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The impact of obesity on oxygen desaturation during sleep-disordered breathing

*Paul E. Peppard[1], Neil R. Ward[2], Mary J Morrell[2]

1. Department of Population Health Sciences, University of Wisconsin-Madison, WARF Building, #685, 610 Walnut St. Madison, WI 53726
2. Clinical and Academic Unit of Sleep and Breathing, National Heart and Lung Institute, Imperial College London, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, United Kingdom

* Corresponding author, and address to which requests for reprints should be sent:

Department of Population Health Sciences

University of Wisconsin-Madison

WARF Building, #685

610 Walnut St.

Madison, WI 53726

608-262-2680 (voice), 608-263-8828 (fax), ppeppard@wisc.edu

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At a Glance Commentary:

Scientific Knowledge on the Subject: Obesity increases the risk of sleep-disordered breathing, but the extent to which excess body weight influences the amount of blood oxygen desaturation during apneic and hypopneic events has not been characterized.

What This Study Adds to the Field: Mixed effects regression analysis of over 37,000 breathing events, occurring in 750 participants of the Wisconsin Cohort Study, has shown that body mass index is a significant independent predictor of the amount of oxygen desaturation during apneas and hypopneas. Thus the impact of sleep disordered breathing may be greater in obesity due to exacerbation of intermittent hypoxia.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: Obesity increases the risk and severity of sleep-disordered breathing. The degree to which excess body weight contributes to blood oxygen desaturation during hypopneic and apneic events has not been comprehensively characterized.

Objectives: To quantify the association between excess body weight and oxygen desaturation during sleep-disordered breathing.

Methods: 750 adult participants in the Wisconsin Sleep Cohort Study were assessed for body mass index (kg/m^2) and sleep-disordered breathing. The amount of blood oxygen desaturation, duration and other characteristics of 37,473 observed breathing events were measured during polysomnography studies. A mixed-effects linear regression model estimated the association of blood oxygen desaturation with participant-level characteristics including body mass index, gender and age; and event-level characteristics including baseline blood oxygen saturation, change in tidal volume, event duration, sleep state, and body position.

Measurements and Main Results: Body mass index was positively associated with oxygen desaturation severity, independent of age, gender, sleeping position, baseline blood oxygen saturation and event duration. Additionally, body mass index interacted with sleep state such that body mass index predicted greater desaturation in rapid eye movement (REM) sleep than in non-REM sleep. Each increment of 10 kg/m^2 body mass index predicted a 1.0% (SE=0.2%) greater mean blood oxygen desaturation for persons in REM sleep experiencing hypopnea events associated with 80% tidal volume reductions.

Conclusions: Excess body weight is an important predictor of the severity of blood oxygen desaturation during apnea and hypopnea events, potentially exacerbating the impact of sleep-disordered breathing in obese patients.

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INTRODUCTION

Obesity is one of the most important risk factors for sleep-disordered breathing (SDB) (1). Epidemiological studies have shown that the prevalence of SDB is strongly associated with excess body weight (2), and that weight gain independently predicts the development of SDB (3). Moreover, most (4) but not all (5) interventional studies have shown that weight loss is effective in reducing apneas and hypopneas. As the prevalence of obesity is increasing across industrialized nations, it is predicted that this will cause a corresponding increase in the prevalence of SDB (1,6).

The frequency of apneas and hypopneas increases with obesity (3,7). Moreover, the frequency of breathing events is an important predictor of the consequences of SDB, with a longitudinal dose-response relationship between the apnea-hypopnea index (AHI) and the prevalence of cardiovascular morbidity (8). The severity of oxygen desaturation during obstructive breathing events, and the cumulative burden of nocturnal hypoxia are important factors in this relationship; they also predict cardiovascular morbidity in SDB patients, independent of the frequency of breathing events (9,10). Since excess body weight is known to predispose to more severe oxygen desaturation during voluntary apneas (11), obese patients with SDB may be disadvantaged by greater oxygen desaturation during apneas and hypopneas, as well as an increased event frequency.

The primary aim of the present study was to measure the impact of obesity on oxygen desaturation in a large population of 30-62 year-old community-dwelling men and women studied as part of the Wisconsin Sleep Cohort Study. Multiple regression analysis of over 37,000 breathing events was used to develop a predictive model to test the hypothesis that obesity was associated with greater oxygen desaturation during apneas and hypopneas independent of confounding variables and covariates.

METHODS

Participants

Participants were 750 adults from the Wisconsin Sleep Cohort Study (3) (described in the online supplement), an ongoing epidemiologic investigation of the natural history of SDB. The study was approved by the University of Wisconsin Health Sciences Institutional Review Board. Participants gave written informed consent.

Measurements

Body habitus, including height (m), weight (kg), waist, neck and hip circumference (cm) were measured using standard procedures (12). Body mass index (BMI) was calculated (kg/m^2). Data on medical history, medication use, smoking habits and alcohol consumption were obtained by questionnaires. Participants underwent attended polysomnography (Polygraph model 78, Grass Instruments, Quincy, MA). Measurements (described in detail in the online supplement) included

electroencephalography, electrooculography, chin electromyography, blood oxygen saturation, oral and nasal airflow, thoracic and abdominal excursions, and body position.

Sleep scoring was performed using conventional criteria (13). Respiratory signals were analyzed with an automated Sleep Analysis Program (SAP). This software program, developed for the Wisconsin Sleep Cohort Study, and designed for the detection and characterization of hypopnea and apnea events of SDB, was previously described and validated (14) and is also described in the online supplement. All breathing events that produced an oxygen desaturation ≥2% were analyzed. The following parameters were recorded for each event: oxygen saturation at the start of the event (baseline SaO_2), end-event SaO_2, ΔSaO_2 (end-event minus initial SaO_2), relative change in tidal volume during an event (ΔV_T), event duration (scored from the V_T signal), body position, sleep state (rapid eye movement [REM] or non-REM [NREM] sleep), and time of event (time since first event). Hypopneas were defined as reduction in $V_T \geq 20\%$, and apneas as cessation of breathing for ≥10 seconds. The AHI was calculated as the mean number of apneas and hypopneas associated with $\Delta SaO_2 \geq 2\%$, per hour of sleep ($AHI_{2\%}$). Additional models that included only events associated with $\Delta SaO_2 \geq 3\%$, were also examined.

Statistical Analysis

Mixed-effects linear regression models were used to examine the effect of excess body weight on ΔSaO_2 during breathing events, after accounting for covariates. The primary predictor variable was BMI. Alternative body habitus measures such as neck and waist circumferences were also examined. Additional variables examined as covariates or interacting variables included: age, gender, ΔV_T, time of event, sleep state, body position in which event occurred, baseline SaO_2, event duration, FEV_1, FVC, FEV_1 %predicted, cigarette smoking, and alcohol consumption.

Using SAS PROC MIXED (SAS Institute Inc, Cary, NC), ΔSaO_2 was regressed on the predictor variables which were modeled as random (intercept and baseline SaO_2) or fixed (all other predictors) effects; interactions among predictor variables were also evaluated. Statistically significant (2-sided p-value<0.05) covariates, interactions and quadratic terms were retained in presented models.

The primary model examined breathing events that produced ≥2% ΔSaO_2. Because most subjects had multiple breathing events, a within-subject correlation structure was fitted in the models. The best-fitting correlation structure (assessed by likelihood ratio tests and the Bayesian Information Criterion) was a “spatial” covariance matrix (spatial exponential anisotropic) with time of event (unequally-spaced, within-subject) as the single “spatial” dimension (15).

RESULTS

1463 participants had technically adequate baseline polysomnography sleep studies. 675 of these were not suitable for SAP analyses as the sleep studies were performed after the Wisconsin Sleep Cohort migrated to an alternative software platform that was not compatible with SAP analysis. Of the 788 remaining SAP-analyzable studies, 17 of these were excluded due to participant-reported physician-diagnosed heart attack, heart failure, stroke or emphysema; 21 were excluded due to the use of sleep apnea treatment (continuous positive airway pressure) at the time of sleep study.

Demographic and anthropometric details of the 750 participants are presented in Table 1 (and Tables E1-E5 on-line supplement). Mean age of participants was 45 years and 56% were male. Mean(SD) BMI was 29(6) kg/m^2 and mean(SD) $AHI_{2\%}$ was 9.5(12.0).

The 750 participants had a mean(SD) sleep time of 6.0(1.1) hours, and a total of 37,473 breathing events. Table 2 shows the number of breathing events by BMI categories. Obese participants (BMI≥30 kg/m^2) comprised 40% of the cohort, but contributed 62% of breathing events.

Table 3 shows descriptive data for all breathing events. The mean(SD) oxygen desaturation (ΔSaO_2) was 4.8(3.1)%. Due to the right-skewed distribution of ΔSaO_2, the majority of events were associated with a ΔSaO_2<4% (median ΔSaO_2=3.7%, range 2–24%). Most breathing events were hypopneas (92%) and a disproportionate number of

breathing events occurred in REM sleep: mean REM sleep time was 18% of total sleep time but encompassed 26% of all breathing events.

Regression Analysis

The regression model (Table 4) fitted a significant linear relationship between BMI and ΔSaO_2, independent of age, gender, sleeping position, baseline SaO_2 and event duration. For example, the model presented in Table 4 predicts that 50 year old non-smoking males with a BMI of 30kg/m^2 and a baseline SaO_2 of 100%, who experience a 30 second hypopnea, with an 80% ΔV_T while on their side in NREM sleep, would be expected to have a mean ΔSaO_2 of 5.9% (95% CI: 5.5 to 6.2%). The primary variable of interest in this study is BMI, with a regression coefficient of 0.055 (SE, 0.014). This indicates that for each increment in BMI of 1 kg/m^2, a mean 0.055% greater ΔSaO_2 is expected. Thus, in the example, if BMI was 40kg/m^2 rather than 30kg/m^2, with all other variables unchanged, we predict an average 0.55% greater desaturation (i.e., total ΔSaO_2 of 6.4%). In addition, the model also showed statistically significant interactions between BMI and sleep state as well as BMI and ΔV_T, indicating that: 1) the effect of BMI on ΔSaO_2 was considerably greater during REM sleep; and, 2) the impact of ΔV_T on ΔSaO_2 increased with increasing BMI (see the 3rd footnote [‡] to Table 4). Thus, for example, for hypopneas occurring during REM sleep, the coefficient would be 0.097 (=0.055 + 0.042) and we predict an additional desaturation of ~1.0% for each 10kg/m^2 increment in BMI (e.g., a total estimated mean ΔSaO_2=6.9% for the 40kg/m^2 vs. 30kg/m^2 example above). No other examined variables (age, gender, etc.) were found to significantly interact with BMI. The interaction of sleep state and BMI from the

regression model is depicted in Figure 1A for men and 1B for women. The additional model that included only events associated with $\Delta SaO_2 \geq 3\%$, yielded very similar results to those presented in Table 4. In the $\Delta SaO_2 \geq 3\%$ model the analogous coefficient for BMI in Table 4 (i.e., 0.055; SE=0.014) was 0.052 (SE=0.015).

The regression model also revealed the importance of other variables (in addition to BMI) in determining the ΔSaO_2 (Table 4). The supine position was associated with increased desaturation, predicting an estimated 0.54% greater ΔSaO_2 compared to that expected during similar events occurring in the prone or lateral position (Figure 2). As expected, longer event duration and greater ΔV_T produced greater ΔSaO_2. Accounting for event-level characteristics, increasing age and smoking also independently predicted greater oxygen desaturation. Men were estimated to have an average 0.26% (SE=0.08%) greater ΔSaO_2 than women. That is, if a hypopnea with a given set of characteristics (duration, ΔV_T, etc.) was expected to produce a 5.00% ΔSaO_2 in a man, then a similar hypopnea in a woman would be expected to produce a 4.74% ΔSaO_2.

Eight percent of all events were identified by SAP as apneas. Due to the relatively few apnea events, we had insufficient power to perform apnea-only modeling. However, in the regression analysis of all respiratory events (Table 4) an indicator variable for apnea was significant (coefficient=0.25; SE=0.07), indicating that apneas produced greater oxygen desaturation than might be expected from extrapolating hypopnea events to ΔV_T=100%.

In addition to BMI, we also examined other measures of body habitus in relation to oxygen desaturation including neck and waist girth and the waist:hip ratio. None were substantially better predictors of ΔSaO_2 than BMI. However, we have included regression model results in the online data supplement (Table E7) that describe the estimated gender-specific associations of BMI, neck girth, waist girth and waist:hip ratio with ΔSaO_2. We also examined the addition of spirometric measures of lung function, including FEV_1% predicted and FEV_1/FVC to the presented models. In this population of healthy working adults, these variables had no appreciable effect on the other predictor variable coefficients, nor were they statistically significant predictors of ΔSaO_2 independent of the other variables in the model.

DISCUSSION

The findings of this study show that BMI is an important predictor of oxygen desaturation during SDB. The regression model estimated a linear relationship between BMI and ΔSaO_2, independent of age, gender, sleeping position, baseline SaO_2 and event duration. The model also showed two interactions. First, the impact of BMI is significantly modified by sleep state; thus, ΔSaO_2 during apnea or hypopnea is predicted to be greater in REM compared to NREM sleep, but especially so in persons with higher

BMI. Secondly, during hypopnea, the (expected) positive association between ΔV_T and ΔSaO_2 is most marked in obese individuals.

Our model also showed that additional variables were significant predictors of the severity of the oxygen desaturation. Supine sleeping position was an independent predictor of greater oxygen desaturation, compared to the lateral or prone position. The SaO_2 at the start of the breathing event (baseline SaO_2), and the reduction in tidal volume occurring during hypopnea, were also predictors of oxygen desaturation.

Previous studies evaluating the effect of obesity on oxygen desaturation during SDB have not systematically examined or accounted for potential interacting or confounding factors (16,17). In the present study we found that body habitus predicts oxygen desaturation severity during apneic and hypopneic events independent of individual- and event-level characteristics. Sleeping position (18), sleep state (19), duration of breathing event (20), gender (21) and baseline oxygen saturation (22) have all been previously reported to influence the severity of oxygen desaturation during an apneic / hypopneic event. Our model has also shown that these variables are significant independent predictors of the severity of oxygen desaturation; thus, for instance, supine sleeping position predicted greater oxygen desaturation during breathing events, compared to the lateral or prone position. Moreover, our model demonstrates that male gender, increasing age and smoking are also significant independent predictors of ΔSaO_2.

Mechanisms by which obesity increases ΔSaO_2 during apnea and hypopnea

The rate of desaturation during apnea is influenced by many physiological variables, including alveolar volume (23). The reservoir of oxygen in the lung is proportional to the alveolar volume, as shown in healthy individuals who experience significantly greater ΔSaO_2 following voluntary apnea at residual volume, compared to voluntary apnea at total lung capacity (24). The effect of excess body weight on lung volume, is the principal mechanism by which BMI influences ΔSaO_2 (23), an effect likely accentuated in the presence of greater whole-body oxygen demand (25). Excess body weight causes significant reduction in all lung volumes, with the greatest reduction in functional residual capacity (FRC) and expiratory reserve volume (ERV) even in mildly obese and overweight individuals (26-28). In morbid obesity, FRC may even approach residual volume (26). In SDB, ERV has been shown to be strongly correlated with the severity of apnea-induced desaturation (29) and mean nocturnal oxygen saturation (17,30). Moreover, weight loss has been shown to result in improvements in overnight oxygen saturation in parallel with increase in the FRC and ERV (31).

In addition to reducing the reserve of oxygen in the lung, excess body weight also impacts the ventilation-perfusion ratio, another important determinant of ΔSaO_2 (23). In obesity, the combined effect of a reduction in FRC and increase in closing volume (32)

results in a greater propensity for small airway closure, causing ventilation perfusion mismatching and pulmonary shunting, thereby exacerbating oxygen desaturation (33,34).

The effect of obesity on lung volume and rate of oxygen consumption may also explain the significant interaction between BMI and sleep state predicted by our model. During REM sleep, further increase in upper airway resistance (35) may increase the work of breathing, while reduction in lung volumes and ventilation perfusion mismatching (36) will increase the rate of oxygen desaturation. Moreover, chest wall excursion is reduced during the atonia of REM sleep and there is a greater dependence upon the diaphragmatic contribution to ventilation, (37,38) which may be impinged by abdominal adiposity.

Reduction in lung volume could also explain the greater oxygen desaturation observed to occur in the supine sleeping position. Compared to the sitting and lateral decubitus position, supine posture causes a significant reduction in FRC and ERV, in healthy individuals (39,40).

Our primary measure of body habitus, the BMI, does not characterize the peripheral and central distribution of excess body fat (41). Thus, we also examined alternative measures of body habitus. Waist girth might be expected to show similar, if not stronger, associations with ΔSaO_2 as BMI since central adiposity may have greater

impact on lung function due to diaphragmatic displacement and thoracic wall impingement by visceral and chest wall fat. Although BMI is highly correlated with end expiratory lung volume (42), a recent study has reported that waist girth is strongly associated with impaired lung function independent of BMI (43). In our sample, the sex- and age-adjusted correlation of BMI and waist girth was 0.90, and only BMI was a significant predictor of ΔSaO_2 when both measures were included in our model simultaneously. Thus, BMI and waist girth might be viewed as essentially interchangeable in our data. We chose to focus our results on BMI as this is the most commonly used metric of excess body weight.

Strengths and limitations

A strength of our study is the use of data from a large community-based sample. Over 37,000 breathing events were detected in participants with a wide spectrum of body habitus and severity of SDB, allowing examination of the independent impact of individual variables and interaction between variables. Previous studies investigating the impact of obesity on ΔSaO_2 have only evaluated selected populations of sleep clinic patients (16) or patients assessed for bariatric surgery (17). As there was little racial diversity in our sample (94% white, see Table E4), we were not able to examine whether associations between obesity and ΔSaO_2 varied by race.

Two limitations in particular need to be considered when interpreting the findings of our study. First, detailed pulmonary function testing was not available in our study

population. Excess body weight predominately results in a restrictive lung defect with reduction in FRC and ERV (26) and it is possible that inclusion of these variables in our predictive model may have altered the measured impact of BMI on ΔSaO_2. The lack of lung volume measurements also limits our physiological interpretation of the model; although we speculate that the impact of excess body weight on lung volume is the key mechanism by which obesity causes greater ΔSaO_2, we can not rule out other factors. For instance, right to left cardiac shunting causes increased oxygen desaturation (44) and recent reports have identified a higher prevalence of patent foramen ovale in sleep apnea patients compared to persons without sleep apnea (45,46). Although we can not exclude unidentified patent foramen ovale causing greater ΔSaO_2 in our study population, we are not aware of any data to suggest that patent foramen ovale becomes more prevalent as BMI increases. Second, although the SAP uses calibrated respiratory inductance plethysmography for measurement of respiratory events, the calibration may become unreliable following a change in sleeping position (47). However, as the SAP measures relative differences in tidal volume based on the preceding breaths, this limitation is unlikely to have strongly influenced our results.

The present study concentrated on oxygen desaturation during discrete apnea and hypopnea breathing events, but obese individuals are also at risk of nocturnal hypoventilation and hypercapnia. This issue could not be evaluated in our model but may also be important in view of the association of the obesity hypoventilation syndrome with increased mortality and morbidity (48).

Clinical Implications

Our predictive model provides clinically important information to show that obese individuals are exposed to a greater burden of oxygen desaturation during sleep-disordered breathing. While this analysis does not confirm the long term adverse consequences of greater oxygen desaturation in obese individuals, the detrimental effects of intermittent hypoxia are well described (49), and there is evidence to show that the severity of intermittent hypoxia is important in the pathophysiologic consequences of SDB. For example, hypopneas associated with a 4% or greater ΔSaO_2 are a better predictor of prevalent cardiovascular disease compared to events associated with a 3% or less ΔSaO_2 (10); and, in a recent, novel experimental model of intermittent hypoxia in humans, healthy adults exposed to intermittent hypoxia during sleep over a 2-week period developed a significant increase in waking mean arterial blood pressure of 5 mmHg (50).

Summary

The body mass index is an important predictor of the severity of oxygen desaturation during apneic and hypopneic events of sleep-disordered breathing, independent of age, gender, sleeping position, smoking history, baseline SaO_2 and event duration. The association of BMI with oxygen desaturation is particularly strong in REM sleep. Excess body weight has been widely demonstrated to be strongly associated with a greater risk of having SDB and increased number of breathing events among persons with SDB.

For the first time, we have comprehensively quantified the additional burden that excess body weight has on the severity of individual breathing events. These findings contribute to a fuller understanding of the impact of excess body weight on SDB.

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TABLES

Table 1. Descriptive characteristics of 750 participants included in Sleep Analysis Program (SAP) analysis

Variable	Mean (SD)	Range
Age (years)	45 (7)	30 – 62
Body mass index (kg/m^2)	29 (6)	18 – 62
Neck circumference (cm)	38 (4)	27 – 53
Waist:hip ratio (men)	0.95 (0.06)	0.79 – 1.24
Waist:hip ratio (women)	0.82 (0.07)	0.34 – 1.08
$AHI_{2\%,\ SAP\text{-}scored}$ (events/hr)	9.5 (12.0)	0.3 – 91
$AHI_{4\%,\ SAP\text{-}scored}$ (events/hr)	4.5 (8.7)	0.1 – 79
$FEV_{1,\ \%\ predicted}$	107 (16)	43-153
FEV_1/FVC	0.82 (0.07)	0.36-1.0
Epworth Sleepiness Scale	8.4 (4.3)	0 – 22
Current smoker N (%)	148 (20%)	

Table 2. Distribution of Participants (N=750) and Breathing Events (N=37,473) by Body Mass Index (BMI) category

BMI Category (kg/m^2)	<25	25-29.9	30-34.9	35-39.9	≥40
Participants					
N (%)	199 (27)	257 (34)	184 (25)	57 (8)	53 (7)
Breathing events					
N (%)	3,889 (10)	10,380 (28)	13,210 (35)	5,013 (13)	4,981(13)

Table 3. Descriptive Data for SAP Analyzed Breathing Events (n=37,473)

Variable	Mean (SD)	Median	Range
ΔSaO_2 (%)	4.8 (3.1)	3.7	2.0 – 24.0
SaO_2 at start of event (%)	95 (3)	95	79 – 100
SaO_2 at end of event (%)	90 (4)	91	75 – 98
ΔV_T (%)	74 (21)	77	20 – 100
Event duration (s)	29 (13)	26	10 – 90

Table 4. ΔSaO_2 prediction model and the impact of changing individual variables on an event with a predicted ΔSaO_2 of 5.9% (the predicted ΔSaO_2 for an event with the characteristics indicated in the "Baseline Value" column).

Variable*	Coefficient† (SE)	Baseline Value	Comparison value	Expected difference in ΔSaO_2 (%)	Expected new ΔSaO_2 (%)
BMI ‡	0.055 (0.014)	30 kg/m^2	40 kg/m^2	+0.55	6.4
Sleep state ‡	0.39 (0.05)	NREM sleep	REM sleep	+0.39	6.3
ΔV_T ‡ $(\Delta V_T)^2$	0.030 (0.002) 0.00054 (0.00005)	80%	90%	+0.35	6.2
Baseline SaO_2 (baseline $SaO_2)^2$	0.52 (0.04) 0.025 (0.003)	100%	98% §	-0.93	4.9
Event type	0.25 (0.07)	Hypopnea	Apnea ‖	+0.25	6.1
Body position	0.54 (0.07)	Lateral	Back	+0.54	6.4
Event duration (event duration)^2	0.025 (0.002) 0.00016 (0.00005)	30 sec	60 sec	+0.88	6.8
Time of event	-0.022 (0.011)	1st event	1 hr after 1st event	-0.02	5.9
Gender	-0.26 (0.08)	Male	Female	-0.26	5.6
Age	0.028 (0.006)	50 yrs	60 yrs	+0.28	6.2
Smoking	0.20 (0.07)	Non-smoking	1 pack/day	+0.20	6.1

* To aid interpretation of the model intercept (5.88, SE=0.17), select variables (BMI, ΔV_T, Baseline SaO_2, event duration, and age) were "centered" in fitting the model by subtracting constants from their observed values as indicated by the "Starting value" column: i.e., BMI was centered at 30kg/m^2 ("BMI"=BMI-30); ΔV_T at 80% ("ΔV_T"=ΔV_T - 80%); etc.

† All coefficients (including quadratic and interaction terms) are significantly different from 0 with a $p<0.001$ except for smoking ($p=0.008$) and time of event ($p=0.04$).

‡ There were also significant interactions of BMI*sleep state (interaction coefficient=0.042, SE=0.009) and BMI*ΔV_T (interaction coefficient=0.00082, SE=0.00018), indicating that the association of BMI and ΔSaO_2 is both stronger in REM compared to NREM sleep, and that the effect of ΔV_T on ΔSaO_2 increases with increasing BMI.

§ The fitted quadratic relationship between Baseline SaO_2 and ΔSaO_2 suggested that baseline SaO_2<80% was strongly associated with greater ΔSaO_2 reductions, but also that there are modest decreased expected reductions in ΔSaO_2 with increasing baseline SaO_2 for baseline SaO_2>80%.

‖ Note that comparing a hypopnea with ΔV_T=80% to an apnea with ΔV_T=100% would yield an expected 1.1% greater ΔSaO_2 (i.e., 5.9+1.1=7.0% “expected new ΔSaO_2”).

FIGURES

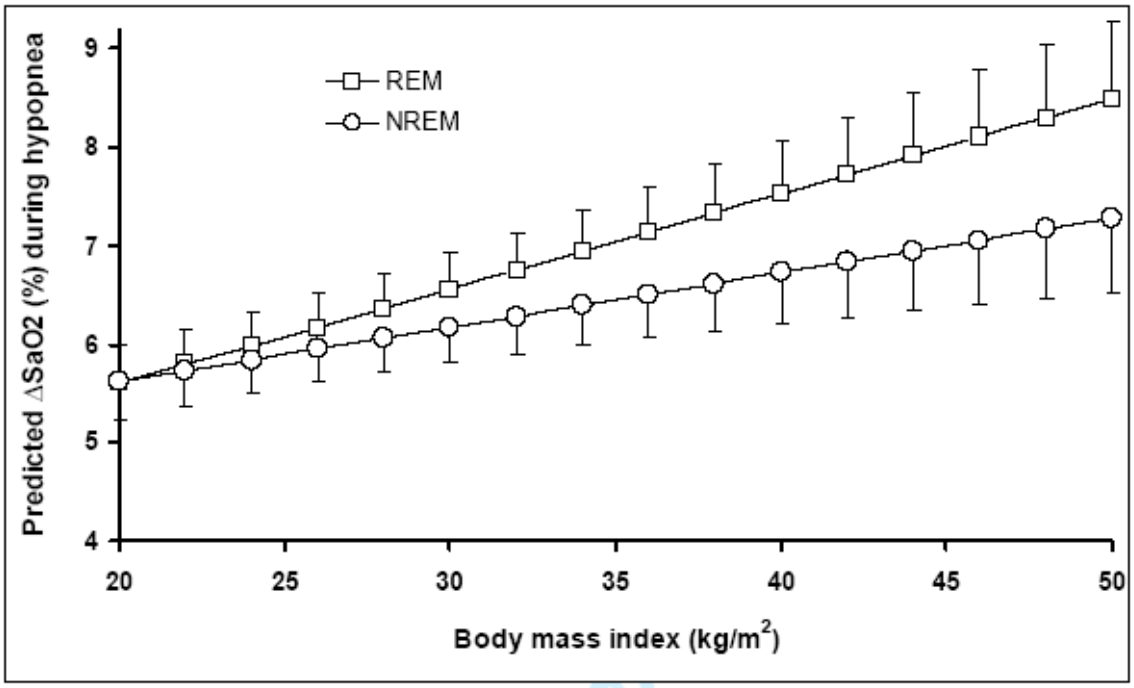
Figure Legends

Figure 1. Predicted ΔSaO_2 for a hypopnea (100% baseline SaO_2, 30 seconds in duration, with an 80% ΔV_T, in supine 50-year olds) by BMI and sleep state in men (Figure 1A) and women (Figure 1B). Error bars indicate upper (REM) and lower (NREM) 95% confidence limit for predicted mean ΔSaO_2.

Figure 2. Predicted ΔSaO_2 for a hypopnea (100% baseline SaO_2, 30 seconds in duration, with an 80% ΔV_T during REM sleep, in supine 50-year olds) by BMI and sleeping position in women. Error bars indicate upper (Supine) and lower (Side) 95% confidence limit for predicted mean ΔSaO_2.

FIGURE 1.

A. Men



B. Women

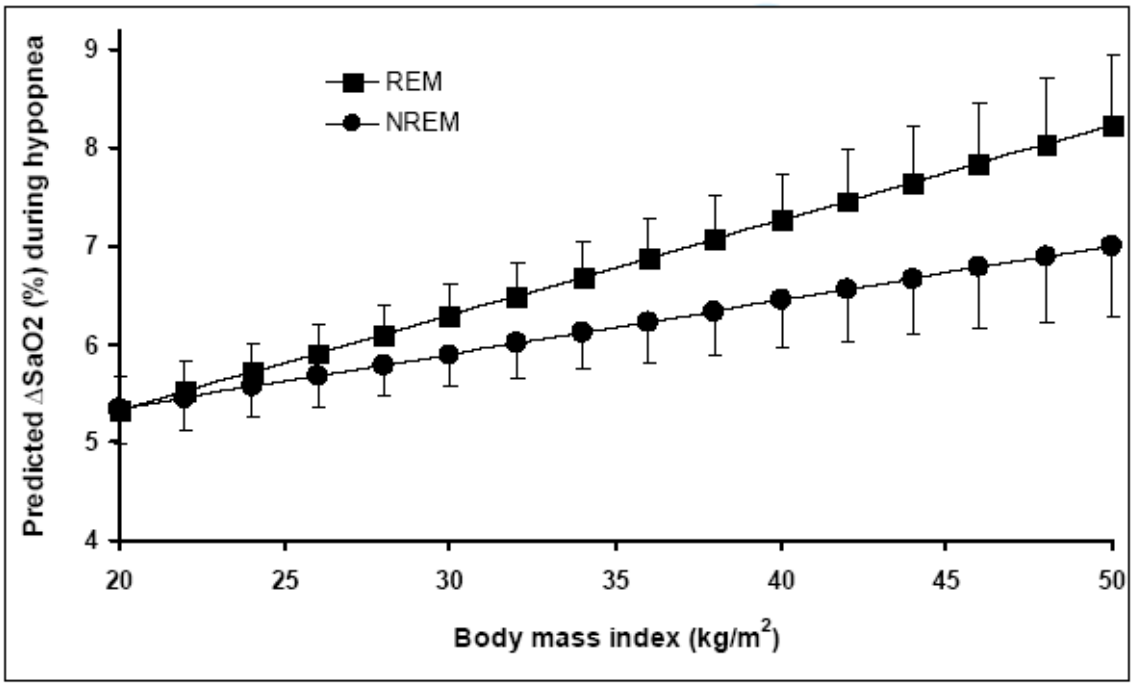
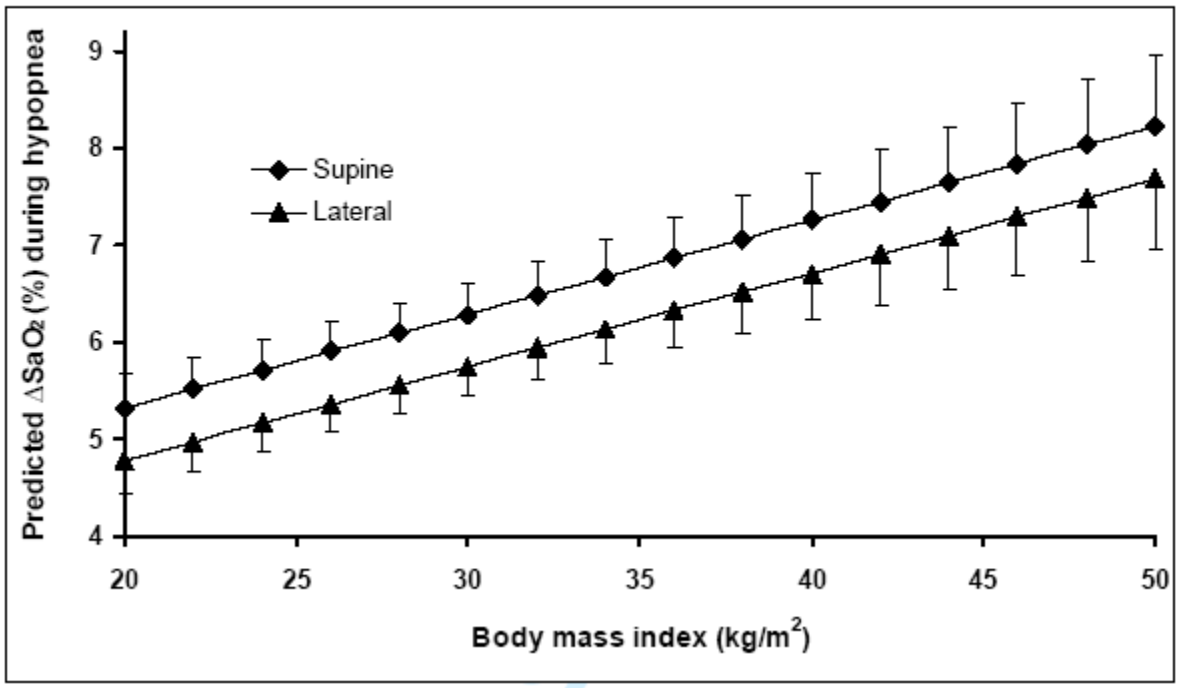


FIGURE 2.


Predicted ΔSaO2 (%) during hypopnea
9
8
7
6
5
4
Supine
Lateral
20
25
30
35
40
45
50
Body mass index (kg/m2)

The impact of obesity on oxygen desaturation during sleep-disordered breathing

Paul E. Peppard, Neil R. Ward, Mary J Morrell

ONLINE DATA SUPPLEMENT

SUPPLEMENTAL METHODS

Details of the Wisconsin Sleep Cohort Study

A random selection of men and women ages 30-60 was recruited from a sampling frame of payroll records of 4 Wisconsin state agencies for a survey of sleep characteristics and other factors. Of 2940 survey participants invited to participate in the overnight polysomnography protocol, 1546 agreed (53%; the primary reported reason for non-participation was the burden of sleeping overnight in a sleep laboratory). These 1546 comprise the Wisconsin Sleep Cohort sample and had baseline polysomnography studies between 1989 and 2000. Of the 1546 participants, 1463 had useable sleep studies (high quality data from all required polysomnography channels and at least 3 hours of objectively measured sleep in the laboratory). Of these 1463 participants with useable sleep studies, 788 participants had polysomnography studies that were suitable for SAP analysis. 675 participants were excluded from SAP analyses as their sleep studies were performed after the Wisconsin Sleep Cohort migrated to an alternative software platform that was unsuitable for SAP analyses (the majority of cases), or there were missing key electronic data channels e.g. the oxygen saturation channel was recorded only to paper records for early studies, or there was electronic storage failure. Of the 788 participants that had SAP-analyzable studies, 21 were excluded from this report due to the use of sleep apnea treatment (continuous positive airway pressure) at the time of sleep study, and 17 were excluded for self-reported history of severe physician-diagnosed cardiovascular or pulmonary medical conditions: 9 for myocardial

infarction, 2 for congestive heart failure, 3 for stroke, and 3 for emphysema. Key Demographic and co morbidity details are given in Table E1 to E5

Body habitus assessment, medical history and covariates

Body habitus measures, including height, weight, body mass index, waist, neck and hip girths were measured using standard procedures (E1). Data on medical history (including diabetes, cardiovascular disease, stroke, and hypertension), medication use, smoking habits (current and past cigarette packs per week), age, and other factors were obtained by interview and questionnaires. Spirometic variables including FEV_1 and FVC were assessed by a water-sealed spirometer using American Thoracic Society standards prevailing at the time of data collection.

Polysomnography

After the assessment body habitus, technicians affixed polysomnography leads to each participant and performed calibrations. An 18-channel polysomnographic recording system (model 78, Grass Instruments, Quincy, Mass.) was used to assess sleep state and respiratory and body position variables. Sleep state was measured with electroencephalography, electrooculography, and chin electromyography. These signals were used to determine the sleep stage for each 30-second interval of the polysomnographic record, according to conventional criteria (E2). Arterial oxygen saturation, oral and nasal airflow, nasal air pressure, and rib-cage and abdominal respiratory motion were used to assess episodes of sleep-disordered breathing. Oxygen

saturation was continuously recorded with a pulse oximeter (Ohmeda 3740, Englewood, CO). Stalk-mounted thermocouples (ProTec, Hendersonville, Tenn.) detected oral and nasal airflow. A pressure transducer (Validyne Engineering, Northridge,CA) measured air pressure at the nares. Respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, N.Y.) recorded rib-cage and abdominal excursions. Body position monitoring (mercury switch, Vitalog) was supplemented by sleep technician observations and notations of body position change.

Description of Sleep Analysis Program (SAP)

A detailed description and validation of SAP is given by Taha et al (E3). The SAP initially identifies a desaturation and then determines if an apnea or hypopnea is responsible for the desaturation. The algorithm analyzes the digitized SaO_2 signal, averaged every 0.5 second, and detects a desaturation if the following conditions are identified; the SaO_2 falls at a rate greater than 0.1% per second but less than 4% per second, there is a minimum ΔSaO_2 of at least 2%, and the SaO_2 returns to a level either 1% below starting saturation or 3% above the nadir saturation. The total time from start to finish must be $\geq$10 and $\leq$60 seconds. These levels are defined to avoid false detection of artifactual fluctuations in the SaO_2 signal.

Breath detection

A breath was defined from the digitized sum respiratory inductance plethysmography (RIP) signal as the period from the start of one inspiration to the start of the next

inspiration. The RIP signal was calibrated by first having subjects perform an isovolume maneuver while adjusting the relative gains of the abdomen and rib cage component signals such that a net zero sum signal was obtained. Following this adjustment the subject was instructed to breathe through a spirometer at increasing tidal volumes. The sum signal was then calibrated against the spirometer readings using a linear regression equation. For each detected breath, the following parameters were computed: inspiratory time (T_I), expiratory time (T_E), breathing frequency per minute (f_b), tidal volume (V_T = average of inspiratory and expiratory volumes), inspiratory duty cycle [$T/(T_I + T_E)$], and minute ventilation ($VE = V_T \times f_b$).

Apnea and hypopnea

An apnea is defined as a period of no inspiration lasting 10-60 seconds, as indicated by the differentiated sum RIP signal. A hypopnea is identified by the algorithm when three or more breaths have a fall in magnitude of ≥20% of the (baseline) breath immediately preceding the onset of hypopnea, followed by a breath returning to ≥90% of the baseline breath within 180 seconds. This analysis did not use SAP to distinguish obstructive, mixed or central apneas since SAP vs. manually-scored sleep studies showed limited correspondence (71% agreement) when scoring apnea subtype (E3).

Validation of SAP

Taha et al. compared the automated scoring algorithm with manual scoring of respiratory events and showed that SAP detected 93.1% of all manually scored apneas and hypopnoeas, with a positive predictive value of 96.9% (E3).

Apnea-hypopnea index measurement

For the primary analysis, only apneas and hyponeas associated with an blood oxygen desaturation ≥2% were included in the $AHI_{2\%}$. In keeping with common clinical thresholds, the $AHI_{4\%}$ was also determined by analysis of breathing events associated with ≥4% oxygen desaturation.

SUPPLEMENTAL RESULTS

Additional demographic and anthropometric details are presented in Tables E1-E5. Table E1 compares subjects included in this analysis with all 1493 subjects with baseline polysomnography studies with the 750 participants used for this study. Because the majority of the excluded subjects had baseline studies that occurred after 1995 (all included subjects had baseline studies prior to 1995), the excluded Wisconsin Sleep Cohort participants tended to be older, heavier and with higher mean AHI at the time of their studies compared to the 750 participants included in this analysis. Table E2 presents the prevalence of selected comorbid conditions in the sample. Table E3 breaks down the racial/ethnic composition of participants. Self-reported snoring category prevalences are given in Table E4. Table E5 presents use of caffeinated beverages in the sample.

The Wisconsin Sleep Cohort typically uses technician-scored apnea-hypopnea indices in which hypopneas are required to have ≥4% ΔSaO_2 ("$AHI_{4\%}$"). In this sample the mean (SD) technician-scored $AHI_{4\%,\ tech\text{-}scored}$ was 4.6 (9.8) events/hr vs. the SAP-scored $AHI_{4\%,\ SAP\text{-}scored}$ which was 4.5 (8.7) events/hr (p-value for difference by paired t-test=0.35, correlation of $AHI_{4\%,\ tech\text{-}scored}$ and $AHI_{4\%,\ SAP\text{-}scored}$=0.94). Table E6 shows the SAP-scored and technician-scored events.

Table E7 summarizes the results of models similar to those presented in Table 4 except that: 1) neck girth, waist girth and waist:hip ratio were substituted for BMI so that readers interested in those measures could compare them to the BMI-specific results; and, 2) gender-specific results are given in addition to models that included both men and women. The models were otherwise analogous to that presented in Table 4: ΔSaO_2 was regressed on the indicated body habitus variable, gender (except in gender-specific models), age, current smoking indicator, sleep state indicator (REM, NREM), ΔV_T, $(\Delta V_T)^2$, baseline SaO_2, (baseline SaO_2)^2, event type indicator (apnea or hypopnea), body position indicator (supine or other), event duration, (event duration)^2, time of event, and interaction terms for body habitus variable–ΔV_T and body habitus variable–event duration. There were no significant differences between body habitus coefficients estimated for men and women. That is, in models (not shown) using all subjects, p-values for gender–body habitus interaction terms were all >0.22, indicating no evidence for different associations between body habitus and ΔSaO_2 between men and women. However, gender was a significant main effect ($p<0.001$) in all such models (men tended to have greater ΔSaO_2 holding all other predictor variables constant).

SUPPLEMENTAL REFERENCES

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E3. Taha BH, Dempsey JA, Weber SM, Badr MS, Skatrud JB, Young TB, Jacques AJ, Seow KC. Automated detection and classification of sleep-disordered breathing from conventional polysomnography data. Sleep 1997;20:991-1001.

ONLINE SUPPLEMENT TABLES

Table E1. Key Demographic and Anthropometric Measurements for Wisconsin Sleep Cohort Participants Included and Excluded from SAP analysis*

Characteristic	Participants with SAP-scoreable sleep studies	All participants with valid sleep studies
N	750	1463
Male (%)	55	53
Age (years)	45	47
BMI (kg/m^2)	29	30
$AHI_{4\%}$, technician-scored (events/hr)	4.6	5.2

*Data presented as mean values, except where otherwise stated.

Table E2. Self-reported physician-diagnosed comorbidity (N=750*)

Co-morbidity	N	%
Atherosclerosis	4	0.5%
Arrhythmia	78	11%
Angina	3	0.4%
Hypertension	117	16%
Diabetes	17	2.3%
Asthma	77	10%

* Note that 17 subjects who reported previous physician-diagnosed heart attack or heart failure were excluded from the analyses.

Table E3. Race/ethnicity of participants (N=750)

Race/ethnicity	N	%
American Indian	6	0.8%
Asian	11	1.5%
Black	9	1.2%
Hispanic	6	0.8%
White	702	94%
Other	5	0.7%
Missing	11	1.5%

Table E4. Self reported snoring (N=750)

Snoring category	N	%
Never	134	18%
Rarely - only once or a few times ever.	68	9.1%
Sometimes - a few nights per month; under special circumstances.	122	16%
At least once a week, but pattern may be irregular.	25	3.3%
Several nights (3 to 5) per week.	88	12%
Every night or almost every night.	254	34%
Do not know.	44	5.9%
Missing	15	2.0%

Table E5. Typical caffeine consumption (N=750)*

Variable	Mean (SD)	Range
Caffeinated soda (12 oz. cans/day)	0.9 (1.3)	0 - 10
Caffeinated coffee (cups/day)	2.7 (2.9)	0 - 20

*5 subjects reported use of caffeine-containing supplements (e.g. No-Doze)

Table E6. SAP and technician scored AHI at varying desaturation thresholds (N=750).

Variable	Mean	Median	Range
$AHI_{2\%,\ SAP\text{-}scored}$ (events/hr)	9.5	5.0	0.3 - 91
$AHI_{4\%,\ SAP\text{-}scored}$ (events/hr)	4.5	1.3	0.1 - 79
$AHI_{4\%,\ tech\text{-}scored}$ (events/hr)	4.6	1.2	0.0 – 82

Table E7: Summary of 12 mixed-effects linear regression models* with body habitus variables predicting ΔSaO_2 for all subjects, as well as men and women separately.

Regression model body habitus predictor variables—for all participants and by gender	body habitus variable coefficient (SE), *p-value*	p-value for body habitus interaction with: ΔV_T	sleep state
BMI, 10 kg/m^2 increment (centered at BMI=30 kg/m^2)			
All (N=750)	0.55 (0.14), *p<0.001*	<0.001	<0.001
Men (N=414)	0.62 (0.20), *p=0.002*	0.01	<0.001
Women (N=336)	0.52 (0.20), *p=0.009*	<0.001	0.002
Neck girth, 5 cm increment (centered at neck girth=38 cm)			
All (N=750)	0.49 (0.09), *p<0.001*	<0.001	0.003
Men (N=414)	0.53 (0.14), *p<0.001*	0.001	0.004
Women (N=336)	0.37 (0.11), *p=0.001*	<0.001	0.014
Waist girth, 10 cm increment (centered at waist girth=95 cm)			
All (N=750)	0.22 (0.05), *p<0.001*	<0.001	0.001
Men (N=414)	0.27 (0.08), *p<0.001*	0.002	0.003
Women (N=336)	0.17 (0.05), *p=0.001*	<0.001	0.047
Waist/hip ratio, 0.1 unit increment (centered at waist/hip ratio=0.90)			
All (N=750)	0.24 (0.08), *p=0.003*	0.001	0.43
Men (N=414)	0.25 (0.14), *p=0.066*	0.028	0.087
Women (N=336)	0.21 (0.10), *p=0.030*	0.12	0.65

*ΔSaO_2 was regressed on the indicated body habitus variable, gender, age, current smoking indicator, sleep state indicator (REM, NREM), ΔV_T, $(\Delta V_T)^2$, baseline SaO_2, (baseline $SaO_2)^2$, event type indicator (apnea or hypopnea), body position indicator (supine or other), event duration, (event duration)^2, time of event, and interaction terms for body habitus variable–ΔV_T and body habitus variable–event duration. The intercept and baseline SaO_2 were modeled as random effects, all other variables as fixed effects. Intrasubject correlation in ΔSaO_2 was modeled as a 1-dimentional (time of event) spatial anisotropic exponential correlation structure.