Published in final edited form as:
WMJ. 2009 August ; 108(5): 263–265.

Sleep Disordered Breathing and Metabolic Syndrome

F. Javier Nieto, MD, MPH, PhD, **Paul E. Peppard, PhD**, and **Terry B. Young, PhD**
Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wis

Abstract

Background—Sleep disordered breathing (SDB) has been associated with cardiovascular disease, hypertension, and insulin resistance. This article examines the association between SDB and the prevalence of metabolic syndrome (MS) in a community-based sample.

Methods—A subset of participants in the Wisconsin Sleep Cohort Study (N=546) participated in an ancillary study to measure vascular and metabolic function. SDB was characterized using the apnea-hypopnea index (AHI) obtained in the polysomnography study closest to the collection of the metabolic measures. MS was defined using the National Cholesterol Education Program definition, and the homeostasis model assessment method (HOMA) was used to characterize insulin resistance.

Results—SDB was significantly correlated with insulin resistance (Spearman r correlation between AHI and HOMA=0.30, $P<0.0001$). Compared with those without SDB (AHI <5), the age-sex-adjusted odds ratios of MS associated with mild (AHA 5-14.9) and moderate/severe SDB (AHI >15 or CPAP) were 4.0 (95% CI 2.6, 6.3) and 5.3 (95% CI 3.2, 8.8), respectively. Additional adjustment for markers of sympathetic or neuroendocrine activation (urinary norepinephrine, cortisol, heart rate variability) did not materially alter these estimates. These associations were weaker but remained statistically significant after adjusting for body mass index.

Conclusion—SDB might be considered an integral component of MS.

Introduction

Recent estimates suggest that more than 20% of US adults have metabolic syndrome (MS).[1] Similarly, sleep disordered breathing (SDB), a condition characterized by repeated episodes of apnea and hypopnea during sleep, is estimated to affect 5%-10% of middle-aged adults and 20%-30% of the elderly.[2-4] Clinical and population-based studies have shown that patients with SDB have many features in common with those with MS, including hypertension,[5-7] diabetes and insulin resistance,[8-11] abdominal obesity,[2-3,12-15] and dyslipidemia.[14,16-17] Postulated mechanisms explaining these associations include the autonomic and hypothalamic-pituitary-adrenal axis (HPA) activation that result from the intermittent hypoxemia and sleep fragmentation associated with SDB.[18]

This article explores the association between SDB and MS and possible mechanisms in a sample of participants in the Wisconsin Sleep Cohort Study (WSCS).

Corresponding Author: F. Javier Nieto, MD, MPH, PhD, Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, 707C WARF Office Building, 610 Walnut St, Madison, WI 53726; phone 608.265.5242; fax 608.263.2820; fjnieto@wisc.edu.

Financial Disclosures: None declared.

Methods

As described in detail elsewhere,[2,19] the WSCS was established in 1989 as a community-based sample of Wisconsin state employees, between the ages of 30 and 60 years at recruitment. Participants have been followed from 1989 to the present through repeated visits that have included a variety of health questionnaires, laboratory data, and clinical exams. These exams included full overnight polysomnography (PSG) exams that were manually scored using standard criteria.[20] SDB was characterized based on the apnea-hypopnea index (AHI), defined as the average number of scored apneas and hypopneas (associated with a ≥4% oxygen desaturation) per hour of sleep. In accordance with common clinical practice, AHI between 5 and 15 was considered indicative of mild SDB and participants with AHI ≥15 or receiving treatment with continuous positive airway pressure (CPAP) were considered to have moderate or severe SDB.

A subset of 546 participants from the WSCS was selected to participate in an ancillary study to measure additional cardiovascular and metabolic parameters between October 2004 and December 2007. The PSG study closest in time to the ancillary study was used to characterize the participants' sleep. The mean lag time between the sleep study and the ancillary study was 2.2 years (range 0.6-9.6 years).

Body mass index (BMI) was calculated as weight (kg) divided by height (meters) squared. Serum glucose, insulin, triglycerides and high-density lipoprotein (HDL) cholesterol, and urinary cortisol and epinephrine were measured in the University of Wisconsin Hospital clinical laboratory using standard methods. Metabolic syndrome was defined using the National Cholesterol Education Program criteria,[21] which requires at least 3 of the following factors: high fasting glucose, high blood pressure, elevated triglycerides, low HDL, and abdominal obesity (defined by waist circumference.) The homeostasis model assessment method (HOMA),[22] based on fasting insulin and glucose values, was used to characterize insulin resistance. Heart rate variability was measured by the standard deviation of the normal-to-normal resting rate intervals in a 5-minute electrocardiogram recording.

Chi-square and t-tests were used to compare proportions and means, respectively. Spearman correlation coefficient (r_s) was used to evaluate the ordinal correlation between continuous variables. Logistic regression was used to assess the relationship between predictors and the MS. All statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

Results

Among participants in the study (N=546), 306 (56%) were male; mean age at the time of the ancillary study was 59.9 years (range 43-77 years); 56 (10%) were current smokers, and 283 (52%) were hypertensive. Mean BMI was 31.1 kg/m^2 (standard deviation, 6.9 kg/m^2).

Mean AHI was 7.6. A total of 150 participants (27%) had mild SDB and 103 (19%) had moderate or severe SDB. AHI was significantly correlated with HOMA (r_s=0.30, P<0.0001) and with urinary norepinephrine levels (r_s=0.22, P<0.0001), but not with urinary cortisol or heart rate variability.

The overall prevalence of MS in the sample was 32% (n=174), and it was higher in females than in males (38% vs 27%, P=0.004). The age- and gender-adjusted odds ratio of MS increased with the level of SDB in a dose-response fashion (Table 1). Participants with moderate or severe SDB were more than 5 times as likely as those with no evidence of SDB to have MS. Adding markers of autonomic or neuroendocrine function to the model (norepinephrine, cortisol, heart rate variability) did not substantially alter these estimates. On the other hand, when BMI was

added to the model, the odds ratios reflecting the association between SDB and metabolic syndrome were weaker but remained statistically significant.

Discussion

In the present cross-sectional analysis, we found that SDB is strongly associated with the prevalence of metabolic syndrome. Our results are consistent with previous reports on the association of SDB with diabetes and insulin resistance.[8-11] They are also consistent with a recent experimental study in 118 nondiabetic subjects, which showed that SDB is associated with a delayed decline in glucose levels following a glucose injection and with decreased insulin sensitivity.[23]

The association in our study appears to be independent of markers of sympathetic and HPA axis activation, which have been postulated as potential mechanisms,[18] but was weakened after additional adjustment for BMI. The latter, however, might be the result of overadjustment and co-linearity stemming from the strong correlation between BMI and waist circumference, 1 of the components of the metabolic syndrome definition.

Conclusion

These results add to the evidence suggesting that metabolic disturbances might be 1 of the pathways for the cardiovascular effects of SDB. Along with evidence that the relation between sleep disorders and obesity might be bi-directional,[24-25] they also support the notion that SDB might be 1 of the components of the MS, constituting a cluster that has been termed “syndrome Z.”[13]

Acknowledgments

The authors thank Diane Austin and Laurel Finn for their assistance with data management, the rest of the WSCS staff for their work, and the WSCS participants for their longstanding commitment.

Funding/Support: This study was supported by the National Heart, Lung, and Blood Institute (NHLBI) grant R01-HL0750350.

References

1. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287(3):356–359. [PubMed: 11790215]
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328(17):1230–1235. [PubMed: 8464434]
3. Olson LG, King MT, Hensley MJ, Saunders NA. A community study of snoring and sleep-disordered breathing. prevalence. Am J Respir Crit Care Med 1995;152(2):711–716. [PubMed: 7633731]
4. Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. Prevalence of sleep-disordered breathing in ages 40-64 years: a population-based survey. Sleep 1997;20(1):65–76. [PubMed: 9130337]
5. Young T, Peppard P, Palta M, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med 1997;157(15):1746–1752. [PubMed: 9250236]
6. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342(19):1378–1384. [PubMed: 10805822]
7. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283(14): 1829–1836. [PubMed: 10770144]
8. Coughlin S, Calverley P, Wilding J. Sleep disordered breathing—a new component of syndrome X? Obes Rev 2001;2(4):267–274. [PubMed: 12119997]

9. Stoohs RA, Facchini F, Guilleminault C. Insulin resistance and sleep-disordered breathing in healthy humans. Am J Respir Crit Care Med 1996;154(1):170–174. [PubMed: 8680675]
10. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002;165(5):670–676. [PubMed: 11874812]
11. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 2004;160 (6):521–530. [PubMed: 15353412]
12. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 2000;284(23):3015–3021. [PubMed: 11122588]
13. Wilcox I, McNamara SG, Collins FL, Grunstein RR, Sullivan CE. "Syndrome Z": the interaction of sleep apnoea, vascular risk factors and heart disease. Thorax 1998;53(Suppl 3):S25–S28. [PubMed: 10193357]
14. Levinson PD, McGarvey ST, Carlisle CC, Eveloff SE, Herbert PN, Millman RP. Adiposity and cardiovascular risk factors in men with obstructive sleep apnea. Chest 1993;103(5):1336–1342. [PubMed: 8486007]
15. Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J. Snoring and sleep apnea in men: association with central obesity and hypertension. Int J Obes Relat Metab Disord 1993;17(9):533–540. [PubMed: 8220656]
16. Grunstein RR, Stenlof K, Hedner J, Sjostrom L. Impact of obstructive sleep apnea and sleepiness on metabolic and cardiovascular risk factors in the Swedish Obese Subjects (SOS) Study. Int J Obes Relat Metab Disord 1995;19(6):410–418. [PubMed: 7550526]
17. Ip MS, Lam KS, Ho C, Tsang KW, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. Chest 2000;118(3):580–586. [PubMed: 10988175]
18. Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. J Appl Physiol 2005;99 (5):1998–2007. [PubMed: 16227461]
19. Young T, Palta M, Peppard PE, Nieto FJ, Hla KM. Understanding the burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort Study. WMJ 2009;108(5):246–249. [PubMed: 19743755]
20. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: 18-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31(8):1071–1078. [PubMed: 18714778]
21. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486–2497. [PubMed: 11368702]
22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412–419. [PubMed: 3899825]
23. Punjabi NM, Beamer BA. Alterations in glucose disposal in sleep-disordered breathing. Am J Respir Crit Care Med 2009;179(3):235–240. [PubMed: 19011148]
24. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004;1(3):e62. [PubMed: 15602591]
25. Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 2008;31(5):619–626. [PubMed: 18517032]

Table 1

Odds Ratio of Metabolic Syndrome According to Sleep Disordered Breathing Severity, Wisconsin Sleep Cohort, n=546

	Mild SDB (AHI 5-14.9)		Moderate/severe SDB (AHI ≥15 or CPAP)	
	Odds Ratio	**95% Confidence Limits**	**Odds Ratio**	**95% Confidence Limits**
Adjusted for age, sex	4.0	2.6, 6.3	5.3	3.2, 8.8
plus urinary norepinephrine	3.9	2.5, 6.2	5.0	2.9, 8.3
plus urinary cortisol	3.9	2.4, 6.2	5.3	3.1, 9.8
plus heart rate variability	4.1	2.5, 6.5	4.5	2.7, 7.8
plus body mass index	2.5	1.5, 4.2	2.2	1.2, 3.9

Abbreviations: SDB, sleep disordered breathing; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure.