ORIGINAL ARTICLE

Gastroesophageal Reflux Disease and Sleep Quality in a Chinese Population

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Background/Purpose: Although evidence suggests that gastroesophageal reflux disease (GERD) may interrupt sleep, the effects of symptomatic and endoscopically diagnosed GERD remain elusive because the patient population is heterogeneous. Accordingly, we designed a cross-sectional study to assess their association.

Methods: Consecutive participants in a routine health examination were enrolled. Definition and severity of erosive esophagitis were assessed using the Los Angeles classification system. Demographic data, reflux symptoms, sleep quality and duration, exercise amount, alcohol consumption, and smoking habits were recorded. Factors affecting sleep quality and sleep duration were revealed by a polytomous logistic regression analysis.

Results: A total of 3663 participants were recruited. Subjects with reflux symptoms, female gender, higher body mass index, and regular use of hypnotics had poorer sleep quality. Exercise was associated with better sleep quality. Either symptomatically or endoscopically, GERD did not disturb sleep duration. Among the 3158 asymptomatic patients, those with erosive esophagitis were more likely to have poor sleep quality. The risk increased with the severity of erosive changes ($p = 0.03$).

Conclusion: The present study highlights the adverse effect of gastroesophageal reflux on sleep, even in the absence of reflux symptoms. This finding has therapeutic implications in patients with silent erosive disease, and future trials are warranted. [*J Formos Med Assoc* 2009;108(1):53–60]

Key Words: endoscopy, gastroesophageal reflux disease, sleep

Sleep is essential for good health. Evidence has shown that sleep disorders might contribute to respiratory, hormonal, gastrointestinal, cardiovascular, and emotional impairment, while the chronic dependence on hypnotics is a substantial economic burden.[1–4]

Gastroesophageal reflux disease (GERD) may play a pathogenic role in sleep disturbance.[5–7] Nocturnal acid reflux can induce sensory stimuli and esophageal clearance, and interrupt sleep-stage progression, even in the absence of cognitive awakening.[8] In addition, reflux events during sleep are characterized by longer acid-mucosal contact that stems from lower saliva production, lower frequency of swallowing, and slower gastric emptying, all of which increase the risk of mucosal damage, intensity of noxious stimuli, and disruption of normal sleep.[9,10]

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Several trials have assessed the therapeutic effect of acid suppressants on sleep but the results were inconclusive. Johnson et al[11] found that proton-pump inhibitors (PPIs) can reduce nighttime heartburn, improve sleep quality, and thus increase work efficacy. Dimarino et al[12] found that decreasing reflux-related arousal with acid suppressant agents increases total sleep time and rapid-eye movement sleep. However, using actigraphy to record sleep efficiency and percentage immobility time, Chand et al[13] found that PPIs improve subjective but not objective measures of sleep quality. In addition, these studies were mainly on patients with reflux symptoms and a favorable response could have been expected. Reflux is a heterogeneous condition and can be categorized as erosive and non-erosive reflux disease (NERD), as well as symptomatic and asymptomatic. Among the general population, some patients with erosive disease have no reflux symptoms, which may lower their awareness of the disease and incentive for treatment.[14–16] Therefore, our aim was to assess the association between GERD and sleep in subjects who were categorized on the basis of their reflux symptoms and endoscopic findings.

Methods

Study design and population

This study was based on a voluntary, routine health examination with a standard protocol conducted at a single referral center. The protocol included physical examination, blood chemical analysis, plain radiography, abdominal ultrasonography, and endoscopy. Our ethics committee approved the study protocol before its implementation. Most of the subjects received upper gastrointestinal endoscopy since esophageal and stomach cancers are prevalent in our country.[17]

Demographic data including age, gender, medical history, exercise, smoking, alcohol consumption, and body mass index (BMI) were recorded. Symptoms suggestive of GERD (at least one episode of heartburn and acid regurgitation per week in the past 3 months) were evaluated and validated during counseling with an internal medicine specialist. These symptoms are considered to be specific for GERD and are generally accepted for use in population research.[18] A Likert scale embedded in the questionnaire assessed sleep quality and sleep duration over the previous 1-month period, including: (1) how do you rate your sleep quality? (poor/acceptable/satisfactory); and (2) how many hours on average do you sleep at night? (< 5/5–6/6–7/7–8/ > 8).

Endoscopy

After an overnight fast, subjects were placed in the left lateral decubitus position. Endoscopy using Olympus GIF 240 or GIF 260 videoendoscopes (Tokyo, Japan) was performed by a single group of endoscopists who had been trained at the National Taiwan University Hospital. The stomach and duodenum were inspected to exclude possible lesions. The distal portion of the esophagus was evaluated carefully to determine the presence of mucosal injury. The esophagus was carefully evaluated and all endoscopic findings were meticulously recorded. Erosive esophagitis was scored using the Los Angeles classification system with standard comparator photographs.[19] The combining of four ordinal ratings into two categories (classes A/B and C/D) was intended to decrease variation in interpretation among observers (change in overall κ from 0.45 to 0.65, which indicated good consistency), and the procedure also increased the statistical power for estimation.[20]

Statistical analysis

Continuous data were expressed as mean ± standard deviation and categorical data as percentage. Logistic regression analysis was used to estimate the effects of various risk factors associated with poor sleep quality and shorter sleep duration. After the univariate models, we selected the best subsets of risk factors by stepwise selection criteria, with entry and stay significance levels of 0.2. We specified the categories of sleep quality and sleep duration as outcome variables, and a test for the trend was used to evaluate the

possible dose-dependent relationship. The interactions between predictive variables were also assessed in each model. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA) and $p < 0.05$ was considered statistically significant.

Results

Demographic characteristics

After excluding subjects who refused endoscopy and those who were not suitable for endoscopy ($n = 436$), and those with missing sleep assessment data ($n = 1327$), a total of 3663 participants were enrolled between June 2003 and June 2004. Their demographic data are shown in Table 1. The mean age of those who were excluded from analysis was 53.5 years, and 56.3% were male, which was similar to the study group. Overall, endoscopic erosive esophagitis was detected in 653 of 3663 (17.8%) participants. Erosive esophagitis with LA classification grades A/B and C/D was diagnosed in 617 (16.8%) and 36 (1%) participants, respectively. Symptomatic reflux was reported in 505 (13.8%) participants. Accordingly, the population could be stratified into the following four categories: (1) no reflux symptom or erosive change ($n = 2604$, 71.1%); (2) NERD ($n = 406$, 11.1%); (3) symptomatic erosive disease ($n = 99$, 2.7%); and (4) asymptomatic erosive disease ($n = 554$, 15.1%).

Regression analysis with poor sleep quality as an outcome variable

In the logistic regression model using sleep quality as an outcome variable (Table 2), reflux symptoms, female gender, higher BMI, endoscopic erosive esophagitis, and use of hypnotics were significant risk factors for poorer sleep quality. After the multivariate adjustment and stepwise model selection, reflux symptoms, female gender, higher BMI, and use of hypnotics remained significant. In contrast, more frequent or more prolonged exercise was associated with better sleep quality. For the aforementioned regression models,

Table 1. Demographic characteristics of the study population*

Characteristics	Participants ($n = 3663$)
Mean age, yr	50.6 ± 11.83
Male gender	2128 (58)
Mean BMI (kg/m^2)†	23.7 ± 3.4
< 18.5	110 (3)
18.5–24.9	2390 (65.2)
25.0–29.9	1018 (27.8)
≥ 30.0	145 (4)
Regular use of hypnotics	323 (8.8)
Reflux symptoms	505 (13.8)
Social habits	
Smoking	601 (16.4)
Alcohol consumption	2508 (68.5)
Sleep parameters	
Sleep duration (hr)	
< 5	283 (7.7)
5–6	838 (22.9)
6–7	1610 (44)
7–8	771 (21)
> 8	161 (4.4)
Sleep quality	
Poor	799 (21.8)
Acceptable	2098 (57.3)
Satisfactory	766 (20.9)
Exercise parameters	
Exercise frequency	
Rarely, < once per wk	1410 (38.5)
1–2 per wk	1073 (29.3)
3–4 per wk	582 (15.9)
5–6 per wk	407 (11.1)
≥ 7 per wk	191 (5.2)
Exercise duration per time (min)	
< 10	1187 (32.4)
10–30	604 (16.5)
30–60	1044 (28.5)
> 60	828 (22.6)
Erosive esophagitis	
Non-erosive	3010 (82.2)
LA A/B esophagitis	617 (16.8)
LA C/D esophagitis	36 (1)

**Quantitative data are expressed as mean ± standard deviation and categorical data as n (%); †WHO classification (underweight is < 18.5; normal is 18.5–24.9; overweight is 25.0–29.9; obese is ≥ 30.0 kg/m^2). BMI = body mass index; LA = Los Angeles classification of esophagitis.*

Table 2. Crude and adjusted OR of risk factors for poorer sleep quality

	Crude OR			Adjusted OR after model selection		
	OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Esophagitis						
Erosive *vs.* non-erosive	1.25	1.06–1.47	0.008†			
LA A/B *vs.* non-erosive	1.99	1.04–3.82	0.04†			
LA C/D *vs.* non-erosive	1.54	0.81–2.9	0.19			
Reflux symptoms	2.25	1.87–2.70	<0.001†	2.05	1.65–2.54	<0.001†
Female gender	1.65	1.45–1.87	<0.001†	1.37	1.16–1.61	<0.001†
Age (yr)	1.00	0.95–1.05	0.99			
BMI (kg/m^2)*						
<18.5	0.69	0.48–1	0.05			
25.0–29.9	1.34	1.17–1.55	<0.001†			
≥30.0	1	0.72–1.38	0.98			
p for linear trend	1.21	1.09–1.35	<0.001†	1.03	1.01–1.05	0.007†
Smoking	1.00	0.84–1.20	1			
Alcohol consumption	0.69	0.60–0.80	<0.001†			
Regular use of hypnotics	5.14	4.09–6.46	<0.001†	4.70	3.55–6.24	<0.001†
Exercise frequency*						
≤1–2 per wk	0.56	0.49–0.64	<0.001†			
1–2 per wk	0.54	0.40–0.73	<0.001†			
3–4 per wk	0.47	0.38–0.59	<0.001†			
5–6 per wk	0.56	0.46–0.68	<0.001†			
≥7 per wk	0.59	0.50–0.69	<0.001†			
p for linear trend	0.81	0.77–0.86	<0.001†	0.89	0.83–0.96	0.002†
Exercise duration*						
10–30 min	0.63	0.51–0.78	<0.001†			
30–60 min	0.61	0.51–0.73	<0.001†			
>60 min	0.55	0.45–0.67	<0.001†			
p for linear trend	0.82	0.77–0.87	<0.001†	0.88	0.82–0.95	0.001†

**In the evaluations of BMI, exercise frequency and exercise duration, only linear trend models were evaluated by model selection: baseline comparators of BMI were 18.5–24.9 kg/m^2, rarely (i.e. <once per week) for exercise frequency, and <10 minutes for exercise duration; †p<0.05. OR = odds ratio; CI = confidence interval; LA = Los Angeles classification of esophagitis; BMI = body mass index.*

the proportional odds assumption was justified. It indicated that, for example, the presence of reflux symptoms was associated with 2.05-fold (95% confidence interval, 1.65–2.54) increased odds of reporting poorer sleep quality.

Regression analysis with shorter sleep duration as an outcome variable

As a result of the small number of subjects with sleep duration <5 hours and >8 hours, we combined five ordinal ratings into three categories to increase the statistical power for estimation: <6 hours (n=1121), 6–7 hours (n=1612), and >7 hours (n=930). When examined as an outcome variable (Table 3), shorter sleep duration was significantly associated with female gender, older age, higher BMI, and use of hypnotics. Smoking and alcohol consumption, however, were associated with longer sleep duration. After the multivariate adjustment and stepwise model selection, female gender, older age, higher BMI, and use of hypnotics were independent factors for shorter sleep duration. Proportional odds assumptions were justified in all of these models.

Table 3. Crude and adjusted OR of risk factors for shorter sleep duration

	Crude OR			Adjusted OR after model selection		
	OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Esophagitis						
Erosive *vs.* non-erosive	0.99	0.85–1.14	0.86			
LA A/B *vs.* non-erosive	0.84	0.47–1.51	0.57			
LA C/D *vs.* non-erosive	1.02	0.88–1.19	0.52			
Reflux symptoms	1.10	0.95–1.29	0.22			
Female gender	1.26	1.14–1.40	<0.001‡	1.34	1.15–1.56	<0.001‡
Age (yr)	1.26	1.20–1.31	<0.001‡	1.16	1.09–1.24	<0.001‡
BMI (kg/m^2)*						
<18.5	0.70	0.52–0.94	0.02‡			
25.0–29.9	0.94	0.83–1.07	0.36			
≥30.0	1.47	1.06–2.04	0.02‡			
p for linear trend	1.15	1.04–1.26	0.005‡	1.04	1.02–1.06	0.001‡
Smoking	0.74	0.63–0.87	<0.002‡			
Alcohol consumption	0.81	0.72–0.92	<0.001‡			
Regular use of hypnotics	1.75	1.44–2.12	<0.001‡	1.45	1.12–1.91	0.007‡
Exercise frequency†						
≤1–2 per wk	0.99	0.88–1.11	0.89			
1–2 per wk	0.88	0.68–1.15	0.35			
3–4 per wk	0.79	0.42–1.16	0.56			
5–6 per wk	0.96	0.81–1.14	0.66			
≥7 per wk	1.11	0.96–1.27	0.16			
p for linear trend	1.06	0.89–1.26	0.23			
Exercise duration†						
10–30 min	0.98	0.81–1.18	0.87			
30–60 min	0.92	0.78–1.08	0.18			
>60 min	1.06	0.89–1.26	0.23			
p for linear trend	0.99	0.94–1.05	0.83			

**Only linear trend items were inputted into the model selection process in the evaluation of BMI (baseline comparator of BMI was 18.5–24.9 kg/m^2); †baseline comparators were <once per week for exercise frequency and <10 minutes for exercise duration; ‡p<0.05. OR = odds ratio; CI = confidence interval; LA = Los Angeles classification of esophagitis; BMI = body mass index.*

Stratified analysis according to the form and grade of reflux disease

Table 4 shows the stratification of the study population on the basis of form and grade of reflux disease. In asymptomatic (n=3158) but not symptomatic (n=505) participants, erosive esophagitis was significantly associated with poorer sleep quality. In addition, the risk was increased with the severity of erosive change (p=0.03 for linear trend). No significant association was noted between erosive changes and sleep duration.

Discussion

The present study analyzed the effects of GERD on sleep in subjects with a spectrum of presenting symptoms and endoscopic findings. We confirmed that GERD itself was associated with poorer sleep quality, regardless of the presence of erosive change. Furthermore, this adverse effect was more pervasive than previously assumed, since it was exhibited by a significant proportion of subjects with silent erosive disease (554/653, 84.4%). In these

Table 4. Influence of endoscopic esophagitis on poorer sleep quality and shorter sleep duration, stratified by form and grade of reflux disease

	Reflux – (n = 3158)			Reflux + (n = 505)		
	OR	95% CI	p	OR	95% CI	p
Sleep quality						
Esophagitis *vs.* non-erosive	1.27	1.06–1.52	0.01*	1.31	0.86–2.00	0.21
LA A/B *vs.* non-erosive	1.31	1.09–1.57	0.03*	0.72	0.47–1.12	0.20
LA C/D *vs.* non-erosive	1.43	0.70–2.94	0.18	1.52	0.36–6.46	0.43
LA C/D *vs.* LA A/B	1.89	0.91–3.85	0.09	2.13	0.48–9.09	0.33
p for linear trend	1.20	1.02–1.42	0.03*	1.20	0.82–1.76	0.35
Sleep duration						
Esophagitis *vs.* non-erosive	1.02	0.87–1.19	0.80	0.98	0.67–1.45	0.92
LA A/B *vs.* non-erosive	0.98	0.83–1.15	0.84	0.97	0.65–1.45	0.42
LA C/D *vs.* non-erosive	1.03	0.53–1.99	0.90	1.71	0.49–5.95	0.39
LA C/D *vs.* LA A/B	1.05	0.54–2.04	0.84	1.75	0.49–6.25	0.42
p for linear trend	1.02	0.88–1.18	0.83	0.94	0.67–1.33	0.73

$p < 0.05$. OR = odds ratio; CI = confidence interval; LA = Los Angeles classification of esophagitis.

subjects, we observed a parallel increase in severity of erosive change with reduced sleep quality, which might strengthen the linkage between GERD and sleep disorders.

Our results suggest that the presence of reflux symptom is an independent risk factor for poorer sleep quality. GERD symptoms are mediated through afferent stimuli from the lower esophagus and gastric fundus to the sensory nucleus in the medulla, and then through efferent signals that mediate transient lower esophageal sphincter relaxation.[21] We assume that subjects with erosive esophagitis or visceral hypersensitivity have more frequent sensory input from the esophagus, and that this input interrupts sleep progression by activating the wake-promoting neurons (located in the posterior hypothalamus, basal forebrain, and mesopontine tegmentum) and inhibits the sleep-promoting neurons (located in the preoptic area of the anterior hypothalamus).[22]

By monitoring cardiac autonomic activity and ambulatory pH measurement, our previous study has shown a generalized decrease in cardiac autonomic function in response to intraesophageal pH during waking or sleeping hours.[23] Bajaj et al have shown that only a minute amount of fluid in the proximal esophagus can induce arousal during stage III/IV non-rapid eye movement sleep, before esophageal sphincter contractile reflux and secondary peristalsis are activated.[24] Using functional magnetic resonance imaging, Kern et al found that esophageal mucosal contact with acid, at a level below that needed to stimulate heartburn, can induce neuronal activity to evoke a cerebral cortical response.[25] These findings support the hypothesis that the central nervous system receives sensory stimuli from the intraesophageal lumen that may subconsciously interrupt sleep.

As poorer sleep quality is associated with increased sympathetic activity and blood pressure, decreased glucose tolerance, and thus a higher risk of cardiovascular events,[26] several therapeutic trials have evaluated the beneficial effect of acid suppressants on sleep in patients with symptomatic GERD. Johnson et al confirmed that PPI therapy might improve sleep quality and work productivity.[11] Dimarino et al found that arousal from sleep is related closely to acid reflux, and acid suppression may reduce the frequency of arousal.[12] Orr et al have shown that acid suppression can improve sleep quality in symptomatic GERD patients.[27–29] Shaheen et al found that a significant minority of subjects with insomnia (4/16, 25%) had abnormal acid exposure and PPI treatment might be of benefit.[30]

It has been recognized that sleep duration can have important effects on health with a U-shaped association between sleep duration and mortality rate.[31] Prolonged sleep is associated with an increased risk of morbidity and mortality, and sleep deprivation may alter neurohormonal regulation, which predisposes to disease. In symptomatic GERD patients, one clinical trial has found that acid suppression therapy might increase the total sleep time.[12] In our study with an epidemiologic design, however, we did not identify any significant association between GERD and sleep duration. This discrepancy might be related to the differences in study design and the use of acid suppressants.[32]

Our results are credible for several reasons. First, this study included a large number of patients with complete clinical data. Asymptomatic subjects were evaluated to elucidate the relationship between intraesophageal damage and sleep. Also, the simultaneous evaluation of symptomatic and asymptomatic subjects enabled us to assess the effect of GERD alone on sleep, and highlighted the need for further clinical trials. Second, our endoscopists completed the same training program and used a standardized rating protocol. This procedure substantially decreased interobserver variability in endoscopic grading and enhanced our ability to identify the association.

However, our study had limitations. The first limitation involved the study sample. Subjects were obtained via advertisement at a routine health examination and therefore probably represent a population with intermediate GERD severity between that of subjects recruited from GI clinics and those randomly selected from the general population. A small number of patients with class C/D esophagitis might have produced insufficient statistical power in this category. Second, the information about sleep quality and duration was self-reported and was not based on objective measurement, although Lockley et al have suggested that self-reported assessment is as valid as actigraphy.[33] In addition, we used a simplified rating scale to assess sleep parameters, but sleep quality is complicated, and may be affected by multiple factors including sleep initiation and maintenance, early awakening, and sleep duration. Several biological and psychosocial factors (e.g. menopause in women, anxiety and depression) were involved but not evaluated in our study. Further studies using an extensive and well-validated questionnaire, including the Pittsburgh Sleep Quality Index and a diary to record sleep duration might better reflect the overall sleep-related symptoms.[34] Third, although endoscopy is the most accurate method for diagnosis of GERD, misclassification of erosive disease as NERD, or vice versa, is still possible.[19] Therefore, we may have underestimated the impact of morphologic changes on sleep because detection of subtle erosive changes, especially in NERD subjects, was limited. Finally, sleep disorder is a heterogeneous disease entity that includes insomnia, sleep apnea and narcolepsy.[35] The interpretation of our results may not apply to patients with severe sleeping disorders.

In conclusion, our study clarified the relationship between GERD (as defined endoscopically and symptomatically) and sleep in a Chinese population. The results may underscore the adverse effect of acid reflux on sleep quality, which may have therapeutic implications in patients with silent erosive disease. Future trials are therefore warranted.

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References

1. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002; 6:97–111.
2. Berry RB, Harding SM. Sleep and medical disorders. *Med Clin North Am* 2004;88:679–703, ix.
3. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of

insomnia: an update. An American Academy of Sleep Medicine report. *Sleep* 2006;29:1415–9.
4. Morin CM, Bootzin RR, Buysse DJ, et al. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). *Sleep* 2006;29:1398–414.
5. Dickman R, Green C, Fass SS, et al. Relationships between sleep quality and pH monitoring findings in persons with gastroesophageal reflux disease. *J Clin Sleep Med* 2007; 3:505–13.
6. Chen CL, Robert JJ, Orr WC. Sleep symptoms and gastroesophageal reflux. *J Clin Gastroenterol* 2008;42:13–7.
7. Yi CH, Hu CT, Chen CL. Sleep dysfunction in patients with GERD: erosive versus nonerosive reflux disease. *Am J Med Sci* 2007;334:168–70.
8. Orr WC, Craddock A, Goodrich S. Acidic and non-acidic reflux during sleep under conditions of powerful acid suppression. *Chest* 2007;131:460–5.
9. Orr WC, Heading R, Johnson LF, et al. Review article: sleep and its relationship to gastro-oesophageal reflux. *Aliment Pharmacol Ther* 2004;20(Suppl 9):39–46.
10. Guda N, Partington S, Shaw MJ, et al. Unrecognized GERD symptoms are associated with excessive daytime sleepiness in patients undergoing sleep studies. *Dig Dis Sci* 2007;52: 2873–6.
11. Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. *Am J Gastroenterol* 2005;100:1914–22.
12. Dimarino AJ Jr, Banwait KS, Eschinger E, et al. The effect of gastro-oesophageal reflux and omeprazole on key sleep parameters. *Aliment Pharmacol Ther* 2005;22:325–9.
13. Chand N, Johnson DA, Tabangin M, et al. Sleep dysfunction in patients with gastro-oesophageal reflux disease: prevalence and response to GERD therapy, a pilot study. *Aliment Pharmacol Ther* 2004;20:969–74.
14. Lee YC, Wang HP, Chiu HM, et al. Comparative analysis between psychological and endoscopic profiles in patients with gastroesophageal reflux disease: a prospective study based on screening endoscopy. *J Gastroenterol Hepatol* 2006;21:798–804.
15. Fass R, Fennerty MB, Vakil N. Nonerosive reflux disease—current concepts and dilemmas. *Am J Gastroenterol* 2001; 96:303–14.
16. Rex DK, Cummings OW, Shaw M, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. *Gastroenterology* 2003;125:1670–7.
17. *Taiwan Cancer Registry*. Taipei: Executive Yuan, Department of Health, 2002. Available at http://crs.cph.ntu.edu.tw/main.php?Page=N1. Updated: January 7, 2008.
18. Farup C, Kleinman L, Sloan S, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. *Arch Intern Med* 2001; 161:45–52.
19. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172–80.
20. Lee YC, Lin JT, Chiu HM, et al. Intraobserver and interobserver consistency for grading esophagitis with narrow-band imaging. *Gastrointest Endosc* 2007;66:230–6.
21. Mittal RK, Holloway RH, Penagini R, et al. Transient lower esophageal sphincter relaxation. *Gastroenterology* 1995; 109:601–10.
22. Sakai K, Crochet S. A neural mechanism of sleep and wakefulness. *Sleep Biol Rhythm* 2003;1:29–42.
23. Lee YC, Wang HP, Lin LY, et al. Circadian change of cardiac autonomic function in correlation with intra-esophageal pH. *J Gastroenterol Hepatol* 2006;21:1302–8.
24. Bajaj JS, Bajaj S, Dua KS, et al. Influence of sleep stages on esophago-upper esophageal sphincter contractile reflex and secondary esophageal peristalsis. *Gastroenterology* 2006;130:17–25.
25. Kern MK, Birn RM, Jaradeh S, et al. Identification and characterization of cerebral cortical response to esophageal mucosal acid exposure and distention. *Gastroenterology* 1998;115:1353–62.
26. Meisinger C, Heier M, Löwel H, et al. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: The MONICA/KORA Augsburg Cohort Study. *Sleep* 2007;30:1121–7.
27. Orr WC, Harnish MJ. Sleep-related gastro-oesophageal reflux: provocation with a late evening meal and treatment with acid suppression. *Aliment Pharmacol Ther* 1998;12: 1033–8.
28. Orr WC, Harnish MJ. The efficacy of omeprazole twice daily with supplemental H2 blockade at bedtime in the suppression of nocturnal oesophageal and gastric acidity. *Aliment Pharmacol Ther* 2003;17:1553–8.
29. Orr WC, Goodrich S, Robert J. The effect of acid suppression on sleep patterns and sleep-related gastro-oesophageal reflux. *Aliment Pharmacol Ther* 2005;21:103–8.
30. Shaheen NJ, Madanick RD, Alattar M, et al. Gastroesophageal reflux disease as an etiology of sleep disturbance in subjects with insomnia and minimal reflux symptoms: a pilot study of prevalence and response to therapy. *Dig Dis Sci* 2008;53:1493–9.
31. Hammond EC. Some preliminary findings on physical complaints from a prospective study of 1,064,004 men and women. *Am J Public Health Nations Health* 1964;54:11–23.
32. Patel SR, Malhotra A, Gottlieb DJ, et al. Correlates of long sleep duration. *Sleep* 2006;29:881–9.
33. Lockley SW, Skene DJ, Arendt J. Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. *J Sleep Res* 1999;8:175–83.
34. Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
35. Roth T, Roehrs T, Pies R. Insomnia: pathophysiology and implications for treatment. *Sleep Med Rev* 2007;11:71–9.