

Isolated nocturnal desaturation in COPD: prevalence and impact on quality of life and sleep

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ABSTRACT

The clinical impact of nocturnal desaturation on health-related quality of life (HRQL) and sleep in COPD has been little studied. We aimed to evaluate the prevalence and clinical impact of nocturnal desaturation in a typical outpatient population with COPD.

Between 2002 and 2005, consecutive patients with COPD attending outpatient services at the study centre underwent resting oximetry, if they were not on domiciliary oxygen therapy. If their resting saturations were less than 95%, overnight pulse oximetry was performed. Significant nocturnal desaturation was defined as spending more than 30% of at least one of two nights with a saturation of less than 90%. The Chronic Respiratory Questionnaire (CRQ) and SF-36 were used to assess HRQL, and the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Score (ESS) and Functional Outcomes of Sleep (FOSQ) questionnaires were used to assess sleep quality and daytime function.

Of 1104 patients, 803 underwent resting oximetry and 79 had resting oxygen saturations of less than 95%. Of these, 59 agreed to undergo overnight oximetry (mean age 70 years, FEV1 37.2 % predicted, resting pO₂ on air 8.9 kPa). Significant nocturnal desaturation was seen in 29 (49.2%) of the 59 subjects. The prevalence of nocturnal desaturation in the whole clinic population could therefore be estimated at 4.8%. There were no significant differences in CRQ, SF-36, PSQI, ESS or FOSQ scores for desaturators when compared with non-desaturators.

Significant nocturnal desaturation was common in COPD patients with resting saturations of less than 95%, but was estimated to have a prevalence of less than 5% in the whole outpatient population. Nocturnal desaturation was not associated with impairment of HRQL, sleep quality or daytime function.

INTRODUCTION

Nocturnal desaturation may occur in COPD in the absence of severe daytime hypoxaemia. The prevalence of such “isolated” nocturnal desaturation has previously been reported at between 25 and 70% (1-3). However, these studies have varied in their inclusion criteria and the definition of nocturnal desaturation used, and therefore uncertainty remains as to the true prevalence of isolated nocturnal desaturation in the stable COPD outpatient population.

Previously, attention focussed on the potential adverse effects of nocturnal desaturation on pulmonary haemodynamics in COPD, but a recent study found no difference in pulmonary artery pressures over two years in patients with and without nocturnal desaturation (4). However, the clinical impact of nocturnal desaturation remains unclear. Four studies have examined the effects of nocturnal desaturation and its correction with oxygen therapy on sleep architecture and quality (5-8). These studies were small, short-term and sleep lab based, employed variable methodology and produced differing results. Only one study attempted to evaluate longer-term sleep quality via questionnaire, but aside from this the effects of nocturnal desaturation in COPD on longer term health-related quality of life (HRQL), sleep quality and daytime function have not been studied. The paucity of data on the prevalence and clinical impact of isolated nocturnal desaturation is reflected in the recent NHLBI research workshop report on supplemental oxygen therapy in COPD, which identified the clinical implications of nocturnal desaturation as one of four areas of oxygen research requiring urgent further study (9).

The aims of this study were to determine the prevalence and predictors of nocturnal desaturation in a COPD outpatient population, and whether the presence of nocturnal desaturation in COPD patients was associated with impaired HRQL, sleep quality or daytime function. Some of the results from this study have been previously reported in abstract form (10).

METHODS

Consecutive COPD patients attending the outpatient and pulmonary rehabilitation services of Auckland District Health Board (comprising Auckland City Hospital and Green Lane Clinical Centre, Auckland, New Zealand) were screened between December 2002 and December 2005. Eligible subjects had (1) moderate to severe COPD with FEV1 < 60% predicted and FEV1/FVC ratio <70% predicted; (2) were clinically stable for the previous four weeks and receiving usual care; and (3) had a resting saturation of less than 95% on room air. This last criterion was based on (1) data from a previous study by our group that showed that patients with saturations of 95% or greater are very unlikely to have nocturnal desaturation (**11**), and (2) the fact that previous studies have shown moderate correlation between daytime oxygenation and nocturnal saturations (**2,11,12**).

Subjects were excluded if they (1) were current smokers, (2) were established on domiciliary oxygen therapy, (3) were unable to answer questionnaires, and (4) were suspected to have obstructive sleep apnoea syndrome (OSAS), defined as a typical clinical history of snoring, witnessed apnoeas, gasping or choking episodes and significant daytime somnolence defined by an Epworth Sleepiness Score of 10 or more (**13**). Written informed consent was obtained from all subjects and the study was approved by the Auckland Ethics Committee.

Subject demographics were collected and Body mass index (BMI) was calculated. Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured to ATS standards (**14**) using a Microloop portable spirometer (Micro Medical Ltd, Kent, UK) and expressed as percent predicted using the European Community Coal and Steel prediction equations (**15**). Cutaneous pulse oximetry using a finger probe (Siemens Micro2 plus) and radial arterial blood gases were taken after the subject had been breathing room air at rest for at least 30 minutes.

Overnight domiciliary pulse oximetry was carried out on two consecutive nights using a portable oximeter with a finger probe and an eight hour memory (Siemens Micro2 plus) (**11**). Subjects were instructed to commence recording on entering bed to sleep and to discontinue recording once fully awake. Mean nocturnal desaturation (MNS) and the time spend with a saturation below 90% (TB90%) were calculated. Subjects with a TB90% of 30% or more on at least one of the nights were defined as “desaturators”. This definition of significant nocturnal desaturation is accepted internationally (**16-18**), was used in previous studies of nocturnal desaturation (**3,4**) and in our group’s study of variability of overnight oximetry (**11**).

Each subject completed an interviewer administered Chronic Respiratory Questionnaire (CRQ), a well validated measure of disease specific HRQL for which the minimum clinically significant change in score has been established

(19,20); the Short Form 36 (SF36) questionnaire measuring generic HRQL (21); the Hospital Anxiety and Depression (HAD) questionnaire (22); the Epworth Sleepiness Score to quantify daytime somnolence (13); the Functional Outcomes of Sleep (FOSQ) questionnaire, to measure daytime function, outcomes, productivity and vigilance (23); the Pittsburgh Sleep Quality Index (PSQI), to assess sleep quality and in which “poor” rather than “good” sleep quality is identified by a score greater than 5 (24), and Likert ratings of four aspects of their sleep (sleep quality, sleep disturbance, morning refreshment and daytime alertness - Appendix).

Analysis

Continuous variables are presented as mean (standard deviation) and categorical variables are presented as frequency (percentage) except where stated. Spearman correlation coefficients were used to assess the association between continuous variables. Differences across groups were compared by using the Mann Whitney U test where distribution was skewed. ANCOVA were applied to adjust for covariates in group comparisons, mixed model ANCOVA were used where variance between groups was heterogeneous. Stepwise multiple logistic regressions were used to select the significant predictors for oxygen desaturation. Model assumptions were assessed by residual plots. SAS released 9.1 software (SAS Institute Inc., Cary, NL, USA) was used in the analysis. A p value <0.05 was considered significant.

RESULTS

Baseline characteristics

Of 1104 patients attending , 803 suitable patients fulfilled criteria for resting pulse oximetry and of these, 79 had resting saturations of less than 95% (Figure 1). The demographic and clinical details of the 59 subjects who consented to further participation are shown in Table 1. These 59 subjects did not differ significantly in terms of age, FEV1, BMI or resting oxygen saturation from the 20 who declined to participate (data not shown). The group mean nocturnal saturation (MNS) was 91.2% and mean time below 90% (TB90%) was 33.2%, during the two nights recorded.

Prevalence of isolated nocturnal desaturation

Significant nocturnal desaturation (with a TB90% of greater than 30% on at least one of two nights) was observed in 29 (49.2%) of the 59 subjects, thus giving a prevalence of nocturnal desaturation of 49.2% in COPD patients with resting saturations of less than 95%. Assuming, as discussed earlier, nocturnal desaturation was not present in the other patients with saturations of 95% or greater, the overall prevalence of nocturnal desaturation in the whole non-smoking COPD clinic population could be estimated as 4.8% (assuming the same prevalence of desaturation in the 20 similar eligible subjects who declined to participate).

Clinical effects of isolated nocturnal desaturation

Comparing desaturators and non-desaturators (as previously defined), resting oxygen saturation and PaO₂ were significantly lower and PaCO₂ higher in desaturators. FVC was slightly lower in desaturators but there were no other significant differences between the groups including FEV1, BMI and smoking history (Table 2).

Overall sleep quality was poor, and there were no significant differences between groups in overall sleep quality as measured by the PSQI, nor daytime productivity, outcomes, activity and vigilance, as measured by the FOSQ, nor in Likert scores for any of the four ratings of sleep quality and daytime function (Table 3). Epworth score was not elevated in either group, and there was no significant difference in Epworth score between groups.

There were no significant differences between groups in disease-specific HRQL as measured by the domains of the CRQ, or in Hospital Anxiety and Depression scores (Table 3). For the SF36, the physical score and general health scores

were significantly better in desaturators, but there were no other significant differences between the groups.

Predictors of isolated nocturnal desaturation

TB90% and MNS were each significantly correlated with daytime pO₂ and pCO₂ (Table 4). Weak correlation was found between TB90% and FVC percent predicted. There was no significant correlation between either TB90% or MNS and FEV₁, FVC in litres, smoking history and BMI.

Variability of nocturnal desaturation

There was little variation in the overall group MNS, TB90% and minimum nocturnal desaturation between nights (Table 2). However, individual subjects exhibited substantial variation in the degree of desaturation between nights when expressed as TB90% (Figure 2). Eight of the 29 desaturating subjects (27.6%) exhibited significant nocturnal desaturation on only one of the two nights. These results are very similar to those from a separate study previously reported by our group (11). There was also some individual subject variability between minimum saturations recorded on each night (Figure 3).

DISCUSSION

This study demonstrated that the prevalence of isolated nocturnal desaturation in a typical COPD outpatient clinic population is estimated to be very low, at under 5%. However, just under half of COPD patients with impaired resting daytime oxygen saturations on air of less than 95% exhibit isolated nocturnal desaturation, similar to previous studies. We have confirmed moderate correlations between nocturnal desaturation and daytime PaO₂ and PaCO₂ but not other physiological variables, and that there is variability in the degree of nocturnal desaturation exhibited by subjects between nights. We found that isolated nocturnal desaturation, as currently defined, was not associated with impairment of sleep quality, daytime function and health-related quality of life.

The prevalence of significant nocturnal desaturation in our study subjects, who had resting saturations of less than 95% on air and subsequently underwent pulse oximetry, was compatible with previous studies. Fletcher et al studied 135 patients with a PaO₂ of greater than 60mmHg and found nocturnal desaturation in 35 (27%), although nocturnal desaturation was defined differently (a fall below 90% for 5 minutes or more, with a nadir saturation below 85%) (1). Vos et al. studied 39 patients with a PaO₂ of over 8kPa and found 10 (25.6%) were desaturators, defined as a mean nocturnal saturation below 90% (2). In neither of these studies are the subjects stated to be identified through consecutive unselected screening. Most recently, Chauoat et al. studied 94 patients with mild to moderate hypoxaemia (PaO₂ 7.4-9.2 kPa) and found nocturnal desaturation in 66 (70.2%), using the same definition as in this study (3).

A strength of this study is that, unlike the previous studies outlined above, we consecutively screened an entire COPD outpatient clinic population with resting oximetry. We excluded smokers from this study, because in our centre and elsewhere smokers would not be eligible for potential therapeutic intervention with domiciliary oxygen (25). We were therefore able to estimate that the overall prevalence of nocturnal desaturation in non-smoking COPD patients not on LTOT was under 5%. This indicates that nocturnal desaturation is a less common clinical problem in practice than would have been suggested by previous studies. We have, of course, had to make two assumptions to produce this estimate. The first is that the prevalence of nocturnal desaturation in the 20 patients who declined oximetry was the same as in the 59 subjects who did have oximetry. As there were no significant differences between these subjects in terms of baseline measures, this assumption seems very reasonable. The second, more important assumption we have made is that none of our patients with resting saturations of 95% or greater who did not undergo oximetry would have had nocturnal desaturation. Given the relationship between pO₂ and nocturnal desaturation in both this and previous studies, we believe that the number of patients with significant nocturnal desaturation in the remainder of our clinic population is likely to be very small, and is unlikely to make a meaningful difference to our estimated prevalence of nocturnal desaturation of 4.8%.

Furthermore, if nocturnal desaturation were found in patients with higher daytime saturations, it is more likely to be caused by other conditions such as obstructive sleep apnoea.

To our knowledge, this is the first study to examine the relationship between nocturnal desaturation and longer term sleep quality and HRQL in a representative COPD population. Previous studies have examined sleep quality of COPD patients in a sleep-lab setting, compared with normal aged-matched controls. Patients with COPD had reduced sleep time, increased sleep stage changes, increased arousal frequency, lower baseline oxygen saturations and episodes of desaturation, often associated with REM sleep (5,8). The correction of nocturnal desaturation with oxygen in these studies did not consistently lead to improvements in sleep architecture or quality – two studies showed improvements in sleep times and decreased arousals (5,6), but two showed no improvement (7,8). This suggests that impairment of sleep quality in COPD is not solely due to hypoxaemia or nocturnal desaturation, and is consistent with the lack of difference in sleep quality and HRQL between desaturators and non-desaturators in this study. The sleep quality of our COPD subjects irrespective of desaturation was poor as rated by the PSQI score, with a mean total score of 7.3, and 36 of 59 subjects were classified as “poor” sleepers (61%). A previous study of 44 healthy elderly controls (over 80 years of age) revealed a mean PSQI score of 4.4 in men and 5.1 in women, with only 31.9% classified as “poor” sleepers (26). In the same study only 1 of 35 young healthy controls (aged 20 to 30) was classified as a poor sleeper. Therefore patients with COPD suffer impaired sleep quality irrespective of nocturnal desaturation, which cannot be accounted for by advanced age alone. Other factors such as cough, bronchospasm, mood disturbance and side effects of medication are likely to adversely impact on sleep quality. It is possible that the “noise” created by these problems also dilutes any “signal” of impaired sleep quality from episodes of desaturation. Finally, as previously (11) we have demonstrated that there is considerable variability in the degree of nocturnal desaturation (as TB90%) between nights in individual subjects. This may in part reflect the nature of the oxyhaemoglobin dissociation curve, in that a small fall in the resting daytime pO₂ may lead to more marked desaturation at night. This innate variation may render more difficult the detection of consistent daytime consequences of nocturnal desaturation.

Our study had limitations which warrant discussion. Firstly, it is possible that due to our sample size, a deleterious effect of nocturnal desaturation has been missed. As this was a pragmatic prospective survey of our clinic population, a formal power calculation was not performed. However, we believe that the number of study subjects should have been sufficient to show any meaningful clinical differences in sleep quality or HRQL, and our data do not reveal any trends or minor differences in favour of our hypothesis which could have been accentuated by larger numbers. Whilst the HRQL questionnaires used are well-validated and sensitive, with extensive previous use in COPD research, the sleep questionnaires used are not validated in this setting, and in particular the PSQI

was designed as a screening tool for sleep disorders rather than as an outcome measure for clinical trials. It is possible that the PSQI was not sensitive enough to detect differences in sleep quality in this study. However, the PSQI scores showed that the overall sleep quality of our patients was poor irrespective of nocturnal saturations. Also, the FOSQ has not been validated as a measure of daytime somnolence in this population, and it is notable that the overall Epworth score in our population was not elevated despite the impaired sleep quality, an observation which has been made previously (27). It would be appropriate for future COPD therapeutic intervention studies to include measures of sleep quality and the daytime consequences of such, and there is therefore a need for development of a COPD specific sleep questionnaire for use in such studies which is valid, reproducible and responsive to change. Finally, this was not an intervention study. It is possible that even though differences are not apparent at baseline, correction of nocturnal desaturation with oxygen therapy may improve sleep quality and HRQL. This would require evaluation in a randomised controlled trial.

In conclusion, in a survey of a typical COPD outpatient population, isolated nocturnal desaturation was very uncommon, but was present in approximately half of patients with resting saturations less than 95%. Patients with nocturnal desaturation did not appear to have impaired sleep quality, HRQL or excess daytime somnolence compared to those without desaturation. Our findings suggest that nocturnal desaturation in COPD is an uncommon phenomenon of limited clinical significance.

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COMPETING INTERESTS

None declared.

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TABLES

Table 1: Baseline patient characteristics

	All patients n=59
Age (years)	70 (9)
Male (n)	33 (56%)
Smoking history (pack-yrs)	40.8 (26.3)
FEV1 (L)	0.9 (0.4)
FEV1 % predicted	37.2% (14.9%)
FVC (L)	1.9 (0.9)
FVC % predicted	62.1% (17.6%)
BMI (kg/m ²)	26.0 (6.5)
Resting PaO ₂ (kPa)	8.9 (1.2)
Resting PaCO ₂ (kPa)	5.6 (0.9)
Resting saturation (%)	92.8 (1.8)
Minimum nocturnal saturation (%)	86.5 (53.6)
Mean nocturnal saturation (MNS) (%)	91.2 (2.7)
Time spent with saturation below 90% (TB90%)	34.8 (34.9)

Table 2: Baseline patient characteristics – comparison of desaturators and non-desaturators

	Desaturators (N=29)	Non-desaturators (N=30)	P value
Demographics			
Age (years)	71 (9.1)	70 (9.3)	0.71
Male (n)	14 (48%)	19 (63%)	0.24
Smoking History (pack-yrs)	36.4 (24.3)	45.0 (27.9)	0.17
FEV1 (L)	0.8 (0.5)	0.9 (0.4)	0.13
FEV1 (% predicted)	35.7 (15.1)	38.7 (14.8)	0.40
FVC (L)	1.7 (0.8)	2.1 (0.8)	0.04
FVC (% predicted)	57.8 (17.5)	66.2 (17.1)	0.04
BMI (kg/m ²)	26.4 (5.4)	25.6 (7.4)	0.74
Resting PaO ₂ (kPa)	8.4 (1.2)	9.4 (1.1)	0.005
Resting PaCO ₂ (kPa)	5.9 (0.9)	5.2 (0.7)	0.005
Resting saturation (%)	92.2 (2.2)	93.5 (0.9)	0.01
Mean nocturnal saturation (MNS) (night 1)	90 % (88%, 91%)	93 % (92%, 94%)	<0.0001
Mean nocturnal saturation (MNS) (night 2)	89 % (87%, 90%)	93 % (92%, 94%)	<0.0001
TB90% (night 1)	67 % (36%, 88%)	3.9 % (0.4%, 8.2%)	<0.0001
TB90% (night 2)	74 % (64%, 94%)	2.0 % (0.2%, 6.0%)	<0.0001
Minimum nocturnal saturation (night 1)	80 % (72%, 83%)	86 % (81%, 88%)	<0.0001
Minimum nocturnal saturation (night 2)	78 % (72%, 83%)	84 % (82%, 88%)	0.0002

Data presented are mean(std) except that % time below 90, nocturnal saturation are presented as median(IQR)

Table 3. Comparison of sleep quality and HRQL for desaturators and non-desaturators

	All patients n=59	Desaturators n=29	Non-desaturators n=30	P value*
PSQI				
Total score	7.0 (4.0,11.0)	8.0 (4.0, 11.0)	7.0 (4.0, 11.0)	0.63
CRQ^T				
Dyspnoea	16.2 (14.8, 17.7)	16.3 (14.2, 18.3)	16.2 (14.1, 18.3)	0.93
Emotional	32.9 (30.9, 34.9)	33.5 (30.3, 36.6)	32.3 (29.7, 35.0)	0.41
Fatigue	15.5 (14.3, 16.7)	16.0 (14.1, 18.0)	15.0 (13.4, 16.5)	0.51
Mastery	19.4 (18.2, 20.6)	19.7 (17.6, 21.7)	19.1 (17.7, 20.5)	0.41
SF36				
Physical functioning	25.0 (10.0, 50.0)	40.0 (15.0, 55.0)	17.5 (10.0,40.0)	0.16
Role physical functioning	0.0 (0.0, 50.0)	25.0 (0.0, 50.0)	0.0 (0.0, 25.0)	0.07
Pain visit	74.0 (51.0, 100.0)	84.0 (61.0, 100.0)	74.0 (42.0, 100.0)	0.27
General health visit	37.0 (25.0, 57.0)	45.0 (30.0, 62.0)	35.0 (20.0, 52.0)	0.03
Vitality visit	50.0 (40.0, 65.0)	55.0 (40.0, 70.0)	50.0 (40.0, 60.0)	0.33
Social functioning	75.0 (50.0, 100.0)	88.0 (62.0, 100.0)	75.0 (50.0, 87.5)	0.11
Role emotional	67.0 (33.0,100.0)	100.0 (0.0, 100.0)	67.0 (33.0, 100.0)	>0.95
Mental health	76.0 (64.0, 84.0)	80.0 (60.0, 84.0)	74.0 (68.0, 84.0)	0.75
Mental score total ^T	50.3 (50.0, 55.3)	50.0 (47.6, 56.4)	50.7 (49.8, 56.6)	0.92
Physical score total ^T	30.3 (28.7,33.1)	33.5 (31.6,36.8)	27.2 (24.5, 30.9)	0.007
FOSQ				
General productivity	3.9 (3.5, 4.0)	3.9 (3.8, 4.0)	3.7 (3.4, 4.0)	0.11
Social outcome	4.0 (3.5, 4.0)	4.0 (4.0, 4.0)	4.0 (3.0, 4.0)	0.26
Activity level	3.5 (3.1, 3.8)	3.7 (3.2, 3.8)	3.5 (3.0, 3.8)	0.28
Vigilance	3.7 (3.3, 4.0)	3.6 (3.3, 4.0)	3.8 (3.4, 4.0)	0.79
Epworth Sleepiness Score				
	5.0 (2.0, 8.0)	5.0 (2.0, 8.0)	5.0 (2.0, 8.0)	0.88
Likert scores				
Patients' described sleep quality	5.0 (4.0,6.0)	5.0 (4.0, 5.0)	5.0 (4.0, 6.0)	0.69
How disturbed sleep is	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	0.47
How refreshed in the morning	4.0 (2.0, 6.0)	4.0 (3.0, 6.0)	4.0 (2.0, 5.0)	0.63
How alert in day time	5.0 (4.0,6.0)	5.0 (4.0, 5.0)	5.0 (4.0, 6.0)	0.87
HAD				
Anxiety score	6.0 (2.0, 8.0)	6.0 (2.0, 8.0)	5.5 (3.0, 8.0)	0.96
Depression score	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	4.0 (2.0, 7.0)	0.36

*Mann-whitney U test.

* ANCOVA were used to adjust the group comparisons on PSQI CRQ, SF 36 summarised total , epworth sleepiness score, sleep quality and HAD by age , gender and FEV1(% predicted). The results made no difference.

^T data presented are mean(95% C.I). The rest of data presented are median(IQR).

Table 4: Correlations between nocturnal saturations and daytime parameters

Measure	Mean nocturnal saturation (MNS)	Time with saturation below 90% (TB90%)
pO ₂	0.51 (p=0.0001)	-0.44 (p=0.001)
pCO ₂	-0.34 (p=0.02)	0.31 (p=0.03)
FEV ₁	0.23 (p=0.09)	-0.23 (p=0.08)
FEV ₁ %predicted	0.17 (p=0.19)	-0.18 (p=0.18)
FVC	0.23 (p=0.09)	-0.24 (p=0.06)
FVC %predicted	0.24 (p=0.07)	-0.26 (p=0.05)
BMI	-0.15 (p=0.3)	0.11 (p=0.40)
Pack-year smoking history	0.21 (p=0.12)	-0.23 (p=0.08)

Results are presented as correlation coefficient (p value)

FIGURE LEGENDS

Figure 1:
Study design and subjects

Figure 2:
Comparison between desaturators and non-desaturators of time spent with saturation below 90% (TB90%) for first and second nights recorded

Figure 3:
Comparison between desaturators and non-desaturators of minimum recorded nocturnal saturation for first and second nights recorded

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APPENDIX

Likert scores used to measure sleep quality and daytime function (Table 3).

How would you describe your overall sleep quality over the last four weeks?

Extremely poor 1 2 3 4 5 6 7 Extremely good

How disturbed or interrupted has your sleep been over the last four weeks?

Not at all 1 2 3 4 5 6 7 Extremely

How refreshed have you felt in the morning after waking up in the last four weeks?

Not at all 1 2 3 4 5 6 7 Extremely

How alert have you felt during the daytime over the last four weeks?

Not at all 1 2 3 4 5 6 7 Extremely



