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Gastro-oesophageal reflux symptoms are related to the presence and severity of obstructive sleep apnoea

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SUMMARY Repetitive airway occlusion during sleep in patients with obstructive sleep apnoea (OSA) results in the generation of negative intrathoracic pressures and ends in arousal, both of which may predispose to reflux during sleep (nocturnal reflux). We aimed to determine and compare the prevalence of nocturnal reflux symptoms and their sleep-associated risk factors in untreated OSA patients, OSA patients using continuous positive airway pressure (CPAP) therapy, and the general population. Gastro-oesophageal reflux and sleep questionnaires were completed by 1116 patients with polysomnography diagnosed OSA and by 1999 participants of the 2007 Busselton population health survey. Of the OSA patients, 137 completed the reflux questionnaire before and after treatment. Risk of OSA in the general population was assessed using the Berlin score. The prevalence of frequent (>weekly) nocturnal reflux symptoms was increased ($P < 0.001$) in OSA patients (10.2%) versus the general population (5.5%), in individuals from the general population at high (8.7%) versus low risk (4.3%) of OSA and in patients with severe (13.9%) versus mild OSA (5.1%). Frequent nocturnal reflux symptoms were associated with high risk (general population) (OR 1.9, $P < 0.01$) and severity of OSA (OSA population) OR 3.0, severe versus mild OSA, $P < 0.001$) after correcting for age, gender and body mass index. Treatment with CPAP decreased the prevalence of reflux symptoms significantly. In conclusion, the prevalence of nocturnal reflux symptoms is increased in those with or suspected of having OSA. This association is independent of other risk factors including age, gender and body mass index, suggesting a causal relationship between OSA and nocturnal reflux.

KEYWORDS acid regurgitation, gastro-oesophageal reflux, heartburn, obstructive sleep apnoea

INTRODUCTION

Obstructive sleep apnoea (OSA) is characterized by narrowing or occlusion of the upper airway during sleep, which results in repetitive arousals and the development of large, negative intrathoracic pressures during inspiratory efforts against the obstructed airway. It is possible that the pressure gradients developed during these obstructive events and/or the arousals from sleep predispose OSA patients to the symptoms of gastro-oesophageal reflux (GER). Indeed, heartburn and acid regurgitation, the two most common symptoms of GER, are reported to occur in up to 60% of OSA patients (Kim *et al.*, 2005; Morse *et al.*, 2004; Valipour *et al.*, 2002) compared with 20% of the general population (Chiocca *et al.*, 2005; Locke *et al.*, 1997).

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When reporting reflux symptoms, most studies have not specified whether symptoms were experienced during the day or night. This may, therefore, underestimate the strength of the relationship between OSA and reflux because OSA is specifically a sleep-related phenomenon. Although a PubMed search using the terms 'obstructive sleep apnoea' and 'gastroesophageal reflux' identified more than 130 separate studies, with several focusing upon the prevalence of GER in OSA patients, only one study to date has reported the prevalence of reflux symptoms during sleep in OSA patients (Green *et al*., 2003). This study found that 62% of patients reported nocturnal GER symptoms (Green *et al*., 2003), markedly greater than the reported prevalence rates of nocturnal GER symptoms in the general population which range from 10 to 25% (Farup *et al*., 2001; Fass *et al*., 2005). The presence of a potentially strong relationship between OSA and GER is also supported by the observation that treatment of OSA with continuous positive airway pressure (CPAP) reduces nocturnal GER events and symptoms in individual cases (Diaz *et al*., 1990; Green *et al*., 2003; Kerr *et al*., 1992; Tawk *et al*., 2006; Wolf and Furman, 2002).

To date, no study has investigated the prevalence of GER and nocturnal GER symptoms in OSA patients relative to the general population or the effect of CPAP on prevalence in the OSA-affected group. This study sought to: (i) determine and compare the prevalence of nocturnal GER symptoms in the general population with a group of OSA patients; (ii) determine the risk factors for nocturnal reflux in these groups; and (iii) determine the effect of CPAP therapy on the prevalence of nocturnal GER symptoms in a group of OSA patients.

METHODS

Overview

Questionnaires regarding GER symptoms were administered to a sample of patients attending a sleep disorders clinic for overnight polysomnography and to a sample of the general population. A subgroup of the patient population completed the questionnaires again following CPAP treatment.

The Human Research Ethics Committee of Sir Charles Gairdner Hospital approved this study and the 2005–2007 Busselton Health Survey was approved by the Human Research Ethics Committee of the University of Western Australia.

Study populations and questionnaires

OSA population

Consecutive sleep clinic patients (n = 1422) underwent diagnostic polysomnography (E-Series; Compumedics, Melbourne, Australia) and completed a GER symptom questionnaire (GERQ). Of these patients, 1093 individuals were diagnosed with OSA (15) and had complete anthropometric, polysomnographic and GER questionnaire data.

The GERQ was developed and validated against physician interview at the Mayo Clinic (Locke *et al*., 1994, 1997), and designed to examine the prevalence of heartburn and acid regurgitation, chest pain, dysphagia, other gastro-oesophageal conditions, medication use and some lifestyle factors. While data were collected on all these symptoms, symptoms of heartburn and acid regurgitation were used in each population of the present study to assess the prevalence of GER and nocturnal GER symptoms. The questionnaire was modified slightly to replace US pharmaceutical names with Australian equivalents.

A further modification was made to the GERQ to investigate the effect of CPAP on GER symptoms: in this modification the questionnaire asked about GER symptoms 'since starting CPAP treatment' rather than 'in the last 12 months'. This modified version was completed by all those patients, over the duration of the study, who were undergoing polysomnography for the purpose of auditing and optimizing their CPAP therapy (n = 477) rather than for initial diagnosis. Of this group, those patients who had undergone both diagnostic and CPAP polysomnography within the time-frame of the study (n = 137) and who had therefore completed the questionnaire both before and after CPAP therapy were utilized for this analysis. On average, these CPAP patient studies, and therefore the second questionnaire, were completed 1–6 months after commencing therapy.

Apnoeas and hypopnoeas were defined using standard criteria (American Academy of Sleep Medicine Task Force., 1999) and divided by hours of sleep to provide an apnoea–hypopnoea index (AHI). In the OSA population, mild OSA was defined as an AHI $5 \geq 15$ events h^{-1}; moderate OSA as an AHI $15 \geq 30$ events h^{-1}; and severe OSA as an AHI >30 events h^{-1}. Snoring was defined as a short increase in sound intensity of >40 dB. Snoring frequency was defined as minimal, if there were fewer than one snore min^{-1}, intermittent if one to two snores min^{-1} or continuous if more than two snores min^{-1}. The arousal index (ArI) was defined as the number of arousals per hour of sleep. ArI was categorized into quartiles (0–20, $>$20–40, $>$40–60 and $>$60 arousals h^{-1}) for analysis.

General population

A stratified (for gender and age) random sample of adults on the Busselton Shire electoral roll was invited to attend the 2005–2007 Busselton Health Survey (61.8% response rate). Busselton is a coastal town in Western Australia, with a population of approximately 26 000 individuals of predominantly western European origin. The community has participated in repeated health studies since 1966 (Welborn *et al*., 1969). A total of 1999 subjects who completed the 2005–2007 survey were included in this study. The survey included a subset of six questions from the GERQ regarding frequency and severity of symptoms. Also included were questions, derived from the validated Berlin questionnaire (Netzer *et al*., 1999), regarding the frequency of witnessed apnoeas, snoring

frequency and volume, frequency of waking tired and frequency of daytime sleepiness. Questionnaire responses were used to define individuals as 'low risk' or 'high risk' for OSA (Netzer *et al*., 1999). Complete questionnaire and anthropometric data were available for 1846 individuals.

Characterizing GER

For both populations, heartburn or acid regurgitation experienced at least once in the last 12 months was defined as 'any GER' and, if experienced at least once a week, was defined as 'frequent GER' (Chiocca *et al*., 2005; Locke *et al*., 1997). The term 'GER symptoms' refers to symptoms experienced at any time during the day or night while 'nocturnal GER symptoms' refers specifically to symptoms which woke the patient from sleep.

Statistical analyses

Analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Population characteristics were compared using unpaired *t*-tests and chi-square tests or Mann–Whitney rank sum tests, when data were not distributed normally. Paired *t*-tests were used to compare questionnaire responses before and after CPAP treatment. Logistic regression was used to examine associations between nocturnal GER symptoms and sleep variables. Body mass index [BMI = weight / height^2 (kg m^{-2})] and age were categorized for regression analyses. Odds ratios and their 95% confidence intervals were calculated for these associations based upon appropriate reference categories. Age, gender and body mass index were forced into the adjusted model because of reported associations with GER. Other risk factors were examined for independent association with any or frequent nocturnal GER symptoms only if they exhibited evidence of a univariate association ($P < 0.1$). Two multivariate models were developed for the general population sample, the first included individual sleep variables (i.e. snoring, witnessed apnoeas, daytime sleepiness, waking tired; model 1) and the second included risk of OSA according to the Berlin score (derived from the individual sleep variables; model 2). Subjects with missing data were excluded from these analyses. A *P*-value of <0.05 was considered significant for all statistical tests.

RESULTS

Prevalence of nocturnal GER symptoms

Compared with the general population, the OSA population was younger, had a greater BMI, proportionately more males and individuals reporting the use of acid suppressive medications (Table 1). While the prevalence of any GER symptoms was not different between the two populations, the prevalences of frequent GER symptoms, any nocturnal GER symptoms and frequent nocturnal GER symptoms were greater in the OSA population ($P < 0.05$) (Table 1).

Table 1 Subject characteristics and prevalence of gastro-oesophageal reflux symptoms

	General population ($n = 1846$)	*OSA population* ($n = 1093$)
Age (years)	56.9 (17.5)	49.5 (13.2)*
BMI (kg m^{-2})	26.9 (4.6)	31.9 (7.5)*
Males (%)	49.2	67.7*
Acid suppressive medications (%)	13.8	26.6*
Gastro-oesophageal reflux		
Any symptoms (%)	63.8	61.2
Frequent symptoms (%)	14.1	25.3*
Nocturnal gastro-oesophageal reflux		
Any nocturnal symptoms (%)	26.6	33.8*
Frequent nocturnal symptoms (%)	5.5	10.2*

Data are presented as mean (standard deviation) or percentage of population. *$P < 0.05$, OSA versus general population.
OSA, obstructive sleep apnoea; BMI, body mass index.

In the general population, 27.5% of individuals were considered to be at high risk for OSA (Table 2). This group had approximately twice the prevalence of frequent GER and frequent nocturnal GER symptoms as the low risk group ($P < 0.05$). In the OSA population, the prevalence of GER symptoms was similar in those with mild, moderate and severe disease, whereas the prevalence of any or frequent nocturnal GER symptoms was increased in those with moderate or severe OSA (Table 2).

Treatment of OSA with CPAP (for between 1 and 6 months) decreased the prevalence of any nocturnal GER symptoms from 44.8 to 6.1% ($P < 0.001$) and of frequent nocturnal GER symptoms from 9.0 to 3.8% ($P < 0.05$) (Table 3). Despite this reduction in symptoms, the proportion of individuals reporting use of acid suppressive medication remained unchanged.

Risk factors for nocturnal GER symptoms in the general population

Within the general population, univariate analyses showed nocturnal GER symptoms to be associated significantly with male gender, increasing age and increasing BMI, increasing frequencies of snoring, witnessed apnoeas, daily waking tired and daytime sleepiness (Table 4).

Multivariate analyses showed that any nocturnal GER symptoms was associated significantly with age category, BMI category, snoring frequency, apnoea frequency and waking tired (Table 5). When the sleep variables were combined to calculate risk of OSA (Berlin score), those at high risk of OSA had a 1.9-fold increased risk of any nocturnal GER symptoms compared with those at low risk (Table 6).

Age, snoring frequency and frequency of waking tired were associated significantly with risk of frequent nocturnal GER symptoms (Table 5). Those at high risk of OSA were 1.9 times as likely to experience frequent nocturnal GER symptoms than

Table 2 Severity of obstructive sleep apnoea and the prevalence of gastro-oesophageal reflux symptoms

	General population		*OSA population*		
	Low risk (n = 1340)	*High risk* (n = 506)	*Mild* (n = 296)	*Moderate* (n = 315)	*Severe* (n = 482)
Age (years)	56.0 (18.0)	59.4 (15.8)*	47.5 (14.1)	49.9 (12.9)†	50.4 (12.8)†
BMI (kg m^{-2})	25.8 (4.0)	29.9 (4.8)*	30.9 (7.3)	31.0 (6.8)	33.0 (7.9)†‡
Males (%)	44.0	63.0*	55.7	69.5†	74.0†
Acid suppressive medications (%)	11.3	20.6*	23.5	28.3	27.6
Gastro-oesophageal reflux					
Any symptoms (%)	61.6	70.0*	57.8	63.4	61.8
Frequent symptoms (%)	11.1	21.9*	20.9	27.0	26.8
Nocturnal gastro-oesophageal reflux					
Any nocturnal symptoms (%)	21.9	38.9*	23.0	34.3†	40.0†
Frequent nocturnal symptoms (%)	4.3	8.7*	5.1	9.2	13.9†

Data are presented as mean (standard deviation) or percentage of population.
*$P < 0.05$ versus low risk (within general population); †$P < 0.05$ versus mild OSA; ‡$P < 0.05$ versus moderate OSA (within OSA population).
OSA, obstructive sleep apnoea; BMI, body mass index.

those at low risk (Table 6). Results were similar when analyses were repeated, excluding those on acid suppressive medication.

Risk factors for nocturnal GER symptoms in the OSA population

Univariate analyses showed that nocturnal GER symptoms were associated significantly with morbid obesity (BMI > 35 kg m^{-2}), severity of OSA and an ArI >60 h^{-1} (Table 7).

Multivariate analyses showed that only gender and severity of OSA were associated significantly with any nocturnal GER (Table 8). Specifically, those with moderate OSA were 1.8 times and those with severe OSA 2.4 times more likely to report any nocturnal GER symptoms than those with mild OSA. Severity of OSA was the only significant risk factor associated with frequent nocturnal GER with an odds ratio of 1.9 for moderate OSA and 3.0 for severe OSA compared to mild OSA (Table 8). Results were similar when analyses were repeated, excluding those on acid suppressive medication.

Table 3 Effects of CPAP treatment on gastro-oesophageal reflux symptoms

	Pre-treatment (n = 137)	*Post-treatment* (n = 137)
BMI (kg m^{-2})	32.3 (6.4)	33.3 (7.4)
AHI (events h^{-1})	38.2 (25.3)	12.7 (13.7)‡
ArI (arousals h^{-1})	39.3 (24.0)	24.4 (13.1)‡
Snoring (snores min^{-1})	5.0 (3.8)	1.4 (2.0)‡
Acid suppressive medications (%)	32.1	30.7
Gastro-oesophageal reflux		
Any symptoms (%)	72.6	54.5‡
Frequent symptoms (%)	27.6	18.2‡
Nocturnal gastro-oesophageal reflux		
Any nocturnal symptoms (%)	44.8	6.1‡
Frequent nocturnal symptoms (%)	9.0	3.8*

Data are presented as mean (standard deviation) or percentage of group.
*$P < 0.05$; ‡$P < 0.001$.
BMI, body mass index; AHI, apnoea–hypnoea index; ArI, arousal index.

DISCUSSION

This study addresses an important gap in current knowledge regarding the relationship between GER and OSA, as it is the first study to investigate the occurrence of both GER and nocturnal GER in OSA patients relative to the general population or the effect of CPAP therapy on the OSA-affected group. Its major findings are that: (i) the prevalence of nocturnal GER symptoms is greater in individuals at high risk of OSA in the general population and in those with diagnosed OSA; (ii) increased risk in the general population and severity of OSA in the patient group is associated with increased risk of nocturnal GER; and (iii) the prevalence of nocturnal reflux decreases substantially in patients with OSA following treatment with CPAP. These findings highlight the importance of specifically assessing nocturnal GER symptoms in individuals with known or high risk of OSA and support the notion of a causal association between OSA and nocturnal GER, although randomized controlled trials are awaited before such a relationship can be established with certainty (Karkos *et al.*, 2009).

There are several potential limitations to our study. First, in both the general and OSA populations, our assessment of GER was on the basis of symptoms: in neither group did we have an objective measure of GER such as 24-h acid contact time or oesophagitis severity and healing rate on treatment. Secondly, in the general population sample we used questionnaire data to determine OSA risk: we did not have an objective measure of OSA severity, as it was not feasible to obtain these measurements on such a large scale. Thirdly, it is possible that the changes in GER symptoms seen with CPAP therapy resulted from changes in diet and lifestyle recommended by their pulmonologist. However, this appears unlikely given that

Table 4 General population: univariate associations with nocturnal gastro-oesophageal reflux symptoms

	Any nocturnal GER (n = 1846)	*Frequent nocturnal GER (n = 1846)*
Gender		
Male	1.0	1.0
Female	0.8 (0.6, 1.0)*	1.0 (0.7, 1.5)
Age category (years)		
< 30	1.0	1.0
30–40	2. 7 (1.3, 5.7)†	2.0 (0.4, 9.5)
40–50	4.3 (2.1, 9.0)‡	2.0 (0.4, 9.6)
50–60	5.2 (2.5, 10.7)‡	4.0 (0.9, 17.6)
> 60	6.3 (3.2, 12.6)‡	4.9 (1.2, 20.2)*
BMI category		
Normal weight	1.0	1.0
Overweight	1.8 (1.4, 2.3)‡	1.6 (1.0, 2.5)
Obese	2.1 (1.6, 2.8)‡	2.0 (1.1, 3.6)*
Morbidly obese	2.6 (1.7, 3.9)‡	1.6 (0.6, 3.9)
Snore		
No	1.0	1.0
Yes	2.0 (1.6, 2.5)‡	2.2 (1.4, 3.5)‡
Snoring frequency		
None	1.0	1.0
1–2 times month^{-1}	1.7 (1.2, 2.4)†	3.2 (1.7, 5.7)‡
1–2 times week^{-1}	2.0 (1.5, 2.7)‡	2.1 (1.2, 3.7)*
3–4 times week^{-1}	2.2 (1.6, 3.0)‡	2.5 (1.3, 4.8)†
Every day	2.0 (1.5, 2.7)‡	2.3 (1.2, 4.1)†
Apnoea frequency		
None	1.0	1.0
1–2 times month^{-1}	2.9 (1.9, 4.3)‡	1.3 (0.6, 3.0)
1–2 times week^{-1}	2.1 (1.3, 3.4)†	1.3 (0.5, 3.3)
3–4 times week^{-1}	1.9 (1.1, 3.2)*	2.6 (1.2, 6.0)*
Every day	2.0 (1.3, 3.2)†	1.6 (0.7, 3.7)
Wake tired		
None	1.0	1.0
1–2 times month^{-1}	0.9 (0.7, 1. 2)	0.8 (0.4, 1.5)
1–2 times week^{-1}	1.2 (0.9, 1.7)	1.6 (0.9, 2.8)
3–4 times week^{-1}	1.4 (1.0, 2.1)	1.0 (0.5, 2.4)
Every day	1.5 (1.1, 2.1)†	2.6 (1.6, 4.3)‡
Daytime sleepiness		
None	1.0	1.0
1–2 times month^{-1}	1.3 (1.0, 1.7)	0.9 (0.5, 1.7)
1–2 times week^{-1}	1.3 (1.0, 1.7)	1.1 (0.6, 1.9)
3–4 times week^{-1}	1.1 (0.8, 1.6)	0.9 (0.4, 1.9)
Every day	1.8 (1.3, 2.4)‡	2.4 (1.4, 4.0)‡
OSA risk		
Low risk	1.0	1.0
High risk	2.3 (1.8, 2.8)‡	2.1 (1.4, 3.2)‡

Data presented as odds ratios (OR) with 95% confidence intervals (CI). BMI, body mass index (weight / height^2, kg m^{-2}); OSA, obstructive sleep apnoea; GER, gastro-oesophageal reflux. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

Table 5 General population: multivariate associations with nocturnal gastro-oesophageal reflux symptoms; model 1

	Any nocturnal GER (n = 1846)	*Frequent nocturnal GER (n = 1846)*
Gender		
Male	1.0	1.0
Female	0.98 (0.77, 1.23)	0.46 (0.77, 1.79)
Age category (years)		
< 30	1.0	1.0
30–40	2.44 (1.14, 5.19)*	1.74 (0.37, 8.27)
40–50	3.78 (1.79, 7.97)‡	1.71 (0.35, 8.25)
50–60	4.18 (2.00, 11.91)‡	3.42 (0.77, 15.15)
> 60	5.86 (2.88, 11.91)‡	4.83 (1.15, 20.34)*
BMI category		
Normal weight	1.0	1.0
Overweight	1.42 (1.10, 1.85)‡	1.26 (0.75, 2.11)
Obese	1.58 (1.14, 2.19)‡	1.54 (0.84, 2.82)
Morbidly obese	1.90 (1.18, 3.07)‡	1.01 (0.39, 2.61)
Snoring frequency		
None	1.0	1.0
1–2 times month^{-1}	1.50 (1.05, 2.15)*	3.27 (1.76, 6.11)‡
1–2 times week^{-1}	1.61 (1.19, 2.18)†	1.99 (1.09, 3.62)*
3–4 times week^{-1}	1.42 (0.98, 2.06)	2.12 (1.09, 4.11)*
Every day	1.27 (0.88, 1.83)	1.58 (0.83, 2.99)
Apnoea frequency		
None	1.0	
1–2 times month^{-1}	2.30 (1.50, 3.51)‡	1.04 (0.45, 2.40)
1–2 times week^{-1}	1.52 (0.92, 2.52)	0.97 (0.36, 2.62)
3–4 times week^{-1}	1.26 (0.70, 2.26)	1.84 (0.75, 4.54)
Every day	1.29 (0.75, 2.24)	0.76 (2.80, 2.06)
Wake tired		
None	1.0	1.0
1–2 times month^{-1}	1.0 (0.72, 1.38)	0.85 (0.42, 1.70)
1–2 times week^{-1}	1.47 (1.07, 2.03)*	1.86 (1.04, 3.33)*
3–4 times week^{-1}	1.77 (1.17, 2.70)†	1.36 (0.60, 3.26)
Every day	1.70 (1.19, 2.42)†	3.46 (1.97, 6.08)‡
Daytime sleepiness		
None	1.0	1.0
1–2 times month^{-1}	1.31 (0.92, 1.87)	0.95 (0.46, 1.96)
1–2 times week^{-1}	1.24 (0.86, 1.78)	0.79 (0.38, 1.66)
3–4 times week^{-1}	1.05 (0.65, 1.70)	0.77 (0.30, 1.98)
Every day	1.35 (0.86, 2.13)	1.33 (0.60, 2.96)

Model 1: sleep variables entered into analysis separately. Data presented as odds ratios (OR) with 95% confidence intervals (CI). BMI, body mass index (weight / height^2, kg m^{-2}); OSA, obstructive sleep apnoea; GER, gastro-oesophageal reflux. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

there were no changes in weight after 6 months of treatment, as might have been expected if such advice was followed.

Prevalence of nocturnal GER symptoms

The majority of previous studies examining the prevalence of reflux in the general population have considered daytime symptoms alone or have combined daytime and night-time symptoms. These studies report a prevalence of any GER symptoms of approximately 60% in both the general population and in OSA patients (Chiocca *et al*., 2005; Guda *et al*., 2004; Locke *et al*., 1997; Morse *et al*., 2004; Valipour *et al*., 2002). Our data are consistent with these previous studies, with 64% of the general population and 61% of the OSA population reporting reflux symptoms at least once in the previous 12 months.

An increase in symptom prevalence was evident in the OSA population compared with the general population when considering nocturnal GER symptoms. Specifically, 34 and 27% of OSA patients and the general population, respectively,

Table 6 General population: multivariate associations with nocturnal gastro-oesophageal reflux symptoms; model 2

	Any nocturnal GER (n = 1846)	*Frequent nocturnal GER (n = 1846)*
Gender		
Male	1.0	1.0
Female	0.94 (0.75, 1.71)	1.20 (0.79, 1.81)
Age category (years)		
< 30	1.0	1.0
30–40	2.61 (1.23, 5.55)*	2.05 (0.44, 9.67)
40–50	4.02 (1.91, 8.43)‡	1.95 (0.41, 9.34)
50–60	4.24 (2.04, 8.79)‡	3.69 (0.84, 16.12)*
> 60	5.37 (2.67, 10.80)‡	4.53 (1.09, 18.78)†
BMI category		
Normal weight	1.0	1.0
Overweight	1.46 (1.13, 1.88)†	1.33 (0.80, 2.21)
Obese	1.36 (0.97, 1.92)	1.41 (0.75, 2.65)
Morbidly obese	1.93 (1.51, 2.48)‡	1.07 (1.18, 2.97)
OSA risk		
Low risk OSA	1.0	1.0
High risk OSA	1.93 (1.51, 2.48)‡	1.93 (1.28, 2.91)†

Model 2: individual sleep variables combined using the Berlin score to define risk of having OSA. Data presented as odds ratios (OR) with 95% confidence intervals (CI).
BMI, body mass index (weight / height^2, kg m^{-2}); OSA, obstructive sleep apnoea; GER, gastro-oesophageal reflux.
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

Table 7 OSA population: univariate associations with nocturnal gastro-oesophageal reflux symptoms

	Any nocturnal GER (n = 1093)	*Frequent nocturnal GER (n = 1093)*
Gender		
Male	1.0	1.0
Female	1.2 (0.9, 1.6)	1.0 (0.7, 1.7)
Age category (years)		
< 30	1.0	1.0
30–40	1.4 (0.8, 2.4)	1.0 (0.4, 2.8)
40–50	1.5 (0.9, 2.6)	1.6 (0.6, 3.9)
50–60	1.2 (0.7, 2.2)	1.5 (0.6, 3.7)
> 60	1.3 (0.7, 2.3)	1.4 (0.6, 3.6)
BMI category		
Normal weight	1.0	1.0
Overweight	1.3 (0.8, 1.9)	1.8 (0.9, 3.9)
Obese	1.4 (0.9, 2.1)	2.1 (1.0, 4.5)
Morbidly obese	1.7 (1.1, 2.5)*	2.2 (1.0, 4.7)*
OSA severity		
Mild	1.0	1.0
Moderate	1.8 (1.2, 2.5)†	1.9 (1.0, 3.6)*
Severe	2.2 (1.6, 3.1)‡	3.0 (1.7, 5.4)‡
Arousal category		
< 20	1.0	1.0
20–40	1.1 (0.8, 1.6)	1.0 (0.6, 1.9)
40–60	1.2 (0.8, 1.8)	1.4 (0.8, 2.7)
> 60	1.9 (1.2, 2.9)†	2.0 (1.0, 3.8)*
Snoring frequency		
None	1.0	1.0
Intermittent	1.2 (0.7, 2.0)	0.6 (0.2, 1.5)
Continuous	1.1 (0.8, 1.6)	0.9 (0.5, 1.5)

Data are presented as odds ratios (OR) with 95% confidence intervals (CI). BMI, body mass index (weight / height^2, kg m^{-2}); OSA, obstructive sleep apnoea; GER, gastro-oesophageal reflux. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

reported any nocturnal GER symptoms and 10 and 6% reported frequent nocturnal GER symptoms. These prevalence estimates in the general population are similar to those reported in previous studies (Farup *et al*., 2001; Fass *et al*., 2005); however, it is notable that the prevalence estimates in our OSA population are significantly less than the 62% of OSA patients reporting nocturnal GER symptoms in the only other comparable study (Green *et al*., 2003). The reasons for this difference are not entirely clear; however, they may be due, in part, to the use of a different definition of nocturnal GER. This study used a well-validated GERQ and frequency of symptoms was estimated and related to OSA risk (in the general population) (Netzer *et al*., 1999) or the severity of OSA (in the OSA group). The Berlin questionnaire is both sensitive and specific in identifying individuals with an AHI > 5 events h^{-1} (Netzer *et al*., 1999). The finding that 27.5% of the general population sample were at 'high risk' of OSA is similar to results reported in a large population-based study from North America (Hiestand *et al*., 2006).

The prevalences of any and frequent GER and nocturnal GER symptoms were significantly greater in individuals from the general population at high risk of OSA, particularly for nocturnal symptoms, where it was 1.8 and 2.0 times that of the low risk group for any and frequent nocturnal GER symptoms, respectively. The prevalence estimates for the high risk general population group of 39 and 9% for any and frequent nocturnal GER symptoms, respectively, are similar to the estimates in those with severe OSA, being 40 and 14%, respectively. Consistent with these findings in the general population, a 'dose–response' relationship was evident between OSA severity and nocturnal GER symptoms in our OSA group (Table 2), supporting the notion that OSA predisposes to nocturnal GER.

Risk factors for nocturnal GER in the general population

Very few studies have investigated the risk factors associated with nocturnal GER symptoms in the general population. Fass *et al*. (2005) characterized risk factors for nocturnal heartburn in a sample of 15 000 members of the general population and showed significant relationships between reported snoring and sleepiness (symptomatic OSA) and insomnia and symptoms of nocturnal heartburn. This study, however, used both heartburn *and* acid regurgitation to define nocturnal GER symptoms and used the validated Berlin questionnaire to define risk of OSA in the general population.

Multivariate analyses revealed an increased risk of any or frequent nocturnal GER symptoms with increasing age. This finding is consistent with some previous reports of an increased risk of GER symptoms with increasing age (Li *et al*., 2007; Nocon *et al*., 2006), although others have shown no effect of age (Locke *et al*., 1997, 1999; Mahadeva *et al*., 2005). Gender

Table 8 OSA population: multivariate associations with nocturnal gastro-oesophageal reflux symptoms

	Any nocturnal GER (n = 1093)	*Frequent nocturnal GER (n = 1093)*
Gender		
Male	1.0	1.0
Female	1.40 (1.06, 1.84)*	1.27 (0.83, 1.94)
Age category (years)		
< 30	1.0	1.0
30–40	1.26 (0.70, 2.27)	0.89 (0.33, 2.40)
40–50	1.31 (0.75, 2.30)	1.31 (0.52, 3.32)
50–60	1.01 (0.57, 1.77)	1.12 (0.44, 2.84)
> 60	1.11 (0.62, 1.96)	1.16 (0.45, 2.99)
BMI category		
Normal weight	1.0	1.0
Overweight	1.18 (0.78, 1.81)	1.64 (0.76, 3.53)
Obese	1.26 (0.81, 1.94)	1.80 (0.83, 3.90)
Morbidly obese	1.41 (0.91, 2.17)	1.80 (0.84, 3.90)
OSA severity		
Mild	1.0	1.0
Moderate	1.84 (1.28, 2.63)†	1.90 (1.00, 3.62)*
Severe	2.39 (1.71, 3.33)‡	3.02 (1.69, 5.40)‡
Arousal category		
< 20	1.0	1.0
20–40	0.88 (0.61, 1.28)	0.76 (0.41, 1.41)
40–60	0.72 (0.44, 1.18)	0.71 (0.33, 1.52)
> 60	1.07 (0.62, 1.82)	0.89 (0.40, 1.99)
Snoring frequency		
None	1.0	1.0
Intermittent	1.25 (0.71, 2.19)	0.59 (0.22, 1.57)
Continuous	1.02 (0.71, 1.48)	0.78 (0.46, 1.33)

Data are presented as odds ratios (OR) with 95% confidence intervals (CI).
BMI, body mass index (weight / height^2, kg m^{-2}); OSA, obstructive sleep apnoea; GER, gastro-oesophageal reflux. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

did not independently influence the risk of any or frequent nocturnal GER symptoms in the general population, a finding consistent with previous studies of either nocturnal GER or GER symptoms (Fass *et al*., 2005; Locke *et al*., 1999; Nilsson *et al*., 2004; Nocon *et al*., 2006).

Epidemiological studies consistently report an association between BMI and GER symptoms (Fass *et al*., 2005; Fisher *et al*., 1999; Jacobson *et al*., 2006; Locke *et al*., 1999). In this study, multivariate analyses also showed that increasing BMI was associated with increased risk of any, but not frequent nocturnal GER symptoms. The mechanism by which increased BMI may predispose to GER has yet to be defined clearly, but could relate to the effects of raised intragastric pressure in obese individuals (El-Serag *et al*., 2006; Nilsson and Lagergren, 2004; Pandolfino *et al*., 2006) and resultant increases in the gastro-oesophageal pressure gradient (Mercer *et al*., 1985; Wu *et al*., 2007). It is also worth considering that obese individuals are more likely to have hiatus hernia (Ronkainen *et al*., 2005; Wajed *et al*., 2001), itself an independent risk factor for GER (Stal *et al*., 1999; Van Herwaarden *et al*., 2004). The presence of hiatus hernia was not investigated in this study.

Of the sleep-related measures, snoring frequency, apnoea frequency and frequency of waking tired were associated independently with any nocturnal GER symptoms. Snoring frequency and frequency of waking tired were associated independently with frequent nocturnal GER symptoms. When 'high risk' for OSA was substituted for individual sleep symptoms in the multivariate model, those at high risk had a 1.9-fold increased risk of both any and frequent nocturnal GER than those at low risk.

Risk factors for nocturnal GER in an OSA population

Female gender was associated with a 30–40% increased risk of nocturnal GER symptoms (Table 8). Valipour *et al*. (2002) also reported a 60% increased risk of overall GER symptoms for females, although this increase was not statistically significant. Morbid obesity (BMI > 35 kg m^{-2}) was associated with approximately a twofold increased risk of any nocturnal GER or frequent nocturnal GER symptoms in the univariate analysis, but this was not a significant risk factor in the multivariate models.

Obstructive sleep apnoea severity was a strong independent risk factor for both any and frequent nocturnal GER symptoms. The risk was related to OSA severity. That these increased risks are independent of age, gender and BMI add support to the notion of an independent causal relationship between upper airway obstruction and nocturnal GER. This is supported further by the improvement in symptoms with CPAP treatment. Despite the high prevalence of GER symptoms and the increased number of GER events reported in individuals with OSA, previous epidemiological studies have generally not found an association between presence or severity of OSA and GER (Kim *et al*., 2005; Morse *et al*., 2004; Valipour *et al*., 2002). A probable explanation is that the majority of studies have not specifically investigated nocturnal symptoms. Notably, when our analyses were performed without separating nocturnal from daytime GER symptoms (data not presented), neither OSA risk or severity were associated significantly with GER symptoms, a finding consistent with most previous studies (Kim *et al*., 2005; Morse *et al*., 2004; Valipour *et al*., 2002).

There are several possible reasons for individuals with OSA to be predisposed to nocturnal GER. First, the generation of substantial negative intrathoracic pressures during upper airway obstructions may result in breach of the lower oesophageal sphincter, the primary barrier to reflux. Secondly, these obstructive events are terminated by disruption of sleep (Remmers *et al*., 1978) which could result in both increased awareness of events and their frequency, as nocturnal GER episodes usually occur during brief arousal or awakening from sleep (Dent *et al*., 1980; Freidin *et al*., 1991; Penzel *et al*., 1999; Tardif *et al*., 1986, 1988).

Although associations between OSA and nocturnal GER in both the general and OSA populations were evident, there were important differences between these two groups. In the general population, univariate analyses showed age, male gender and BMI to be associated with increased risk of

nocturnal GER symptoms and age and BMI to be associated independently with nocturnal GER symptoms in multivariate analyses. Conversely, in the OSA population, while age and BMI were not related to nocturnal GER symptoms, female gender was associated with an increased risk of nocturnal GER symptoms. These results highlight the importance of a reference population when examining risk factors.

Effect of CPAP on GER symptoms

Previous studies have suggested that application of CPAP for anywhere between 1 night and 39 months will reduce GER in individuals with and without OSA (Diaz *et al*., 1990; Graf *et al*., 1995; Green *et al*., 2003; Kerr *et al*., 1992, 1993; Shoenut *et al*., 1994; Tawk *et al*., 2006; Wolf and Furman, 2002). We considered it likely, therefore, that 1–6 months of therapy, the time-frame for which our CPAP group was receiving treatment before completing the post-treatment questionnaire, would be sufficient for CPAP to affect nocturnal GER symptoms. Indeed, there was a striking decrease in the prevalence of nocturnal GER in OSA patients after treatment with CPAP, to levels similar to or lower than that observed in the low risk group in the general population. It is unlikely that this was a 'placebo effect', as the patients were not informed ahead of time that they would be asked to complete the questionnaire again, nor were they informed of the purpose of completing it for a second time.

While the precise mechanism underlying this effect is undefined, it may be due to an associated decrease in arousal frequency (Mcardle and Douglas, 2001) or to mechanical effects acting to increase the integrity of the barrier to GER (Kerr *et al*., 1993; Shepherd *et al*., 2007). It was notable, however, that despite the improvement in GER symptoms, the number of individuals reporting acid suppressive medication use was unchanged. This finding suggests that acid suppressive medication use in patients with OSA be re-evaluated after commencement of CPAP therapy.

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