

Longitudinal Association of Sleep-Related Breathing Disorder and Depression

Paul E. Peppard, PhD; Mariana Szklo-Coxe, PhD; K. Mae Hla, MD; Terry Young, PhD

Background: Sleep-related breathing disorder (SRBD) and depression have each been independently associated with substantial morbidity, impairment, and disability. The development of clinical strategies for screening and managing depression in patients with SRBD requires elucidation of the association between the 2 conditions. This population-based epidemiological study assesses SRBD as a longitudinal predictor of depression.

Methods: Men (n=788) and women (n=620) randomly selected from a working population were evaluated for SRBD by in-laboratory polysomnography and for depression by the Zung depression scale. Results of multiple studies, performed at 4-year intervals, were available for most participants. Sleep-related breathing disorder was characterized by the apnea-hypopnea index (AHI; events per hour) categories: AHI=0, no SRBD; $0 < \text{AHI} < 5$, minimal SRBD; $5 \leq \text{AHI} < 15$, mild SRBD; and $\text{AHI} \geq 15$, moderate or worse SRBD. Depression was defined as a score of 50 or higher on the Zung scale or use of antidepressants. Potential confounding, interacting, and mediating factors were assessed by clinical measurements and questionnaires.

Results: In purely longitudinal models, an increase of 1 SRBD category (eg, from minimal to mild SRBD) was associated with a 1.8-fold (95% confidence interval, 1.3-2.6) increased adjusted odds for development of depression. In adjusted models combining longitudinal and cross-sectional associations, compared with participants with no SRBD, the odds for development of depression were increased by 1.6-fold (95% confidence interval, 1.2-2.1) in participants with minimal SRBD, by 2.0-fold (95% confidence interval, 1.4-2.9) in participants with mild SRBD, and by 2.6-fold (95% confidence interval, 1.7-3.9) in those with moderate or worse SRBD.

Conclusion: Our longitudinal findings of a dose-response association between SRBD and depression provide evidence consistent with a causal link between these conditions and should heighten clinical suspicion of depression in patients with SRBD.

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SLEEP-RELATED BREATHING DISORDER (SRBD) is a highly prevalent condition characterized by repeated episodes of high-resistance breathing, reduced breathing (hypopnea events), and breathing pauses (apnea events) during sleep. The disorder is associated with multiple sequelae including cardiovascular disease and impaired daytime functioning.¹ Like SRBD, depression is prevalent in adults in the United States, is related to a variety of comorbid conditions and impaired functioning, and exacts a substantial public health burden.²⁻⁴ The high prevalence of SRBD and depression in the general public makes urgent the characterization of causal associations, if present, between the 2 conditions. Characterization of the relationship of SRBD to depression can, for example, guide screening for depressive symptoms in patient populations with SRBD, suggest strategies for managing SRBD-related depression, and alert clinicians about the possibility of untreated depression complicating adherence to SRBD mitigation strategies and treatments such as weight loss and use of continuous positive airway pressure devices.

Clinical investigations of depression or depressive symptoms in patients with SRBD⁵⁻⁷ and of SRBD in patients with depression^{8,9} have suggested a relation between SRBD and depression.¹⁰⁻¹² Most clinical studies report positive associations between SRBD and depression, with variation in findings attributed to differing methods and diagnostic criteria for the 2 conditions.^{13,14} Improvement in depression after treatment of SRBD by continuous positive airway pressure provides evidence consistent with a causal association.^{5,15,16} Proposed mechanisms for an association include the sleep fragmentation, intermittent hypoxia, daytime sleepiness, and fatigue that accompany SRBD.^{6,13,15,17} Sleep fragmentation affects mood,¹⁸ worsens psychological symptoms,⁶ and is hypothesized to

Author Affiliations:
Departments of Population Health Sciences (Drs Peppard, Szklo-Coxe, and Young) and Medicine (Dr Hla), University of Wisconsin–Madison.

increase depressive symptoms via disruption of slow wave sleep and sleep maintenance.¹²

Valid inferences based on SRBD-depression associations in clinical samples are difficult, given the high prevalence of comorbid conditions, because of potential referral biases in patient populations, a limitation exacerbated in that 80% of existing SRBD in the general population remains undiagnosed.¹ To our knowledge, only 1 previous study, reporting a positive association of self-reported SRBD and depression (based on a phone survey), has used a population-based sample.¹⁹ We are unaware of any population-based, longitudinal studies of polysomnographically assessed SRBD as a risk factor for depression. We sought to investigate this association in 1408 adults, most having multiple SRBD and depression evaluations, participating in the Wisconsin Sleep Cohort Study, a population-based investigation of causes and consequences of SRBD. In this article, we examine the hypothesis that SRBD is associated with depression (depressive symptoms or use of antidepressant agents) in a dose-response fashion. We also examine the effect of adjustment for potential confounding, interacting, or mediating factors including sex, age, and body habitus; medication use and comorbid conditions; insomnia and daytime sleepiness; and other sleep-related, lifestyle, and sociodemographic factors.

METHODS

PARTICIPANTS

Informed consent documents and study protocols, described in detail elsewhere,²⁰ for the ongoing Wisconsin Sleep Cohort Study were approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. In 1988, employees of 5 Wisconsin state agencies, aged 30 to 60 years, were surveyed by mail about sleep habits and problems. From these data, a sampling frame was constructed, and 2884 randomly selected respondents were invited to participate in the Wisconsin Sleep Cohort Study. As of May 2005, there were 1524 eligible participants with at least 1 adequate sleep study (53% of those invited for baseline studies). The primary reported reason for nonparticipation was the burden of sleeping overnight in a sleep laboratory.

Participants undergo sleep studies at the University of Wisconsin General Clinical Research Center at 4-year intervals. Currently, 1 to 4 sleep studies are available per participant. The follow-up rate, calculated from average rate of refusal to participate in follow-up studies, is approximately 80%, although recruitment continues to accrue follow-up studies.

For this analysis, participants were excluded if they used continuous positive airway pressure therapy to treat SRBD on the evening of the sleep study (0.7% of studies) or had missing depression data (0.8%) or key covariate information (6.2%). The final sample was 1408 participants (788 men and 620 women) with 3202 sleep studies (449 participants with 1 study, 382 with 2 studies, 319 with 3 studies, and 258 with 4 studies).

MEASUREMENTS

Overnight studies include polysomnography and other clinical assessments including body mass index (calculated as weight in kilograms divided by height in meters squared). Data on medical history including diabetes, cardiovascular disease, stroke, and

hypertension; medication use; alcohol use (drinks per week); smoking habits (current and past cigarette packs per week); age; educational achievement; and exercise habits (hours per week) are obtained by means of interviews and questionnaires. The frequency of common sleep problems including the insomnia symptoms of difficulty falling asleep and getting back to sleep after awakening, and waking repeatedly throughout the night were reported as occurring never, rarely (1-2 times per month), sometimes (3-5 times per month), often (5-14 times per month), and always or almost always (15 times or more per month). Participants were also asked separate questions about whether either fatigue or an uncontrollable urge to fall asleep (excessive daytime sleepiness) during a typical day interfered with activities of daily living, work, mood, or relationships.

The Zung self-report depression scale,^{21,22} a 20-item survey, was used to assess depressive symptoms. The scale ranges from 25 to 100, with scores lower than 50 indicating normal, 50 to 59 indicating mild depression, and 60 or higher indicating moderate or more severe depression. The Zung scale contains 2 sleep-related items: "I have trouble sleeping through the night" and "I get tired for no reason." Since these also can also be symptoms of SRBD and, thus, may create an inherent association between SRBD and depression,²³ they were excluded. The resulting Zung score was rescaled to retain the original range and cutoff points. Three similarly scaled Zung subscores using items assessing depressed affect, and somatic and psychological components²¹ were also analyzed.

Medication use, obtained by means of interview and questionnaire, was coded into pharmacological categories. These included classes of antidepressant drugs (selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors), hypnotic agents, benzodiazepines, stimulants, antihypertensive drugs, and other agents.

An 18-channel polysomnography system (polygraph model 78; Grass Instruments, Quincy, Mass) is used to assess sleep state, and respiratory and cardiac measurements. Sleep state is determined by electroencephalography, electro-oculography, and electromyography. Arterial oxyhemoglobin saturation, oral and nasal airflow, nasal air pressure, and thoracic cage and abdominal respiratory motion are used to assess SRBD events. Oxyhemoglobin saturation is recorded by pulse oximetry (Ohmeda Biox 3740; Englewood, Colo). Thermocouples (ProTec; Hendersonville, Tenn) are used to detect airflow. A pressure transducer (Validyne Engineering Corp, Northridge, Calif) is used to measure air pressure at the nares. Respiratory inductance plethysmography (Respirace; Ambulatory Monitoring, Ardsley, NY) is used to record thoracic and abdominal excursions. Sleep state and respiratory event scoring is performed by trained sleep technicians. Each 30-second epoch of the polysomnographic records is scored for sleep stage using conventional criteria²⁴ and for breathing events. Cessation of air flow for at least 10 seconds defines an apnea event. A discernible reduction in the sum of thoracic plus abdominal respiratory inductance plethysmography amplitude associated with a reduction in oxyhemoglobin saturation of 4% or more defines a hypopnea event. The mean number of apnea plus hypopnea events per hour of sleep defines the apnea-hypopnea index (AHI), our summary parameter of SRBD. Additional examined sleep parameters include sleep efficiency (time spent asleep divided by time in bed) and percentage of time in specific sleep stages (stages 1-4 and rapid eye movement sleep).

STATISTICAL ANALYSES

Analyses were performed with SAS software (version 8.02; SAS Institute Inc, Cary, NC). Two types of regression models were used to estimate odds ratios, associating categories of SRBD se-

Table 1. Key Descriptive Statistics* by SRBD Status and Sex†

Characteristic	SRBD Category‡				All
	None (AHI = 0 Events/h)	Minimal (0 < AHI < 5)	Mild (5 ≤ AHI < 15)	Moderate or Worse (AHI ≥ 15)	
Men (n = 788)					
Sleep studies	140 (8)	999 (55)	405 (22)	261 (14)	1805
Age, mean (range), y	46 (30-63)	50 (30-74)	53 (31-73)	54 (31-75)	51 (30-75)
Body mass index, mean (SD)‡	27 (4)	28 (4)	31 (5)	34 (6)	30 (5)
History of cardiovascular disease	3 (2)	55 (6)	39 (10)	33 (13)	130 (7)
Antidepressant use	7 (5)	66 (7)	25 (6)	20 (8)	118 (7)
Zung score ≥ 50 or antidepressant use	11 (8)	148 (15)	59 (15)	50 (19)	268 (15)
Zung score ≥ 60 or antidepressant use	7 (5)	72 (7)	28 (7)	20 (8)	127 (7)
Women (n = 620)					
Sleep studies	194 (14)	912 (65)	201 (14)	90 (6)	1397
Age, mean (range), y	46 (31-68)	50 (31-74)	54 (34-73)	54 (35-71)	50 (31-74)
Body mass index, mean (SD)‡	27 (6)	30 (7)	35 (8)	42 (10)	31 (8)
History of cardiovascular disease	2 (1)	28 (3)	10 (5)	8 (9)	48 (3)
Antidepressant use	15 (8)	166 (18)	41 (20)	25 (28)	247 (18)
Zung score ≥ 50 or antidepressant use	36 (19)	251 (28)	63 (31)	31 (34)	381 (27)
Zung score ≥ 60 or antidepressant use	18 (9)	177 (19)	44 (22)	26 (29)	265 (19)

Abbreviations: AHI, apnea-hypopnea index; SRBD, sleep-related breathing disorder.

*Statistics are reported using sleep studies as units of analysis.

†Data are given as number (percentage) unless otherwise indicated.

‡Calculated as weight in kilograms divided by height in meters squared.

verity with depression. Generalized estimating equation models²⁵ were fit to all available data, including multiple sleep studies per participant, when available. Resulting odds ratios represent weighted averages of cross-sectional and longitudinal associations between SRBD and depression while accounting for within-subject correlation due to the use of multiple sleep studies per participant.²⁶

Purely longitudinal models were fit using conditional (intra-subject) logistic regression²⁶ to estimate the increased likelihood of development of depression associated with progression of SRBD from one category to a more severe category during 4-year follow-up intervals. This approach also accommodates participants initially identified as having depression but no longer reporting depression at a later study visit. The conditional model implicitly controls for fixed within-person characteristics such as sex and genetic profile.²⁶ The mixed longitudinal-cross-sectional approach was used for most analyses because it used all available data (N=3202 studies) and matched closely the results of the purely longitudinal conditional models, which use only participants transitioning from not depressed to depressed, or vice versa, during 4-year intervals (n=259).

Sleep-related breathing disorder severity was categorized using AHI cutoff points: AHI=0 events per hour, no SRBD; 0 < AHI < 5, minimal SRBD; 5 ≤ AHI < 15, mild SRBD; and AHI ≥ 15, moderate or worse SRBD. The primary depression outcome variable was presence of mild or worse depressive symptoms (Zung score ≥ 50) or antidepressant use, which we refer to as depression. We performed supplemental analyses examining alternative outcomes: Zung score 50 or higher, excluding antidepressant users; Zung score 60 or higher or antidepressant use; Zung subscores 50 or higher for depressed affect, and somatic and psychological items; and the full Zung score including sleep-related items. We found no meaningful differences in analyses that included, vs excluded, these sleep-related items, but we maintained their exclusion as a conservative measure.

Covariates that substantially altered regression coefficients for SRBD were retained in final models. Interactions between covariates and SRBD were tested for statistical significance. We examined the effect of adjustment for possible mediators of an

SRBD-depression association, including excessive daytime sleepiness, fatigue, and polysomnographically assessed parameters such as sleep efficiency and time in rapid eye movement and slow wave sleep. We also assessed the effect of adjustment for insomnia symptoms and use of benzodiazepine medications, which may exacerbate SRBD.²⁷

RESULTS

Table 1 gives descriptive statistics by SRBD status and sex. The prevalence of mild or worse SRBD in men is approximately twice that in women. For example, 14% of SRBD assessments in men were moderate or worse (AHI ≥ 15) compared with 6% in women. Conversely, women report approximately twice the prevalence of depression (Zung score ≥ 50 or antidepressant use): 27% of women vs 15% of men. Among antidepressant users, most used selective serotonin reuptake inhibitors (64%) or tricyclic antidepressants (24%).

Table 2 gives results from purely longitudinal, within-subject models. During 4-year follow-up periods, there were 259 instances of participants transitioning from depressed to not depressed, or vice versa. Among these studies, an increase in SRBD to the next higher category (eg, from no SRBD to minimal SRBD) was associated with a 1.8-fold (95% confidence interval, 1.3-2.6; *P* = .002) increased odds for development of depression compared with unchanging SRBD (adjusted model, Table 2), controlling for age, body mass index, alcoholic drink consumption, and history of cardiovascular disease. Adjustment for other covariates did not affect the associations.

Table 3 gives the mixed longitudinal-cross-sectional associations between SRBD and depression. Participants demonstrated significant dose-response trends of increasing odds of depression with increasing SRBD

Table 2. Longitudinal Association of Change in SRBD Category With Change in Depression Status*

Model	Conditional Odds Ratio (95% Confidence Interval) for 4-Year Change in SRBD Category Predicting Change in Depression Status†		
	No 4-Year Change in SRBD Category (n = 150)	1-Category SRBD Transition (n = 94)‡	2-Category SRBD Transition (n = 15)§
Unadjusted	1.0	1.7 (1.2-2.3)	2.7 (1.4-5.3)
Adjusted for age, body mass index, alcoholic drink consumption, cardiovascular disease, and fixed within-subject factors such as sex	1.0	1.8 (1.3-2.6)	3.3 (1.6-6.9)

Abbreviations: AHI, apnea-hypopnea index; SRBD, sleep-related breathing disorder.

*N = 259 with changes in depression status.

†Change in depression status from a Zung score less than 50 and not using antidepressants to a Zung score of 50 or higher or use of antidepressants, or vice versa.

‡That is, from no SRBD (AHI = 0 events/h) to minimal SRBD ($0 < \text{AHI} < 5$) or from minimal SRBD to mild SRBD ($5 \leq \text{AHI} < 15$) or from mild SRBD to moderate or worse SRBD ($\text{AHI} \geq 15$), or vice versa.

§That is, from no SRBD to mild SRBD or from minimal SRBD to moderate or worse SRBD, or vice versa. One participant who changed depression status experienced a 3-category SRBD transition (ie, from AHI = 0 to $\text{AHI} \geq 15$).

severity. Fully adjusted models showed stronger associations than did unadjusted models, primarily reflecting the effect of adjusting for sex, because women are more likely to be classified as having depression but, on average, have less severe SRBD. While sex was an important confounding variable, there was no significant interaction ($P = .60$) between sex and SRBD.

The first model in **Table 4** gives adjustment (to the mixed longitudinal–cross-sectional models) for measures of sleepiness, fatigue, and sleep quality. These adjustments resulted in only minor and inconsistent changes in associations compared with the fully adjusted models in Table 3. The second model in Table 4 excludes antidepressant users. Associations between SRBD and depressive symptoms among nonusers of antidepressants is stronger than when antidepressant use is incorporated into the definition of depression. The final model in Table 4 demonstrates the associations of SRBD with moderate or more severe depressive symptoms (Zung score ≥ 60) or antidepressant use. This association was less strong than with mild or worse depression. Individual odds ratios were statistically significant, but an increasing dose-response trend was only marginally so.

Associations of SRBD and Zung questionnaire subscales (depressed affect, and somatic and psychological items) are given in **Table 5**. Some minor variations in associations were observed among the subscales, but no subscale was especially related to SRBD relative to the fully adjusted model in Table 3.

Table 3. Associations of SRBD and Depression (Zung Score ≥ 50 or Antidepressant Use)

Model	Odds Ratio (95% Confidence Interval) Predicting Depression*			P Value Trend†
	Minimal SRBD ($0 < \text{AHI} < 5$)	Mild SRBD ($5 \leq \text{AHI} < 15$)	Moderate or Worse SRBD ($\text{AHI} \geq 15$)	
Unadjusted	1.4 (1.1-1.9)	1.6 (1.2-2.3)	1.9 (1.3-2.7)	.01
Age- and sex-adjusted	1.6 (1.2-2.2)	2.0 (1.4-2.9)	2.5 (1.7-3.7)	<.001
Fully adjusted‡	1.6 (1.2-2.1)	2.0 (1.4-2.9)	2.6 (1.7-3.9)	<.001

Abbreviations: AHI, apnea-hypopnea index; SRBD, sleep-related breathing disorder.

*Reference category is no SRBD (AHI = 0 events/h; odds ratio = 1.0).

†P value for linear trend in the log of the odds ratios.

‡Fully adjusted models control for age, body mass index, antihypertensive medication use, education, history of cardiovascular disease, usual alcoholic beverage consumption, physical exercise habits, and intrasubject correlation owing to the use of multiple studies per participant.

Table 4. Supplemental Analyses: Association of Depression With SRBD

Model†	Odds Ratio (95% Confidence Interval) Predicting Depression*			P Value Trend‡
	Minimal SRBD ($0 < \text{AHI} < 5$)	Mild SRBD ($5 \leq \text{AHI} < 15$)	Moderate or Worse SRBD ($\text{AHI} \geq 15$)	
Zung score ≥ 50 or antidepressant use, additionally adjusted for excessive daytime sleepiness, fatigue, sleep efficiency, percent of sleep in REM and sleep stages 3 and 4	1.8 (1.3-2.4)	2.1 (1.4-3.1)	2.3 (1.5-3.6)	<.001
Zung score ≥ 50 ; antidepressant users excluded	1.7 (1.1-2.6)	2.5 (1.5-4.2)	3.2 (1.8-5.8)	<.001
Zung score ≥ 60 or antidepressant use	1.5 (1.1-2.2)	1.6 (1.0-2.5)	1.9 (1.1-3.2)	.06

Abbreviations: AHI, apnea-hypopnea index; REM, rapid eye movement; SRBD, sleep-related breathing disorder.

*Reference category is no SRBD (AHI = 0 events/h; odds ratio = 1.0).

†All models are adjusted for age, body mass index, antihypertensive medication use, education, history of cardiovascular disease, usual alcoholic beverage consumption, physical exercise habits, and intrasubject correlation owing to the use of multiple studies per participant.

‡P value for linear trend in the log of the odds ratios.

Table 5. Associations of Zung Depression Subscales and SRBD

Model†	Odds Ratio (95% Confidence Interval) Predicting Depression*			P Value Trend‡
	Minimal SRBD (0<AHI<5)	Mild SRBD (5≤AHI<15)	Moderate or Worse SRBD (AHI≥15)	
Depressed affect (scaled Zung score ≥50)	1.4 (1.1-1.7)	1.8 (1.4-2.4)	2.3 (1.6-3.2)	<.001
Somatic items (scaled Zung score ≥50)	1.6 (0.9-2.7)	2.5 (1.3-4.6)	1.7 (0.8-3.8)	.03
Psychological items (scaled Zung score ≥50)	1.7 (1.3-2.4)	1.7 (1.1-2.5)	2.6 (1.6-4.1)	.007

Abbreviations: AHI, apnea-hypopnea index; SRBD, sleep-related breathing disorder.

*Reference category is no SRBD (AHI = 0 events/h; odds ratio = 1.0).

†All models are adjusted for age, body mass index, antihypertensive medication use, education, history of cardiovascular disease, usual alcoholic beverage consumption, physical exercise habits, and intrasubject correlation owing to the use of multiple studies per participant.

‡P value for linear trend in the log of the odds ratios.

Adjustment for symptoms of insomnia and for hypnotic or benzodiazepine medication use had no effect on presented models. We found no evidence of important interactions between SRBD, depression, and sex, age, comorbid conditions, or other examined covariates. As a check for selection bias, we examined whether there was variation in associations according to study visit (1, 2, 3, or 4). The SRBD–visit interaction term was not significant ($P=.08$), although the SRBD–depression association estimated using only baseline study visit data ($n=1408$) demonstrated slightly stronger associations than those using all available data. Adjusted depression odds ratios for minimal, mild, and moderate or worse SRBD compared with no SRBD were, respectively, 1.9, 2.0, and 3.2 at baseline, compared with analogous odds ratios of 1.6, 2.0, and 2.6 from the fully adjusted model in Table 3.

COMMENT

In our population-based, longitudinal investigation, polysomnographically assessed SRBD was associated in a dose-response fashion with elevated odds for depression. In strictly longitudinal models, increased SRBD was strongly related to depression in persons who initially did not have depression but in whom depression developed. For example, persons initially without SRBD (AHI=0) but in whom minimal SRBD developed during a 4-year period are estimated to be at 80% greater odds for development of depression than those who remain without SRBD.

Mixed longitudinal–cross-sectional models (Tables 3 through 5) demonstrated dose-response associations between SRBD and depression that were closely comparable with the purely longitudinal models. These models allowed for a wider range of adjustments for covariates because of the enhanced study power available when between-subject comparisons of SRBD were fully exploited. Even minimal to mild SRBD was related to substantially elevated risk for depression: participants with mild SRBD were at approximately 60% greater odds for depression compared with participants without SRBD. Sleep-related breathing disorder was also associated with more severe depression (Zung score ≥60 or antidepressant use), though to a lesser degree.

In supplementary analyses, we did not find that further adjustment for insomnia, daytime sleepiness, fa-

tigue, use of hypnotic agents or benzodiazepines, or other comorbid conditions such as diabetes meaningfully altered associations. We also examined symptoms of SRBD, including excessive daytime sleepiness, fatigue, and polysomnographic features such as sleep efficiency and percent of time in slow wave sleep, as possible intermediaries of an SRBD–depression association. Contrary to our expectation, associations changed little with adjustment. Thus, unlike clinical studies,^{6,17} we found no evidence that these are strong explanatory factors. If SRBD is causally related to depression, it seems likely that pathways initiating with cardinal features of SRBD, for example, sleep fragmentation and intermittent hypoxia, are involved. However, potential mechanisms remain speculative and await research methods that can disentangle multiple correlated pathophysiologic consequences of SRBD.

Depressive symptoms in patients with SRBD have been described as part of a medical–depressive syndrome rather than primary depression^{12,28} and as part of an SRBD vegetative prototype⁵ or SRBD personality,^{5,12} characterized more by somaticism and cognitive items^{5,7,11} rather than the depressed affect found in typical depression.⁷ However, we did not find evidence that the SRBD–depression association reflects a specific depressive typology in the analyses of the depressed affect, and somatic and psychological components symptom subscales.

Our findings of an SRBD–depression association corroborate patient-based findings of the elevated comorbidity of SRBD and depression,^{7,8} a correlation between AHI and depression in depressed patients,⁹ and increased depressive symptoms with more severe SRBD.⁵ Our results are also consistent with those from the population-based study of Ohayon¹⁹ and extend those findings with the use of longitudinal data, polysomnographically measured SRBD, and depression constructs that exclude measures of sleep disturbance or sleepiness.

Our study has important strengths, including longitudinal data on a large nonclinical sample, high-quality SRBD assessment, and examination of a wide range of confounding factors. However, our assessment of an association of SRBD with depression may be limited by selection and measurement error biases and confounding due to unmeasured factors. The Wisconsin Sleep Cohort Study experiences some participant dropout, largely because of participant burden of sleeping overnight in a dedicated sleep

laboratory. Among participants invited for follow-up studies (a subset of baseline participants), follow-up rates are approximately 80%, depending on study visit. Associations did not statistically vary according to study visit. Slightly stronger associations were seen when only baseline sleep studies were examined, indicating that biases owing to study dropout, if present, may have led to slight underestimates of positive associations.

We used in-laboratory, technician-attended polysomnography, the diagnostic “gold standard,” to classify SRBD status. However, night-to-night variability and instrumentation errors are involved in the assessment of SRBD. These errors should, however, produce a bias toward a diminished association²⁹ because they are unlikely to depend on depression status.

Limitations of the Zung depression scale include its reliance on self-reported symptoms rather than clinical psychiatric evaluation and that its correspondence to a diagnosis of major depressive disorder is, to our knowledge, unknown. Nevertheless, its strengths include a high correlation with clinical evaluation of patients^{21,22} and wide use in epidemiological investigations. Furthermore, depressive symptoms measured by psychometric scales rather than clinical assessment have typically been examined in clinical studies of patients with SRBD,^{5,11,30-32} and even minor, subclinical depression is importantly associated with a range of adverse outcomes including increased health service use and psychosocial impairment.²

Antidepressant use was relatively common in our sample (7% of men and 18% of women), and we incorporated it into our definition of depression. That is, persons using antidepressants were classified as having depression regardless of their Zung scale responses because the medications might, as intended, improve symptoms. However, participants may misreport the use of such medications or use them for purposes unrelated to depression. When antidepressant use was removed from our depression definition, associations between SRBD and Zung scale-defined depression were slightly stronger. Thus, our definition that includes antidepressant use is conservative and not likely to have spuriously resulted from misclassification of individuals without depression who reported using antidepressants.

Even highly prevalent mild SRBD, found in 24% of men and 9% of women,²⁰ was substantially related to our measure of depression. Our findings of an important longitudinal association of SRBD with depression expands the well-established role of SRBD as a risk factor for multiple adverse outcomes such as hypertension, cardiovascular disease, and daytime sleepiness, among others.¹ We recommend that future research examine the potential for synergistic amplification of morbidity, disability, and impairment related to SRBD and depression in patients with both conditions. Based on our present results and others' previous findings, clinicians should be aware of the enhanced probability of the co-occurrence of SRBD and depression in patients with either condition, that consequences of SRBD may include suboptimal mental health, and that medical treatment (eg, continuous positive airway pressure therapy) or behavioral modification of SRBD (eg, weight loss) may help mitigate or prevent depressive symptoms in patients with SRBD.

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Correspondence: Paul E. Peppard, PhD, Department of Population Health Sciences, University of Wisconsin–Madison, 1300 University Ave, Room 1036, Madison, WI 53706 (ppeppard@wisc.edu).

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Call for Papers

Preventive Intervention Theme Issue

In an effort to encourage research on the topic, a special issue of the ARCHIVES will be devoted to papers on the topic of preventive interventions. Specifically, we are interested in receiving papers focused on the efficacy or effectiveness of interventions. While we will primarily concentrate on randomized controlled trials that assess efficacy, we will also consider papers that employ observational methods of investigation or economic analyses that reasonably estimate theoretical cost-effectiveness of interventions. All kinds of preventive interventions are welcomed—those in the community, in medical offices, in clinics, and in hospitals or other advanced-care settings. However, priority for this theme issue will be given to those papers that are applicable to the practicing internist.

Papers for the preventive intervention theme issue should be submitted no later than October 1, 2006. Pending completion of our peer review process, papers that are accepted for publication will appear in an issue of the *Archives of Internal Medicine* in the first half of 2007.