±11.79	26.40±10.72	.001	.003
Awake HF_{nu}	39.72±10.61	30.61±9.0	.010	.029
NREM LF_{nu}	51.12±11.71	60.32±10.72	.021	.035
REM LF_{nu}	59.93±11.79	73.61±10.72	.001	.003
Awake LF_{nu}	60.29±10.61	69.40±9.0	.010	.029
NREM LF/HF	1.49± .90	2.19±1.17	.057	.046
REM LF/HF	2.12±1.47	4.20±2.71	.007[a]	.005
Awake LF/HF	2.07± 1.06	3.09± 1.77	.022[b]	.041

P1: test results between IBS group and control group; P2: test results between IBS group and control group after controlling for age, BMI, BSI-53, first four NREM-REM sleep cycle duration.
[a]Equal variances not assumed; [b]Mann-Whitney U Test.

3.3.4 *Coherence Analysis*

The coherence between HFnu and the $delta_{nu}$ was slightly poorer in women with IBS compared to healthy control women, but this did not reach statistical significance. The maximum peak frequency of the cross-spectrum ($f_{x,y}$) and gain between HFnu and the $delta_{nu}$ were similar in both groups. Women with IBS tended to have a longer phase shift than control women (11.6 min vs. 6.3 min, p=. 000). (Table 3.4)

Table 3.4 Coherence analysis between HF_{nu} and $delta_{nu}$ in women with IBS and healthy controls across the first four NREM-REM cycles

	IBS	Control	P1	P2
$F_{x,y}$(10^{-4}Hz)	2.19± .16	2.17± .23	.339 [a]	.350
Coherence	.54± .18	.58± .17	.442	.195
Gain	.88± .30	.82± .24	.431[a]	.648
Phase shift (min)	11.6±4.8	6.3±3.0	.000	.013

P1: test results between IBS group and control group; P2: test results between IBS group and control group after controlling for age, BMI, BSI-53, first four NREM-REM sleep cycle duration.
[a]Mann-Whitney U Test.

3.4 Discussion

In our study of women on the second night in a sleep laboratory, those with IBS showed a trend towards a weaker correlation between a marker of cardiac vagal activity and delta EEG power band compared to controls. Women with IBS also had a longer time lag between normalized HF and delta band power. In addition, we found that women with IBS had higher percentage of NREM in the first four NREM-REM sleep cycles and the whole night; had higher cardiac PSNS activity at all time points during both NREM and REM.

There is a growing interest in the study of the relationship between cardiac ANS activity and EEG spectral power band.(28, 29, 32-36, 46-49) However, the majority of these studies have been conducted in healthy participants (29, 46, 49) and none to date in persons with IBS. Other patient groups, such as those with insomnia (28, 50) and sleep apnea-hypopnea (35, 51) have been examined this relationship with mixed results. Branderberger et al.(30) found that delta band power inversely correlated with the LF/(LF+HF) in a study of nine healthy men. In a study of 8 healthy men Jurysta et al.(29) further proved that all EEG power bands correlated with normalized HF of HRV and the gain was highest for delta band. Similar results also were found in a recent study with 197 midlife women.(51) Rothenberger et al.(51) reported a positive correlation between the whole night delta band power of EEG and HF of HRV. Further analysis indicated that the strongest correlations were before and after the peak delta power during the first NREM sleep period. They found that the correlations between delta of EEG and HF of HRV were stronger in participants with sleep-disordered breathing and self-reported insomnia. The investigators suggested that the loss in time lag between HF of HRV and delta power of EEG might contribute to the difference in the strength of correlation. Also, the analysis method (temporal correlation) was different than the Jurysta's research group (coherence analysis). Jurysta et al.(28) also found decreased linear correlation between HF of HRV and delta in patients with chronic primary insomnia compared to controls. However, another research group (Dumont et al.(35)) reported there was no evidence that sleep apnea-hypopnea influences the synchronization between HF of HRV and EEG power bands. In contrast, this same research group recently reported that the coherence between HF of HRV and delta EEG power was compromised in untreated patients with severe sleep apnea-hypopnea syndrome and the long-term continuous positive airway pressure (CPAP) improved the coherence. Whether these results in patients with sleep apnea have relevance to IBS patients is questionable since women were screened for sleep apnea during the adaptation night. However, the findings from the insomnia group do suggest that chronic poor sleep may be the cause or the outcome of dysregulation of the ANS-EEG relationship. In our study, we did not find there was no difference in strength of coherence between normalized delta band power of EEG and normalized HF of HRV between groups, but there was a trend that women with IBS to have less coherence than controls.

In the current study we found that the phase shift from cardiac change to EEG change was longer in IBS group than in control group, and the cardiac change preceded the delta band power change. Our findings are consistent with two studies that found that cardiac changes preceded EEG changes when simultaneously recorded.(28, 30) Although Jurysta and colleagues found no differences in phase shift between patients with chronic primary insomnia and controls in their study, the phase shift in patients showed bigger variances than found in the control group.(28) Our phase shift of controls was shorter compared to with Jurysta's study (12±5 min) (29) and longer than Brandenberger's report (5min). The difference in terms of phase shift may due to subjects' individual difference or the intervals of the time series. All participants in our study were women versus all men in Jurysta and Branderberger's studies, and also their participants were younger (mean age=20.5 in Jurysta's study and age range 20-30 in Branderberger's study) than ours (mean age=28.6). In our study, we used 30s interval for comparisons. Since HF of HRV was assessed every 5 min, therefore we chose to fill 10 consecutive epochs with the same data in order to pair with the EEG data without losing resolution by aggregating the EEG data into 5 min epochs. Branderberger and Jurysta used 5 min and 20 s epochs, respectively.

Similar to findings from other studies that used a single night PSG monitoring in a sleep laboratory in patients with IBS, we found no significant differences in sleep architecture between patients with IBS and controls on the second night.(11, 13, 23, 52, 53) In our study, the only difference in sleep stage variable was a higher percentage of NREM sleep in the first four NREM-REM sleep cycles in women with IBS compared to healthy controls. We also found that there was a trend for the IBS group to have a higher percentage of slow wave sleep (SWS, Stage3+Stage4) after controlling for age, BMI, BSI score and the duration of first four NREM-REM sleep cycles. In our previous study (22), the poor sleep quality on the first night sleep in a sleep laboratory with PSG monitoring was noticed in both IBS patient and control groups. However, subgroup analyses revealed that IBS participants with more severe symptom intensity tended to demonstrate greater differences in time in bed, sleep efficiency, sleep onset latency to stage 2 sleep and percentage of REM sleep between nights 1 and 2 when compared to IBS with mild-to-moderate symptom severity and controls. Several researchers reported that people with IBS were more vulnerable to external stressors, such as new environment.(54, 55) Recovery sleep, which is the sleep after total or partial sleep deprivation, showing increased depth and length in sleep is common after sleep deprivation.(56, 57) NREM sleep is characterized by relatively inactive brain activity and usually considered as a restorative period for muscles and energy balance. The slow wave EEG activity (frequency between 0.5 and 4 Hz), such as sleep spindles, K complexes, and delta waves, is an marker for sleep intensity.(58) Therefore, the higher percentage in NREM sleep in IBS group was likely due to the 'sleep recovery' after the sleep disturbance of the first night of sleep in the sleep laboratory. Of note, while the IBS group had a higher percentage of NREM sleep they did not have more delta activity. In fact, the whole night normalized delta and the normalized delta of first four NREM-REM sleep cycles in IBS group were significantly less compared to controls. The mechanism is unknown, and the chronic sleep disturbances in these women with IBS could contribute to it. Further studies are needed.

We found that women with IBS had higher PSNS activity, higher HF_{nu}, lower LF_{nu} and lower LH/HF ratio across the whole night and sleep stages compared to controls. These group differences were still statistically significant even after controlling for age, BMI, BSI score and the duration of first four NREM-REM sleep cycles. This finding is the opposite of the common findings of ANS activity, including our own, in people with IBS. Many researchers reported that IBS patients showed a vagal withdrawal or lower PSNS activity during the night compared to controls.(10, 16, 17, 19) However, most of these studies involved only one night sleep in a sleep laboratory. Therefore, the partial sleep deprivation due to the first night effect may play a role in the alternation of ANS activity during the night. In a study with 11 healthy young men, Glos et al.(56) found that people had decreased LF and LF/HF ratio after 40 hours of sleep deprivation. Further analysis revealed that the influence of sleep deprivation on HRV was only on NREM sleep. To date, there is no study that examined the effects of sleep deprivation in ANS activity among people with IBS.

There are several limitations to our study. First, the relationship between the two time series in our study was not perfectly stationary, which is a requirement for time series analysis. We limited our analysis to the first four NREM-REM sleep cycles to decrease the possible effect of non-stationary. Second, not all of our subjects had four NREM-REM sleep cycles. One subject in control group had only two NREM cycles and two REM cycles, one subject in IBS group had three NREM cycles and two REM cycles, another subject in IBS group had three NREM cycles and three REM cycles. We used the mean duration of first four NREM-REM sleep cycles as one of four covariates when doing the ANOVA test between groups and there were very few difference in statistical significance with or without these covariates.

In conclusion, based on the coherence analysis, there was evidence of dysfunction in communication between ANS and CNS in women with IBS. The cardiac change preceded the EEG delta change in both groups and IBS group has longer phase shift. In addition, our study demonstrated that women with IBS had more recovery sleep in NREM, however, they did not seem to get more high quality deep sleep. Finally, women with IBS had higher PSNS dominance than controls both in the first four NREM-REM sleep cycles and the whole night.

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Chapter 4. CONCLUSION

In conclusion, our systematic review suggests that sleep disturbances are common in people with IBS. However, study findings do not consistently support the prevalence of specific types of sleep disturbances, especially when measured objectively, and there is a discrepancy between subjective and objective sleep measurements. Whether this discordance is due to misperception of sleep, insufficiently sensitive measures or methods, or other undetermined factors needs to be determined. A positive relationship between sleep disturbances and GI symptoms is also found. ANS function may be interrelated with sleep and may be an underlying mechanism for IBS in a subset of patients. Gender may play a pivotal role in modulating IBS, and more male participants should be involved in further studies. For future studies, standardized definition of sleep disturbances, proper sleep measurement, and sensitive data analysis methods may help understand the interrelationship among sleep, ANS function, and GI symptoms better. Solving these puzzles may benefit the development of a multi-component treatment plan for patients with IBS.

Based on the coherence analysis in the second study, there was evidence of dysfunction in communication between ANS and CNS in women with IBS. The cardiac change preceded the EEG delta change in both groups and IBS group has longer phase shift. In addition, our study demonstrated that women with IBS had more recovery sleep in NREM, however, they did not seem to get more high quality deep sleep. Finally, women with IBS had higher PSNS dominance than controls both in the first four NREM-REM sleep cycles and the whole night.

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APPENDIX A IRB FORM

UNIVERSITY of WASHINGTON
HUMAN SUBJECTS DIVISION
Box 359470
Seattle, WA 98195-9470
Phone: 206-543-0098
Fax: 205-543-9218

APPLICATION: Specimen or Data Use, Non-Identifiable (and self-determination)

FOR HSD OFFICE USE ONLY

APPLICATION NUMBER:	50230	COMMITTEE: ED	DATE RECEIVED STAMP:
[X] MASTER COPY	[X] ACCEPTED – See Notice of Determination		RECEIVED Human Subjects Division JUL 30 2015 UW
☐ RESEARCHER COPY	☐ NOT ACCEPTED – Activity is considered to be Human Subjects Research		
ADMINISTRATOR SIGNATURE:	[signature]		
SIGNATURE DATE:	8/7/15		

1. Research Study & Contact Information

Full Application Title:	IRB # (if assigned):	Committee: (if assigned)
Sleep-Related Autonomic Nervous System (ANS) Function in Women with Irritable Bowel Syndrome (IBS)		

Lead Researcher Information

Name:	Title:	Position (e.g. Asst. Professor or Director):
Qian Tu	Student	
Home Institution (or source of paycheck): **UW Student? Home Institution is UW.**	Other Home Institution:	
UW		
UW Department:	UW Division (Department of Medicine):	
Biobehavioral Nursing and Health Systems	School of Nursing	

UW Position or Appointment (choose the most appropriate one)

Faculty:
[ ] Regular Faculty Appointment [ ] Research Faculty Appointment [ ] Clinical Faculty Appointment
[ ] Affiliate Faculty Appointment [ ] Visiting Faculty Appointment [ ] Dual Appointment with PNNL
[ ] Other (Describe):

Student: [X] Graduate or Professional Student (Matriculated or Approved "On Leave") [ ] Matriculated Undergraduate Student [ ] WWAMI Student

[ ] UW Resident, Fellow, or Post-Doc. [ ] UW Administration or Staff [ ] None

Phone #:	Campus Box#:	Email:	Other address if not at UW:
206-661-7978	357266	qiantu@uw.edu	

Contact Person (if other than lead researcher)

Name:	Title:	Position (e.g. Asst. Professor or Director):
Home Institution (or source of paycheck):	Other Home Institution:	
UW Department:	UW Division (Department of Medicine):	

Phone #:	Campus Box #:	Email:	Other address if not at UW:

Name and mailing Address for all paper-based correspondence (If blank, correspondence will be directed to contact person, or lead researcher if no contact person.)		
Name:	Campus Box#:	Other address if not at UW:

2. Assurances, Signatures and Certification/Researcher Responsibilities

DEPARTMENT OR DIVISION CHAIR, CENTER DIRECTOR of Lead Researcher
If it is unclear which department should provide this assurance, consult document #931, Signatures on IRB Forms.

- I certify that the ***researcher is qualified*** to conduct the research, and that there are ***adequate resources*** (researcher time, personnel, financial support, equipment, facilities) available.
- I certify that this research has received an intramural review and approval of ***scientific merit***, if it did not go through an extramural review process.
- (If applicable) I concur with the student's choice of an ***appropriate faculty advisor***.

Margaret Heitkemper — [signature] — 7/29/2015
Typed name — Signature of DEPARTMENT CHAIR — Date

LEAD RESEARCHER
If your research activity is determined to be "Not Human Subjects Research" it is your responsibility to:

2.1. Ensure that the data/specimens were/are collected in an appropriate and ethical manner

2.2. Determine whether a Materials Transfer Agreement (http://depts.washington.edu/uwc4c/for-researchers/material-transfers/) or Data Use Agreement is necessary for obtaining and using the data/specimens.

2.3. Promptly notify HSD of any new information about the risks of this research to the specimen/data donors or others.

2.4. Notify the IRB if you are **including** Co-investigators to your study who were part of the initial collection of these data and/or specimens. If so, the research activity would be considered to involve human subjects.

2.5. Notify the IRB if you obtain data/specimens about individuals in which you may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained specimens/data pertain, then the research activity now would involve human subjects under the regulation.

This signature certifies that this document provides a complete and accurate description of the proposed activity and that the researchers agree to abide by the conditions and responsibilities of this determination.

[signature] — 07/29/2015
Signature of LEAD RESEARCHER — Date

FACULTY ADVISOR of Student Lead Researcher

- I confirm that ***I am responsible*** for working with the Student Lead Researcher to ensure that this research is performed in an ethical manner that complies with appropriate human subjects regulations and with the information provided in this IRB application.
- I have ***reviewed and concur with this research proposal***, including: purpose, design, methodology, procedures, subjects, and the provided description of risks and benefits.
- I will assist the student and the IRB as requested if any problems develop with the research.

- I will provide ***continued oversight and guidance*** to the student during the course of the research, as appropriate.
- If I will be unavailable (such as during a sabbatical leave or vacation), I will **arrange for an alternate faculty advisor** to assume responsibility during my absence, and I or the Student Lead Researcher will advise the IRB in advance.

Margaret Heitkemper	heit@uw.edu	[signature]	7/29/2015
Typed name	Email	Signature of FACULTY/ADVISOR	Date

END PART TWO

3. Funding Information

3.1. Are you receiving any federal support for this research?

Federal support includes:

- **Direct funding** from any federal agency to support this specific research. This includes direct federal awards, as well as federal awards to a non-UW institution that are then provided to the UW through a subcontract or similar arrangement, and pilot projects and small grants funded through a group that receives federal funds specifically for the purpose of awarding pilot projects and small grants.
- **Indirect funding** from any federal agency. This is generic (i.e., not tied to this specific study) federal salary support for the time that any key personnel spend on the research. Examples: many training grants, fellowships, and career development awards.
- Federal facilities or personnel are engaged in the research, as defined by the WORKSHEET: Engagement.

[ ] **YES**

[X] **NO**

3.2. Is the research activity part of a larger research study such that the UW is considered a 'site'?

[ ] **YES**

[X] **NO**

END PART THREE

4. Human Subjects Determination

Section A

Use this form only if your research does not involve direct contact with human subjects for research purposes. If you check any of the boxes that are asterisked (*) then your project must be submitted to HSD because it involves human subjects.

YES	NO	N/A	
[ ]*	[X]	[ ]	4.A.1. If you are using specimens, are they being used to test the effectiveness of a medical device with the possibility that the data may eventually be submitted by you or the sponsor to the Food and Drug Administration (FDA)? *"Medical device" includes in-vitro diagnostic devices.*
[ ]	[X]	[ ]	4A.2. Are the specimens/data you will study ***publicly available***? **If they are publicly available, then your project does not meet the definition of "human subjects research"**
[ ]*	[X]		4A.3. Will **you or any other investigators** in this research have **any** information which would allow you or the other investigators to readily identify an individual? This may include what is considered ***protected health information*** or ***health care information***, about the individuals from whom the specimens/data are or will be obtained. For example, will you or any of the investigators directly access records (clinical, medical, educational, etc.) that contain identifiable information?
[ ]*	[X]		4A.4. Could **you or any other investigators** in this research obtain identifying information about individuals through a constellation of variables accompanying the specimens/data?

For Coded Data Only: COMPLETE THE FOLLOWING QUESTIONS IN THIS SECTION ONLY IF YOU ARE USING **CODED** DATA

[ ]*	[X]	[ ]	4A.5. Will the individuals who provide the coded information or specimens collaborate on other activities related to the conduct of this research? Examples of such activities include, but are not limited to: (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; **and** (2) authorship of presentations or manuscripts related to the research.
[ ]*	[X]	[ ]	4A.6. Were the data or specimens collected specifically for the current proposed research project through an interaction or intervention with an individual by **you or any other investigators**?

4A.7. Please check the reason(s) that **you or any other investigators** in this research will not be able to link the specimens/data with identifying information about the individuals:

[X]	The key to decipher the code (the identifying link between specimens/data and individuals) has been destroyed.
[ ]	You and your research team have entered into an agreement with the holder of the key to the code (i.e. source of specimens/data) prohibiting the release of the key to you and your research team under any circumstances.
[ ]	There are IRB-approved written policies and operating procedures for the specimen/data repository(s) or data management center that prohibit the release of the key to you and your research team under any circumstances.
[ ]	There are other legal requirements prohibiting the release of the key to you and your research team. Identify the legal requirement(s) below: identify here
[ ]	Other. Please explain below: explain here
[ ]*	None of the above apply

END PART FOUR Section A

Section B:

Please complete this section (along with Section A) if you need documentation for funding agencies, administrators, or collaborators.

Research Purpose

4B.1. Using Lay terms, explain the specific purpose of the research and why it is important.
Please limit your response to provide only a basic understanding of your research. Generally, a paragraph is sufficient.

The purpose of this secondary data analysis is to describe the characteristics of autonomic nervous system (ANS) function and sleep microstructure, and to explore the relationship of ANS activity with sleep microstructure and daily gastrointestinal (GI) symptom ratings in women with irritable bowel syndrome (IBS). This study will help understand the role of ANS in IBS, which will help understand the etiology of IBS and potentially lead to a better treatment plan.

Description of Specimens/Data

4B.2. Please describe the type of specimens that you will use (e.g. plasma samples, liver biopsy, etc.)

N/A

4B.3. Please describe the type of data that you will use (e.g., interview transcripts, quality assurance/improvement data, health information, educational records, etc.) and the general content (e.g., oncology data, familial history, educational history, etc.):

Electrocardiogram (EKG) and electroencephalogram (EEG) data during sleep in a sleep laboratory at UW School of Nursing.

4B.4. Please list all demographic data variables that you will acquire:

Age, race and ethnicity, marital status, education, occupation, personal and family income levels.

4B.5. Please list all other variables (excluding demographic variables) that you will acquire, including those that may be considered "sensitive" (e.g. medical dates of service). *If possible, please include a data collection sheet in lieu of listing all variables.*

Symptom diaries (daily GI symptom ratings) and Brief Symptom Inventory (BSI-53)

4B.6. Who is providing you with the specimens/data? Include the name and location of the individual, entity, or institution for each source. If a UW study, please specify HSD study number and PI name.

HSD study number 05-9418-V01, PI name: Margaret Heitkemper.

4B.7. How were the specimens/data obtained initially? Who did the initial collection, and under what circumstances?

Three nights' EKG and EEG were collected in the sleep laboratory in School of Nursing with trained research assistant and the demographic data, symptom diaries, BSI-53 were collected in the subjects' own house by filling the forms.

4B.8. Is the data being provided by a co-investigator of this current research activity? Please explain:

The data is from a closed study (HSD study number 05-9418-V01) by Dr. Margaret Heitkemper.

4B.9. From what population(s) were the specimens/data derived (i.e., healthy adults; patients with tuberculosis; children infected with the HIV virus)?

Adult menstruating women with IBS.

4B.10. How many individuals (i.e., subjects) are included in the specimens/data (i.e., about a dozen; 100-200; more than a thousand) that you will receive?

About 80 adult menstruating women with IBS.

4B.11. Are some or all of the specimens/data from individuals with a rare condition or disease, or from a small and easily identifiable group (i.e. Werdnig-Hoffman disease; Native American tribe such as the La Push)?

[X] **NO**

[ ] **YES** → If "YES", please describe below:

describe here

Research Procedures

4B.12. Provide a brief description of how you will use the specimens/data. _Please limit your response to provide only a basic understanding of the procedures you will use. Generally, a paragraph is sufficient._

Before analyzing, both EKG and EEG data will be cleaned for artifacts by an experienced sleep laboratory technician. Power spectral analysis will be used to analyze both EKG and EEG data, then the relationship between these two will be analyzed by traditional coherency analysis. All the demographic data variables will be analyzed to establish the compatibility between IBS group and control group. Brief Symptom Inventory (BSI-53) will be used as a control variable. GI symptom ratings will be used to analyze the relationship between heart rate variability (HRV) variables and GI symptoms.

Potential for Harm

4B.13. Describe the potential for harm, if any that could result from this research. Include: the type of harm, the circumstances in which it could occur, the individuals or groups who could experience it, and the likelihood, magnitude, and duration of harm. *(Examples: Harm may occur due to accidental disclosure or harm may result to individuals, or to the groups or communities to which they belong, even when specimens/data are anonymous.)*

Information leakage harm. The data related to subjects may be accidentally disclosed. However, the likelihood is extremely low since all the data come from a closed study and the original file that can connect the data back to each subject was destroyed. Also, only authorized personnel directly involved in this study have access to the data and all of them have received proper training for handling human subjects data.

4B.14. Describe the steps you have taken or will take to minimize any risk of harm to individuals or groups that could result from this research. *(Example: the source of the specimens/data will be described in publications or presentations only as a Native American tribe in the Western United States.)*

First, all people who have access to the data have been properly trained for handling human subjects data. Second, all the research related data are kept in a safe place in a locked cabinet or internet drive that is open only to authorized people. Third, all the data will be only referred in publication or presentations as a group of women with IBS diagnosis recruited from the local community advertisement.

END PART FOUR Section B

UNIVERSITY *of* WASHINGTON
HUMAN SUBJECTS DIVISION

August 7, 2015

Qian Tu
Behavioral Nursing and Health Systems

Re: HSD reference #50230, "Sleep-Related Autonomic Nervous System (ANS) Function in Women with Irritable Bowel Syndrome (IBS)"

Dear Mr. Tu,

The Human Subjects Division received your determination request application on August 7, 2015. Your research activity described in the above-referenced application has been by reviewed by Subcommittee D.

As outlined in your application, the research activity will only involve the receipt and analysis of data that is not individually identifiable, as the data cannot be linked to specific individuals by the investigators either directly or indirectly through coding systems. Information in your application indicates that:

(1) The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals;

and

(2) If the information is coded, the investigators cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain because the investigators and the holder of the key have entered into an agreement prohibiting the release of the key to the investigators under any circumstances.

Given this information and the definition of "human subject" under 45 CFR 46.102(f), the research has been determined to not meet the federal regulatory definition of "human subjects research". Therefore, you do not need IRB review and approval to perform your activities. Please keep this memo and a copy of your returned application for your records.

If you have further questions or concerns, feel free to contact me by email at <your email> or by phone 206-616-9321.

Best regards,

Nat Krancus,
IRB Administrator
University of Washington, Human Subjects Division

4333 Brooklyn Ave. NE, Box 359470 Seattle, WA 98195-9470

main 206.543.0098 fax 206.543.9218 hsdinfo@u.washington.edu www.washington.edu/research/hsd

VITA

Qian Tu is from China and has studied in University of Washington in Seattle, Washington since 2011. Her research interests are sleep disturbances and autonomic nervous system function in persons with irritable bowel syndrome. She was a full-time nursing instructor in for two years before she came to US. She received her Bachelor of Science in Nursing at Third Military Medical University in China and Master of Science in Nursing at Wenzhou Medical University in China.