

Resting Energy Expenditure in Adults With Sleep Disordered Breathing

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Objective: To examine the association between sleep disordered breathing severity and resting energy expenditure (REE).

Design: Cross-sectional.

Setting: University-based academic medical center.

Participants: Two hundred twelve adults with signs or symptoms of sleep disordered breathing underwent medical history, physical examination, level I attended polysomnography, and determination of REE using an indirect calorimeter.

Main Outcome Measure: Mean REE.

Results: Seventy-one percent (151 of 212) of the study population were male, and the mean (SD) age was 42.3 (12.6) years. The mean (SD) body mass index, calculated as weight in kilograms divided by height in meters squared,

was 28.3 (7.3). The mean (SD) apnea-hypopnea index was 25.4 (27.2), and the lowest oxygen saturation during the sleep study was 86.9% (9.5%). The mean (SD) REE was 1763 (417) kcal/d. Analysis of variance and univariate regression analysis showed an association between REE and several measures of sleep disordered breathing severity that persisted after adjustment for age, sex, and self-reported health status in multiple regression analysis. Only REE and the apnea-hypopnea index demonstrated an independent association after additional adjustment for body mass index (or body weight and height separately). This association did not differ between individuals with normal vs elevated body mass index.

Conclusions: Sleep disordered breathing severity is associated with REE. Although this association is largely confounded by body weight, there is an independent association with the apnea-hypopnea index.

Arch Otolaryngol Head Neck Surg. 2008;134(12):1270-1275

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OBESITY IS A MAJOR RISK factor for the development of sleep disordered breathing (SDB), and changes in body weight are associated with changes in SDB severity. Using data from 690 adults in the Wisconsin Sleep Cohort Study, Peppard et al¹ found that a 10% weight gain during 4 years was associated with a 32% increase in apnea-hypopnea index (AHI) and that a 10% weight loss was associated with a 26% decrease in AHI. This same 10% weight gain was associated with a 6-fold increase in the odds of developing moderate to severe SDB. Because of this and other similar findings, there has been considerable interest in treating SDB using a range of obesity interventions such as dietary changes, behavioral modification, and, for selected patients, bariatric surgery. Unfortunately, the success of these interventions has been inconsistent.

It is unclear whether weight gain is simply a cause of SDB or whether SDB may

be associated with alterations in energy metabolism that, in turn, lead to weight gain and complicate the treatment of these 2 disorders that often coexist. Studies²⁻⁸ have identified hormonal changes related to weight homeostasis that occur in SDB, but data are limited concerning the association between SDB and metabolic rates.

Ultimately, body weight is based on the balance between energy intake and expenditure. Total energy expenditure (TEE) includes resting energy expenditure (REE [60%-75% of TEE]), dietary thermogenesis, thermic effect of exercise, and facultative thermogenesis (energy expenditure that occurs in response to environmental stressors). All of these may be affected by SDB. For example, REE may be affected by adrenergic changes that occur in SDB, and REE has been shown to increase with experimental sleep disruption in healthy human adults⁹ and in rats.¹⁰ Dietary thermogenesis is lower in individuals with obesity,¹¹ and daytime somnolence seen in many patients with SDB can reduce levels

of exercise and related energy expenditure. In addition, facultative thermogenesis is, in part, regulated by the hypothalamic-pituitary axis and other hormonal factors that have demonstrated reversible abnormalities in patients with SDB.¹²

The objective of this study was to examine the association between SDB severity and REE. This was evaluated in a large population of adults.

METHODS

This study was approved by the institutional review board at Stanford University, Stanford, California. Women and men aged 18 to 65 years were eligible if seeking treatment for or if recently diagnosed as having SDB. Subjects were healthy and were without significant pulmonary or cardiac disease, unstable psychiatric disorder, or history of alcohol or other drug abuse. Pregnant women were excluded from the study. A convenience sample of patients was recruited after undergoing routine medical history and physical examination. Height and weight were recorded on physical examination, and patients provided a self-report of their health status (good, moderate, fair, or poor). Daytime sleepiness was evaluated by completion of the Epworth Sleepiness Scale.¹³

Resting metabolic rate was evaluated using indirect calorimetry according to the validated method by Weir.¹⁴ All subjects were fasting for a minimum of 6 hours. For 24 hours before testing, they were instructed not to engage in exercise or strenuous physical activity and to avoid caffeine intake. A handheld indirect calorimeter (MedGem; HealtheTech, Inc, Golden, Colorado) was used to measure oxygen consumption and carbon dioxide production, and these were used to determine REE (in kilocalories per day). Each subject completed a baseline evaluation before polysomnography (if previous polysomnography was not performed) or before any treatment, whether medical or surgical. Testing required normal breathing for a 5- to 10-minute trial via a personal plastic mouthpiece attached to a 140-g handheld oxygen uptake computer; testing was performed in the standard fashion as described in the operating manual for the device. If multiple tests of indirect calorimetry were performed before the initiation of treatment, the REE results were averaged across all such tests.

All patients underwent overnight attended level I polysomnography with or without esophageal pressure monitoring at Stanford University Sleep Disorders and Research Center. Some patients had undergone polysomnography at outside facilities before their referral; this was not repeated unless clinically indicated. Polysomnography included finger pulse oximetry, bilateral electrooculography, chin and leg electromyography, airflow (by nasal pressure recording), electrocardiography (modified V₂ lead), thoracic and abdominal respiratory effort, and electroencephalography (C3-A2, C4/A1, Fp1/A2, and O2-A1 electrodes of the international electrode placement system). Sleep stages and arousals were scored using standard criteria.¹⁵ Apneas were defined as a complete or almost complete cessation of airflow, and hypopneas were identified as a clearly discernible ($\geq 30\%$) reduction in respiratory sensor channels associated with at least 4% oxygen desaturation or sleep arousal. Arousals were defined as an abrupt shift in electroencephalographic frequency of 3 seconds or longer and requiring an increase in chin electromyographic activity if occurring during rapid eye movement sleep. Apneas associated with evidence of effort on both thoracic and abdominal channels were considered obstructive.^{16,17}

Polysomnography variables measured directly included time in bed and total sleep time; the ratio (time in bed:total sleep time) was defined as the sleep efficiency index. Calculated vari-

ables were arousal index (arousals per hour of sleep), lowest oxygen saturation (LSAT) level during sleep, AHI (obstructive apneas plus hypopneas per hour of sleep), obstructive apnea index (obstructive apneas per hour of sleep), and hypopnea index (hypopneas per hour of sleep). Sleep stage distribution was also determined with the percentages of sleep time spent in stage 3 or 4 sleep, slow wave sleep, and rapid eye movement sleep. Periodic limb movements were recorded, and the periodic limb movement index was defined as the number of limb movements per hour. All polysomnography variables were evaluated as continuous variables.

Esophageal pressure monitoring was performed in most patients. A fluid-filled catheter was passed through the nose into the esophagus to measure variations in transmitted intrathoracic pressure with respiration. The maximum negative esophageal pressure (Pes) was recorded as a measure of maximal respiratory effort. Normal values of Pes have been described previously.¹⁸ Upper airway resistance was defined as a continuous variable, with the following categories: normal (Pes, ≤ 10 mm Hg), moderate increase in respiratory effort (Pes, >10 to ≤ 20 mm Hg), or clear increase in respiratory effort (Pes, >20 mm Hg).

Data were analyzed using commercially available statistical software (STATA 8.0; StataCorp LP, College Station, Texas). Resting energy expenditure, descriptive statistics, and polysomnography results are given as means (SDs). One-way analysis of variance was used to test for differences in REE between SDB severity groups defined by commonly used cutpoints (based on AHI and Pes). Univariate linear regression analysis was used to test the association between REE and polysomnography measures. Multiple linear regression analysis was used to test these associations with adjustment for age, sex, and self-reported health status. Additional adjustment was performed with inclusion of body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) or, separately, body weight and height in the multiple regression equation. To evaluate whether the association between SDB severity and REE varied according to BMI, an interaction term (the product of SDB severity measures as continuous variables and a dichotomous BMI variable corresponding to whether BMI was >25 or >28.3 , with the latter representing the mean BMI of the sample) was included in the regression equations that incorporated BMI. Regression coefficient estimates are given with their 95% confidence intervals. For all analyses, $P < .05$ was considered statistically significant.

RESULTS

A convenience sample of 212 patients was enrolled. Seventy-one percent (151 of 212) of the study group members were male, and the mean (SD) age was 42.3 (12.6) years. The mean (SD) BMI was 28.3 (7.3); body weight was 85.9 (24.5) kg, and height was 174 (10) cm. The distribution among BMI categories was as follows: underweight (BMI, ≤ 20) in 5.7% (12 of 212), normal (BMI, >20 to ≤ 25) in 30.7% (65 of 212), overweight (BMI, >25 to ≤ 30) in 34.4% (73 of 212), and obesity (BMI, >30) in 29.2% (62 of 212). Self-reported health status was good (64.2% [124 of 193]), medium (25.4% [49 of 193]), fair (7.3% [14/193]), or poor (3.1% [6 of 193]). The mean (SD) Epworth Sleepiness Scale score was 9.3 (4.9).

Polysomnography results are given in **Table 1**. Ninety-four percent (200 of 212) of patients had polysomnography performed at Stanford University Sleep Disorders and Research Center. Overall, the population demonstrated a roughly even distribution of AHI across the fol-

Table 1. Sleep Study Results

| Variable | Mean (SD) | Minimum | Maximum |
|---------------------------------------|-------------|---------|---------|
| Time in bed, min | 408 (105) | 88 | 610 |
| Total sleep time, min | 314 (103) | 48 | 584 |
| Sleep efficiency index, % | 77 (15) | 18 | 97 |
| Apnea-hypopnea index | 25.4 (27.2) | 0.0 | 110.1 |
| Obstructive apnea index | 11.4 (21.5) | 0.0 | 107.0 |
| Hypopneas per hour of sleep | 11.6 (14.1) | 0.0 | 80.4 |
| Slow wave sleep, % | 8.6 (10.5) | 0.0 | 67.8 |
| Rapid eye movement sleep, % | 14.3 (8.5) | 0.0 | 53.8 |
| Lowest oxygen saturation during sleep | 86.9 (9.5) | 32.1 | 96.1 |
| Periodic limb movement index | 6.4 (15.7) | 0.0 | 110.6 |

Table 2. Resting Energy Expenditure (REE) According to Sleep Disordered Breathing (SDB) Severity

| Variable | No. | REE, Mean (SD), kcal/d | P Value ^a |
|---|------------|------------------------|----------------------|
| Total | 212 | 1763 (417) | |
| Apnea-hypopnea index | | | .16 |
| ≤5 | 54 | 1626 (351) | |
| >5 to ≤15 | 59 | 1646 (342) | |
| >15 to ≤30 | 37 | 1748 (371) | |
| >30 | 62 | 1999 (463) | |
| Maximum negative esophageal pressure, mm Hg | | | .42 |
| ≤10 | 33 | 1637 (445) | |
| >10 to ≤20 | 51 | 1696 (391) | |
| >20 | 67 | 1790 (395) | |

^aAnalysis of variance for differences among SDB severity groups.

lowing 4 categories defined by commonly used cutpoints: normal (AHI, ≤5) in 24.5% (52 of 212), low (AHI, >5 to ≤15) in 28.8% (61 of 212), medium (AHI, >15 to ≤30) in 17.5% (37 of 212), and high (AHI, >30) in 29.2% (62 of 212). Seventy-one percent (151 of 212) of patients underwent esophageal pressure monitoring. Maximum (SD) negative esophageal pressure was -21.6 (17.0) mm Hg and had the following distribution among categories: 21.8% (33 of 151) normal (Pes <10 mm Hg), 33.8% (51 of 151) with moderate increase in respiratory effort (Pes ≥10 and <20 mm Hg), and 44.4% (67 of 151) with clear increase in respiratory effort (Pes >20 mm Hg).

Indirect calorimetry results are given in **Table 2**. The mean values for REE increased with greater SDB severity, although there were no statistically significant differences across groups defined by these commonly used AHI and Pes cutpoints.

Univariate linear regression results are given in **Table 3**. Resting energy expenditure was associated with several measures of SDB severity, including AHI, obstructive apnea index, hypopnea index, LSAT, and Pes, as well as percentage of rapid eye movement sleep. Resting energy expenditure was not associated with Epworth Sleepiness Scale score (coefficient estimate, -0.36; 95% confidence interval, 12.20-11.48; *P* = .95).

Multivariate regression results for AHI are given in **Table 4**. With adjustment for age, sex, and self-reported

Table 3. Univariate Linear Regression Results

| Variable | Coefficient Estimate (95% CI) | P Value |
|---------------------------------------|-------------------------------|---------|
| Apnea-hypopnea index | 5.93 (3.97 to 7.89) | <.001 |
| Obstructive apnea index | 6.66 (4.13 to 9.20) | <.001 |
| Hypopneas per hour of sleep | 6.29 (2.41 to 10.20) | .002 |
| Lowest oxygen saturation during sleep | -14.60 (-20.30 to -8.94) | <.001 |
| Slow wave sleep | -3.68 (-9.19 to 1.83) | .19 |
| Rapid eye movement sleep | -7.79 (-14.60 to -0.92) | .03 |
| Periodic limb movement index | -2.17 (-5.86 to 1.52) | .25 |
| Maximum negative esophageal pressure | -4.74 (-8.53 to -0.94) | .02 |

Abbreviation: CI, confidence interval.

health status in model 1, the association between REE and AHI was similar to the univariate regression finding in Table 3. However, with additional adjustment for BMI (model 2 in Table 4), the relationship between REE and AHI was attenuated but remained statistically significant, suggesting that the association between REE and AHI was confounded largely, but not completely, by BMI. After adjustment for BMI, a 10-U increase in AHI was associated with a 26.9 (95% CI, 6.3-47.4) kcal/d increase in REE. Similar findings were obtained if model 2 was modified to include adjustment for body weight and height independently rather than BMI (data not shown). The interaction terms for AHI and BMI were not significant (data not shown), and the results summarized in Table 4 are for regression equations without an interaction term.

Multivariate regression results for other polysomnography measures are given in **Table 5**. Adjustment for age, sex, and self-reported health status (as in model 1 of Table 4) also produced findings similar to those in univariate analysis (compare with Table 3). The association between REE and these other measures was almost entirely confounded by BMI after additional adjustment (as in model 2 of Table 4), although there remained an association with the arousal index, as well as a trend toward an association with the obstructive apnea index and hypopnea index. Similar findings were obtained with adjustment for body weight and height independently instead of BMI (data not shown). The interaction terms for SDB severity measures and BMI were not significant (data not shown), and the results summarized in Table 5 are for regression equations without an interaction term.

COMMENT

Increased REE is associated with greater SDB severity. This association is largely confounded by BMI or body weight. However, there is an independent association with AHI (and a trend toward association with the obstructive apnea index and hypopnea index separately) but not with other measures of SDB severity such as LSAT and Pes. This association between AHI and REE does not differ between individuals with normal and elevated BMI.

The independent association between REE and AHI, among the various measures of SDB severity, is interest-

Table 4. Multiple Linear Regression Results for Resting Energy Expenditure and Apnea-Hypopnea Index

| Variable | Model 1 ^a | | Model 2 ^b | |
|----------------------|-------------------------------|---------|-------------------------------|---------|
| | Coefficient Estimate (95% CI) | P Value | Coefficient Estimate (95% CI) | P Value |
| Apnea-hypopnea index | 5.37 (3.27 to 7.46) | <.001 | 2.69 (0.63 to 4.74) | .01 |
| Age | -5.50 (-9.57 to -1.42) | .008 | -5.86 (-9.52 to -2.19) | .002 |
| Male | 304 (189 to 419) | <.001 | 268 (164 to 372) | <.001 |
| Health | | | | |
| Good | -4 (-196 to 188) | .97 | 43 (-129 to 217) | .62 |
| Medium | -26 (-230 to 177) | .80 | -8 (-191 to 175) | .93 |
| Poor | 683 (360 to 1005) | <.001 | 595 (305 to 885) | <.001 |
| Body mass index | ... | ... | 26.3 (18.6 to 33.9) | <.001 |

Abbreviations: CI, confidence interval; ellipsis, not applicable.

^aModel 1 results are coefficient estimates for a regression equation that includes apnea-hypopnea index and adjustment for age, sex, and self-reported health status.

^bModel 2 results are coefficient estimates from a similar model, adding adjustment for body mass index.

Table 5. Multiple Linear Regression Results for Resting Energy Expenditure and Other Polysomnographic Measures

| Variable | Model 1 ^a | | Model 2 ^b | |
|---------------------------------------|-------------------------------|---------|-------------------------------|---------|
| | Coefficient Estimate (95% CI) | P Value | Coefficient Estimate (95% CI) | P Value |
| Obstructive apnea index | 5.24 (2.64 to 7.83) | <.001 | 2.03 (-0.43 to 4.49) | .10 |
| Hypopneas per hour of sleep | 5.62 (1.83 to 9.42) | .004 | 2.75 (-0.62 to 6.12) | .11 |
| Arousal index | 5.79 (3.77 to 7.81) | <.001 | 3.12 (1.13 to 5.12) | .002 |
| Lowest oxygen saturation during sleep | -9.93 (-15.70 to -4.16) | .001 | -2.16 (-7.68 to 3.37) | .44 |
| Slow wave sleep | 1.80 (-3.92 to 7.53) | .53 | 1.76 (-3.12 to 6.64) | .48 |
| Rapid eye movement sleep | -4.19 (-10.80 to 2.45) | .21 | -0.91 (-6.67 to 4.84) | .75 |
| Periodic limb movement index | -0.07 (-3.83 to 3.68) | .97 | -0.80 (-4.02 to 2.42) | .62 |
| Maximum negative esophageal pressure | -3.60 (-7.19 to -0.01) | .05 | -1.07 (-4.49 to 2.34) | .54 |

Abbreviation: CI, confidence interval.

^aModel 1 results are coefficient estimates for separate regression equations that include a polysomnographic measure (left column) and adjustment for age, sex, and self-reported health status.

^bModel 2 results are coefficient estimates from a similar model, adding adjustment for body mass index.

ing. This finding contrasts with the findings for other measures of SDB severity (particularly LSAT and Pes), in which the associations with REE may be entirely confounded by BMI. The distinction may lie in the fact that AHI captures the frequency of airflow and sleep disruption throughout total sleep time better than other measures such as LSAT or Pes, which can represent single events. This study did not collect data to evaluate other frequency measures such as oxygen desaturation index (number of oxygen desaturations per hour). The potential relevance of frequency in metabolic disturbances was demonstrated in 2 previous studies. Bonnet et al⁹ demonstrated an increase in REE related to the frequency of sleep fragmentation in healthy adults. Sulit et al¹⁹ showed in a population of adults from the Cleveland Family Study that impaired glucose tolerance was most strongly correlated with the percentage of time spent with an oxygen saturation below 90% (among several measures of SDB severity derived from polysomnography).

Previous research concerning SDB and metabolic rates has demonstrated inconsistent findings in small groups of patients. Ryan et al¹² found no differences for REE or dietary thermogenesis between 14 adults with moderate to severe obstructive sleep apnea (OSA) and 8 BMI-matched control patients, after adjustment for lean body mass. Their small sample size and related low statistical

power may explain the difference in our findings. Their sample size was only able to detect a raw difference in REE of 15% between the OSA and control groups, a large difference in REE; furthermore, they were unable to adjust for potential confounders.¹² Our larger sample size was also able to detect smaller associations between REE and SDB. To place our findings in perspective, a 15% difference in REE for our population (mean [SD] REE, 1763 [417] kcal/d) would be 264 kcal/d. Our results indicate that a 10-U increase in AHI is associated with an increase in REE of 27.6 kcal/d, a smaller but nontrivial amount. Most important, our sample size demonstrates an association that, while attenuated, persists after adjustment for several factors that are also associated with REE, including age, sex, and self-reported health status (primarily poor health).

The bulk of earlier work related to metabolic rates and SDB focused on TEE or sleep energy expenditure (SEE [analogous to REE during sleep]). Stenlöf et al²⁰ found higher TEE and SEE in 5 adults with OSA vs 6 controls with snoring and found that continuous positive airway pressure therapy reduced TEE and SEE. No difference was noted in the ratio of TEE to SEE between the 2 groups. For 8 adults with OSA compared with a control group of 86 adults without apnea, Hins et al²¹ found no association between OSA and TEE or sleep metabolic rates

(no difference between measured and predicted values); however, there was an association between severity of nocturnal desaturation (percentage of sleep time with an oxygen saturation of <90% on polysomnography) and both TEE and sleep metabolic rate (greater desaturation associated with lower than predicted values). Finally, Lin et al²² found higher SEE (but not morning basal metabolic rate) in a group of 25 adults with moderate to severe OSA compared with 15 controls. After undergoing laser-assisted uvulopalatoplasty, 6 patients with OSA who responded to this surgical treatment (AHI decreased by $\geq 50\%$ to an absolute level <20) demonstrated a reduction in SEE but no change in basal metabolic rate; there were no changes among 19 nonresponders.²²

The evidence concerning SDB and metabolic rates in children is also mixed. In 11 children with OSA compared with controls, Bland et al²³ showed no differences in overall TEE. Li et al²⁴ also demonstrated no relationship between SEE and OSA severity (measured using AHI) in a group of 24 children with OSA. In 14 children experiencing resolution of OSA after undergoing adenotonsillectomy, Marcus et al²⁵ showed reduction in SEE.

The major limitation of this study is the lack of data regarding body composition or lean body mass. Body composition has a well-described association with REE because, for example, muscle has greater metabolic activity than adipose tissue. Data on body composition would enhance this examination; however, the complexity of such an assessment is the basis for the fact that the studies described herein that assessed body composition or lean body mass have small sample sizes. We believe our findings are valid because, although we are unable to adjust for body composition, the study findings are robust to 2 different methods of adjustment for body weight. Our larger sample size enables a broader distribution of SDB severity, increasing statistical power and enhancing generalizability. Finally, this sample included 30.7% with normal BMI, and the association between SDB severity and REE did not differ for subjects with normal BMI vs elevated BMI. It would have been more challenging to assess body composition in a study population of this size, but future research can incorporate such evaluations.

This study advances our knowledge concerning SDB and metabolic rates, but it does not define the connection between SDB and body weight. Body weight is determined by the balance between energy intake and expenditure. Although the findings of this study suggest that SDB increases energy expenditure, it ignored 2 important aspects of this balance. First, SDB often results in fatigue and other decrements in daytime functioning that can limit physical activity. Second, this work does not specifically incorporate the emerging evidence that suggests that SDB may alter energy intake, whether through hormonal or other mechanisms. Future research considering the effect of SDB on body weight can include the effects on energy intake and expenditure.

Increasing SDB severity is associated with increasing REE. Although this association is largely confounded by body weight, there is an independent association with AHI.

Submitted for Publication: January 2, 2008; final revision received March 24, 2008; accepted April 7, 2008.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by grant KL2RR024130 from the National Center for Research Resources, a component of the National Institutes of Health (Dr Kezirian). The study was conducted in cooperation with Stanford University Sleep and Research Center and was supported in part by the registered public nonprofit Sleep Education and Research Foundation, Palo Alto (Drs Riley and Powell).

Disclaimer: The contents of this article are solely the responsibility of the authors and do not necessarily represent the official view of the National Center for Research Resources or the National Institutes of Health.

Additional Contributions: David V. Glidden, PhD, assisted with the statistical analysis.

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