The effect of sleep deficiency on esophageal acid exposure of healthy controls and patients with gastroesophageal reflux disease

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Running title: Sleep Deficiency and Esophageal Acid Exposure

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Abstract

Background:

Studies have demonstrated a bi-directional relationship between sleep deficiency and gastroesophageal reflux disease (GERD). However, there is limited data on how sleep deficiency affects esophageal acid exposure. The aim of this study was to compare the effect of sleep deficiency on esophageal acid exposure of healthy controls versus GERD patients.

Methods:

Eleven patients from each of 2 groups were randomized to undergo pH testing after 2 consecutive days of 7-8 hours of sleep per night (normal sleep) or 2 consecutive days of 4 hours of sleep per night (deficient sleep). All subjects then crossed over to the other arm, after 1-week washout period. While subjects were instructed to follow the study sleep protocol, actigraphy ensured subjects followed required sleeping time during study period.

Key Results:

After normal sleep, all healthy controls had normal esophageal acid exposure. After deficient sleep, 5 healthy controls (45.5%) demonstrated an abnormal pH test. Overall, there was a significant increase in reflux parameters after deficient sleep as compared with normal sleep (% total time 6.15 ± 5.89 vs 1.74 ± 1.54, % upright time 4.72 ± 5.36 vs 0.87 ± 1.28, $p < 0.05$, respectively). After normal sleep, 6 GERD patients (54.5%) demonstrated an abnormal pH test. After deficient sleep, 10 GERD patients (90.9%) demonstrated an abnormal pH test. GERD patients demonstrated significantly higher reflux parameters than healthy controls after normal sleep (% total time-5.02 ± 3.45 vs 1.74 ± 1.54, % upright time-4.11 ± 3.98 vs 0.87 ± 1.28, $p < 0.05$, respectively).

Conclusions & Inferences

Sleep deficiency increased esophageal acid exposure in both healthy controls and GERD patients. Sleep deficiency also resulted in abnormal pH tests in almost half of healthy controls.

KEYWORDS

GERD, sleep deficiency, pH, esophagus, actigraphy

Key Points

- There are numerous studies demonstrating the effect of GERD on sleep quality. However, there is paucity of information on how sleep deficiency per se effects GERD.
- This study demonstrated that sleep deficiency can increase esophageal acid exposure in both healthy controls and GERD patients.
- Sleep deficiency appears to be an important underlying mechanism for abnormal esophageal acid exposure and thus should be considered and addressed in patients with GERD.

1 INTRODUCTION

Recent studies have demonstrated a close relationship between sleep deficiency and gastroesophageal reflux disease (GERD). In addition, during the last century, 2 hours were lost from our nighttime sleep duration (from 9 hours in 1910 to 7 hours in 2002).[1] In fact, more than 50 % of the adult population in the United States sleeps between 5-6 hours per night and thus are sleep deficient.[1] Much of our sleep deficiency is the result of lifestyle choices and/or work schedule. Sleep deficiency has an important impact on quality of life and health status. People who are sleep deficient have a higher chance of being involved in an accident at home or at work. They often feel listless and have an increased risk for type 2 diabetes, obesity, heart disease, psychiatric disorders and dementia.[1]

It has been demonstrated that sleep quality may be affected by GERD. Approximately 25 % of the general population and 50 % of the patients with GERD report heartburn that awakens them from sleep during the night.[2,3] Additionally, many patients with GERD may experience short, amnestic, arousals during acid reflux events that result in sleep fragmentation and lead to poor quality of sleep. In turn, poor quality of sleep may enhance perception of intraesophageal stimuli through brain-gut interaction. In one study, it was demonstrated that overall poor sleep quality was related to longer acid reflux events documented by both total and supine time during an esophageal pH test.[4] When individual parameters assessing sleep quality were investigated, more awakenings during the night were associated with a larger number of acid reflux events longer than 5 minutes in the supine position, a greater duration of the longest acid reflux event, and a longer length of the longest acid reflux events while supine during the 24-hour esophageal pH test. The authors also analyzed their data as a function of subjective sleep quality. The study showed that patients with poor sleep quality had a higher mean percent time pH < 4 when compared to those with good sleep quality. Significant associations were found such that the more hours a person slept, the less sensitive

they were at perceiving actual acid reflux events ($r = 0.28$, $p < 0.05$).[4] However, these data were obtained from patients with GERD. It is unclear whether sleep deficiency impacts esophageal acid exposure in normal individuals and if it is quantitatively different from GERD patients. Therefore, this study compared the effect of sleep deficiency on esophageal acid exposure parameters of healthy controls versus patients with GERD. Our hypothesis was that sleep deficiency increases esophageal acid exposure in both healthy controls and patients with GERD. In addition, we hypothesized that sleep deficiency may lead to abnormal esophageal acid exposure in healthy controls.

2 MATERIALS AND METHODS

2.1 Participants

Eleven healthy controls and 11 GERD patients with history of typical GERD symptoms (heartburn and/or regurgitation) at least three times a week for a minimum of 3 months were prospectively recruited into this study. GERD patients had to have either documented erosive esophagitis on endoscopy or an abnormal pH test off anti-reflux treatment in the absence of esophageal mucosal injury.

GERD patients who were on anti-reflux treatment were asked to discontinue proton pump inhibitors (PPI) or H_2 blocker treatment for periods of 2 weeks and 72 hours, respectively, prior to the first pH test.

Exclusion criteria were the following: use of sleep altering medications such as psychotropics, narcotics or benzodiazepines, diagnosis of psychological abnormalities (depression, anxiety, etc.) and other comorbidities that can interfere with patient's normal sleep (cardiopulmonary, renal, endocrine, etc.), unwillingness to sign an informed consent or inability to complete all stages of the study, and prior history of upper GI surgery, diabetes, neuropathy, history of seizure or sleep apnea. This study was approved by the human study

committee of University of Arizona and was conducted at the Southern Arizona VA Health Care System.

2.2 Study Design

This was a prospective, randomized cross-over study. GERD patients were recruited from outpatient gastroenterology clinics and had to meet the aforementioned criteria. Normal controls had to undergo an upper endoscopy to evaluate for the presence of esophageal, gastric or duodenal mucosal abnormalities.

Initially, patients were screened by the Berlin questionnaire which assesses the risk for obstructive sleep apnea (OSA) and the Epworth Sleepiness Scale questionnaire (ESS), which differentiates persons with excessive daytime sleepiness from alert individuals by measuring their sleep propensity. Any subject with medium or high risk for OSA or a score above 10 on the ESS were excluded from this study. Subsequently, all subjects were randomized to undergo a 24-hour esophageal pH test, either after having 8 hours per day of sleep during 2 consecutive days (normal sleep) or after having 4 hours per day of sleep during 2 consecutive days (deficient sleep). All subjects then crossed over to the other arm. There was a 1-week washout period between the two sleep protocols (Figure 1). For normal sleep, participating subjects were instructed to sleep 7-8 hours per night for 2 nights in a row. For deficient sleep, patients were instructed to sleep 4 hours per night for 2 nights in a row. Patients were instructed to sleep 4 hours from the time they enter bed. This time should have been their usual bedtime. Patients were not allowed to consume coffee during the sleep deficiency protocol or use sleeping pills during the normal sleep protocol. This sleep protocol was previously reported by Schey et al.[5] Subjects were assessed by actigraphy to objectively measure sleep time and to verify compliance with both the normal sleep and the sleep deficiency protocol. Esophageal reflux parameters were compared in each subjects' group

between good and deficient sleep. In addition, esophageal reflux parameters were compared between GERD patients and healthy controls after normal and deficient sleep.

2.3 Ambulatory 24-hour esophageal pH monitoring

After an overnight fast, a pH probe with lower esophageal sphincter (LES) identifier (Digitrapper MK 111; Medtronic, Minneapolis, Minnesota) was inserted through the nostril and into the stomach. The LES identification manometry assembly is a simple system for water-perfused manometry using the combined pH and water-perfused pressure catheter. The pressure lumen is located 5 cm above the distal pH sensor. By using the station pull-through technique with 0.5 cm increments, identification of the proximal margin of the LES was achieved. The pH probe was placed 5 cm above the proximal margin of the LES and connected to a digital portable recorder. Subjects were instructed to pursue their everyday activities and regular diet during the pH test and avoid napping or sleeping during daytime. This prevented other sleep periods during the pH test besides the nighttime sleep period. Subjects were also instructed to keep a diary to record mealtimes, position changes and the time and type of their symptoms. Before and after each study, the electrode and the system were calibrated in pH 1 and pH 7 solutions for standardization purposes. Reflux events were defined as $pH < 4$, and reflux time as the interval until pH is greater than 4 again. The test was considered positive when the percent total time $pH < 4$ was more than 4.2 %. Abnormal esophageal acid exposure in the upright and supine positions were defined as $pH < 4$ of more than 6 % and 1.2 %, respectively. Analysis of the recorded data was carried out using the standard and commercially available computer software (Medtronic, Minneapolis, Minnesota).

2.4 Questionnaires

Berlin Questionnaire

The Berlin Questionnaire is used to assess risk factors for obstructive sleep apnea including the presence and frequency of snoring, wake-time sleepiness or fatigue, and history of obesity or hypertension.[6] Subjects were excluded if their responses placed them at medium or high risk according to the questionnaire scoring algorithm for obstructive sleep apnea.

Epworth Sleepiness Scale questionnaire (ESS)

The ESS differentiates persons with excessive daytime sleepiness from alert individuals by measuring their sleep propensity in eight different activities.[7] A score greater than 10 is considered indicative of sleepiness.

2.5 Actigraphy

During the study period, subjects underwent actigraphy to objectively measure total sleep time and to verify that they followed the normal and deficient sleep protocol. The actigraph, a watch-like device, worn on the non-dominant wrist of the subjects, records motion with accelerometers that is stored digitally in the device (Ambulatory Monitoring Inc. Ardsley, NY). The stored digital information is then downloaded and analyzed by proprietary software to yield periods of quiescence that can be inferred as sleep time.[6,8]

2.6 Statistical Analysis

Descriptive statistics were used to compare patients and controls with respect to demographics and underlying risk factors. The main analyses were reflux parameters as determined by the 24-hour esophageal pH test. Data that were normally distributed were analyzed with Student's t-test. Non-normally distributed data were analyzed using the Wilcoxon signed-ranks test. This nonparametric test is ideally suited for analyzing small

samples. Analysis of variance was used to model the impact on % time pH < 4 of sleep duration (healthy/deficient), experimental group (control/GERD), age, sex and experimental order. All analyses were two-sided, using an a priori alpha level of 0.05. Assuming that the 33% change in time to initial perception of heartburn after acid perfusion noted by Schey et al[5] would be similarly translated to % time with pH <4 in the current study, we had 88% power to detect a 2% absolute difference in acid exposure within subjects, but only 61% power between groups.

3 RESULTS

A total of 11 subjects were included in both healthy controls and GERD patients. Table 1 shows the demographics of these subjects. Overall, there were more males in the GERD group (72.7 %) as compared with the control group (45.5 %). In addition, the mean age was somewhat lower in the control versus the GERD group. Actigraphy showed similar sleep duration during both nights in each group and both groups during sleep deficiency.

The healthy control group had significantly higher % total and % upright time pH < 4 after deficient sleep as compared with normal sleep (% total time-6.15 ± 5.89 vs 1.74 ± 1.54, % upright time-4.72 ± 5.36 vs 0.87 ± 1.28, $p < 0.05$, respectively). During the supine position, the % total time pH < 4 was numerically higher after deficient sleep as compared with normal sleep (5.75 ± 6.31 vs 2.39 ± 2.75) but it did not reach statistical significance (Figure 2).

There was no significant difference in reflux parameters after deficient sleep as compared with normal sleep in the GERD group (% total time- 7.59 ± 3.54 vs 5.02 ± 3.45, % upright time- 5.46 ± 5.73 vs 4.11 ± 3.98, % supine time- 6.67 ± 6.57 vs 4.9 ± 5.2, respectively). However, all reflux parameters were numerically higher after deficient sleep as compared with normal sleep (Figure 3).

Table 2 shows a statistical comparison of the impact of posture for the healthy controls and the GERD patients on % time pH < 4. Each posture was modeled adjusting for sleep quality (normal/deficient), sleep by group interaction, period, sex and age. We found that sleep quality was the only statistically significant effect in all subjects. In addition, period was not significant in all subjects, this means that there was no cross-over effect.

When reflux parameters were compared between control and the GERD group, GERD patients showed a significantly higher % total time and % upright time after normal sleep as compared with the control group (% total time- 5.02 ± 3.45 vs 1.74 ± 1.54, % upright time-4.11 ± 3.98 vs 0.87 ± 1.28, $p < 0.05$, respectively). Percent supine time pH < 4 was

numerically higher in the GERD group after normal sleep but did not reach statistical significance. There were no significant statistical differences between the 2 groups in any of the reflux parameters assessed after deficient sleep. Overall, 5 (45.5 %) of the healthy controls demonstrated an abnormal pH test (% total time pH < 4) after deficient sleep (Figure 4).

4 DISCUSSION

Our study demonstrated that both healthy controls and GERD patients had a significantly greater esophageal acid exposure parameters after deficient sleep as compared with normal sleep. In addition, almost half of normal controls demonstrated an abnormal esophageal acid exposure after deficient sleep.

Recent studies have suggested a strong association between sleep deficiency and abnormal gastrointestinal function.[3,9,10] Approximately 50 % of the GERD patients have nighttime reflux symptoms resulting in an increased risk of sleep deficiency. Similar to our results, a population-based cohort study revealed that sleep disturbances were associated with new-onset of gastroesophageal reflux symptoms (RR: 2.70, 95 % CI: 1.93 - 3.76); insomnia was associated with new-onset gastroesophageal reflux symptoms (RR: 3.42; 95 % CI: 1.83 - 6.39) and gastroesophageal reflux symptoms were associated with new-onset sleep disturbances (RR: 1.41; 95 % CI: 1.14 - 1.75).[11] These results suggest that sleep deficiency per se can exacerbate or lead to reflux symptoms possibly by increasing esophageal acid exposure. While GERD can lead to sleep disturbances which can further exacerbate GERD, the study demonstrated that in this bi-directional relationship, the effect of sleep on GERD is similar to the effect of GERD on sleep.

Our study did not assess reports of GERD-related symptoms in our subjects primarily because several studies have already showed that sleep deficiency increases GERD-related

symptoms. For example, Schey et al. randomized 10 healthy subjects and 10 GERD patients to both sleep deficiency (2 days of < 3 hours) and normal sleep (3 days of ≥ 7 hours). The authors demonstrated that sleep deficiency can lead to visceral hyperalgesia by increasing esophageal chemoreceptor sensitivity to acid and consequently worsen heartburn symptoms in GERD patients. However, the study did not assess overall esophageal acid exposure. Nevertheless, the findings showed that sleep deficiency is likely an important central factor that can exacerbate GERD symptoms by enhancing perception of intraesophageal stimuli.[5] Furthermore, the results suggest that a subset of GERD patients also develop abnormal esophageal acid exposure.

In our study, there was a significant difference in the total and upright time pH < 4 between normal sleep and deficient sleep only in the healthy control group. While similar changes were noted in the GERD group, they did not reach statistical significance. Although it is possible that this was simply related to insufficient study power or an already abnormal esophageal acid exposure at baseline, the acute sleep deficiency protocol used in this study may have had a more pronounced effect on healthy controls than GERD patients because the latter group is also more likely to be exposed to chronic sleep deficiency. This explanation is supported by a recent study reporting that NERD patients had a significantly higher proportion of subjects whose average sleeping time was less than 5-hours (sleep deprived) as compared with a control group (without esophagitis and symptoms). Short sleep duration was a significant risk factor for NERD.[12]

Nighttime reflux pattern is clearly different from daytime reflux pattern.[13] Several physiological changes have been reported during sleep, such as delayed gastric emptying,[14] decreased frequency of transient lower esophageal sphincter relaxation,[15,16] decreased upper esophageal sphincter pressure,[17] decreased primary and secondary esophageal peristalsis,[18] significant reduction in saliva secretion and flow and decreased frequency of swallowing.[19]

While less reflux events occur during sleep time, they tend to be of longer duration due to impaired clearing mechanisms during sleep. The mechanisms by which sleep deficiency can increase esophageal acid exposure is not known. Some of the proposed mechanisms include increased inflammatory cytokines and alteration in levels of ghrelin and leptin.

Several studies have evaluated the relationship between sleep and the immune system.[20-22] Inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 have been shown to be associated sleep disturbances.[23-25] On the other hand, sleep disturbances have been demonstrated to elevate these inflammatory cytokines.[26] Thus, it is possible that sleep deficiency may elevate inflammatory cytokines which may increase gastroesophageal reflux.

Another potential mechanism is lifestyle changes due to sleep deficiency as compared with normal sleep. Sleep deficiency results in increase in the ghrelin (hunger hormone) levels and decrease levels of leptin (satiety hormone) resulting in increase in craving and thus food consumption.[27] In addition, sleep deficiency provides more awake time that patients can use for further food consumption. These two important effects of sleep deficiency can result in increase in gastroesophageal reflux.

Our study has several limitations. First is the inclusion of a relatively small number of subjects in each group. This may have limited study power to detect small differences between and within groups. Another limitation is the utilization of pH monitoring instead of pH-impedance or wireless pH capsule. However, the study attempted to assess the effect of sleep deficiency on esophageal acid exposure of healthy controls and patients with GERD and this could be also accurately and properly fulfilled with a 24-hour pH test. The last limitation is that we did not assess subjects' GERD-related symptoms in response to sleep deficiency or normal sleep. However, at least in GERD patients, studies have shown that sleep deficiency is highly associated with increase in GERD symptoms.

In summary, our study is the first to demonstrate that sleep deficiency significantly increases esophageal acid exposure in both healthy controls and patients with GERD. This further supports that there is a bi-lateral relationship between GERD and sleep, where increase in GERD alone can lead to sleep deficiently and increase in sleep deficiency alone can exacerbate or lead to gastroesophageal reflux (Figure 5a).Importantly, decrease in GERD per se can reduce sleep deficiency, and improvement in sleep deficiency by itself can reduce GERD (Figure 5b). In addition, 45.5 % of normal subjects and 90.9 % of GERD patients demonstrated an abnormal pH test after sleep deficiency. When reflux parameters were compared between control and the GERD group, GERD patients demonstrated significantly higher acid exposure parameters after normal sleep as compared with healthy controls. The results of our study suggest that sleep deficiency per se can increase esophageal acid exposure not only in GERD patients but also in healthy controls. The effect of sleep deficiency on gastroesophageal reflux is so pronounced that normal healthy subjects may develop abnormal esophageal acid exposure.

It suggests that sleep deficiency is an important underlying mechanism for abnormal esophageal acid reflux and thus should be always evaluated and addressed in patients with abnormal pH or pH-impedance tests.

ACKNOWLEDGMENTS

None

DISCLOSURES

None

AUTHOR CONTRIBUTIONS

TY analyzed and interpreted the data and drafted the manuscript. SFQ interpreted the data and participated in drafting the final version of the manuscript. RF designed the study, conducted the research, collected, analyzed and interpreted the data, and drafted the manuscript. All authors have approved the submitted final draft.

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TABLE 1 Demographics of the study participants

	Control (n = 11)	GERD (n = 11)
Gender (M/F)	5/6	8/3
Age (yrs.)	40.7 ± 19.3	57.3 ± 11.9
Race		
White	7	6
Hispanic	2	3
African American	1	1
Other	1	1

TABLE 2 Comparison of each posture in healthy controls and GERD patients on % time pH < 4.

	Total		Upright		Supine	
Effect	*F*-value	p-value	*F*-value	*p*-value	*F*-value	*p*-value
Sleep quality (Normal/Deficient)	14.31	0.0013	6.30	0.0213	4.58	0.0456
Group (Control/GERD)	2.88	0.1071	3.11	0.0946	0.49	0.4909
Sleep by Group interaction	1.00	0.3304	1.47	0.2398	0.51	0.4846
Period	0.03	0.8726	0.02	0.8814	0.76	0.3953
Sex	0.02	0.9028	1.78	0.1987	0.45	0.5107
Age	0.21	0.6529	3.49	0.0782	0.35	0.5639

Figure Legends

Figure 1. Algorithm of the study design

*7-8 hours sleep per day for 2 consecutive days

**4 hours sleep per day for 2 consecutive days

GERD, gastroesophageal reflux disease; ESS, epworth sleepiness scale questionnaire

Figure 2. Comparison of reflux parameters after normal and deficient sleep in the healthy control group

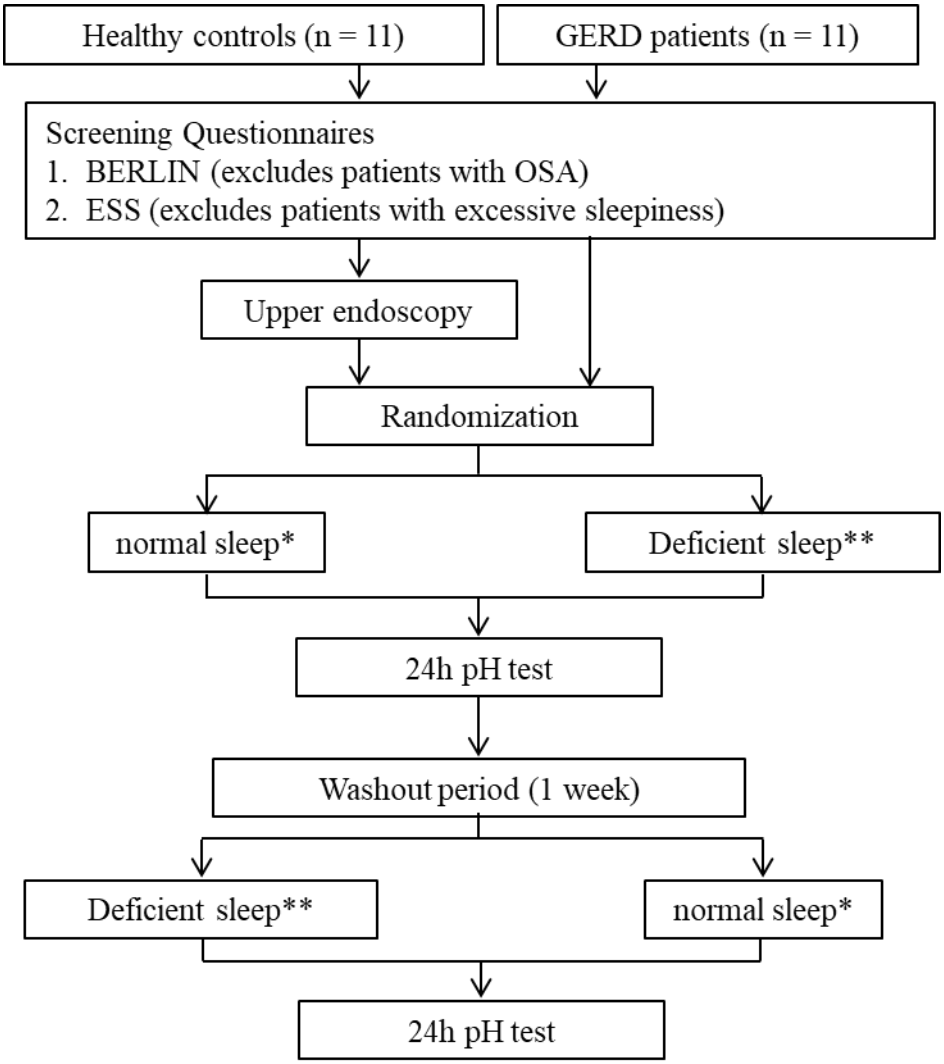
* $p < 0.05$

Figure 3. Comparison of reflux parameters after good and deficient sleep in the GERD group (p = n.s.)

Figure 4. Individual changes in reflux parameters after normal and deficient sleep (A) healthy control group; (B) GERD group

Figure 5. A bi-lateral relationship between GERD and Sleep. (A) (B)

Figure 1.



*7-8 hours sleep per day for 2 consecutive days

**4 hours sleep per day for 2 consecutive days

GERD, gastroesophageal reflux disease; ESS, epworth sleepiness scale questionnaire

Figure 2.

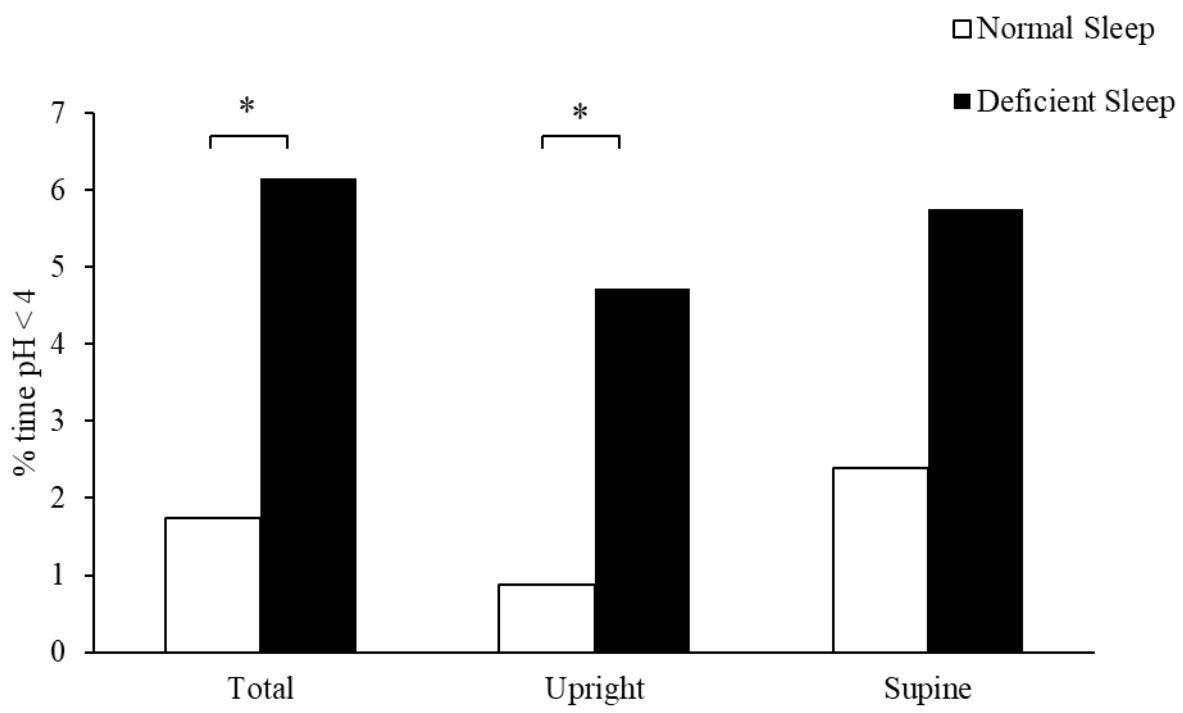

Normal Sleep
Deficient Sleep
% time pH < 4
0
1
2
3
4
5
6
7
*
*
Total
Upright
Supine

Figure 3.

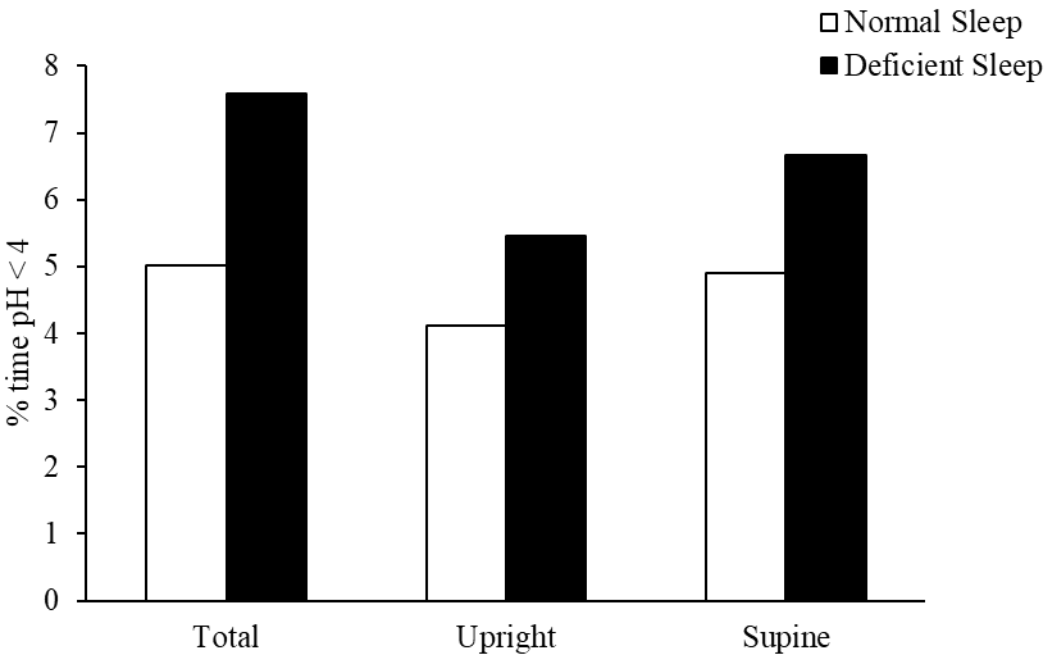

Normal Sleep
Deficient Sleep
% time pH < 4
0
1
2
3
4
5
6
7
8
Total
Upright
Supine

Figure 4.

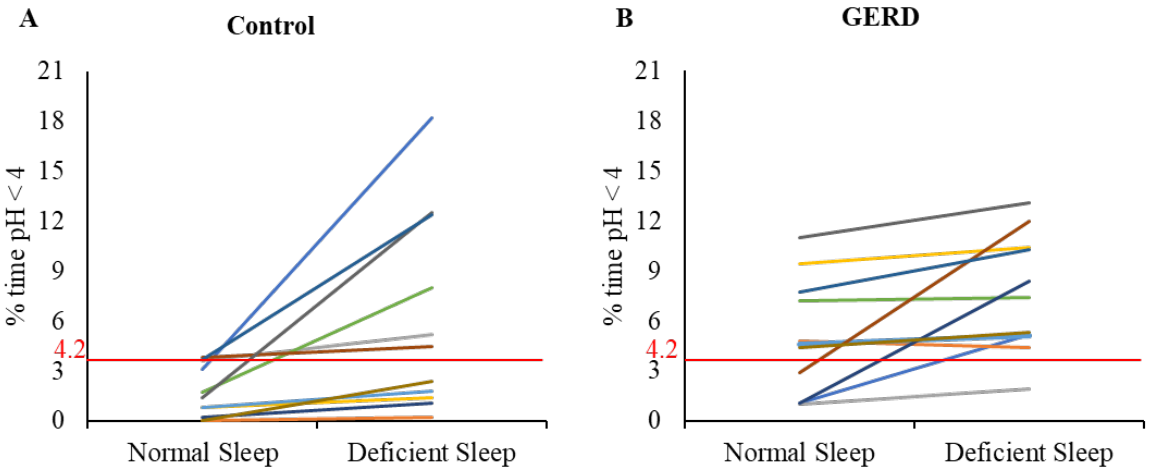
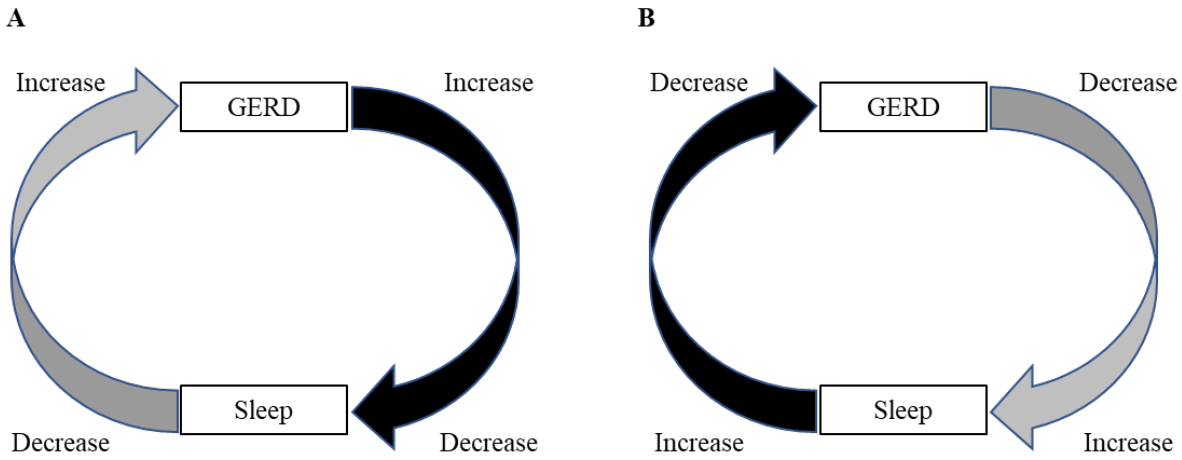

A
Control
B
GERD
% time pH < 4
21
18
15
12
9
6
4.2
3
0
Normal Sleep
Deficient Sleep

Figure 5.


A
Increase
GERD
Increase
Sleep
Decrease
Decrease
B
Decrease
GERD
Decrease
Sleep
Increase
Increase