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Original Contribution

Prospective Associations of Insomnia Markers and Symptoms With Depression

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Whether insomnia, a known correlate of depression, predicts depression longitudinally warrants elucidation. The authors examined 555 Wisconsin Sleep Cohort Study participants aged 33–71 years without baseline depression or antidepressant use who completed baseline and follow-up overnight polysomnography and had complete questionnaire-based data on insomnia and depression for 1998–2006. Using Poisson regression, they estimated relative risks for depression (Zung scale score $\geq$50) at 4-year (average) follow-up according to baseline insomnia symptoms and polysomnographic markers. Twenty-six participants (4.7%) developed depression by follow-up. Having 3–4 insomnia symptoms versus none predicted depression risk (age-, sex-, and comorbidity-adjusted relative risk (RR) = 3.2, 95% confidence interval: 1.1, 9.6). After multiple adjustments, frequent difficulty falling asleep (RR = 5.3, 95% confidence interval: 1.1, 27.9) and polysomnographically assessed (upper or lower quartiles) sleep latency, continuity, and duration (RRs = 2.2–4.7; *P*'s $\leq$ 0.05) predicted depression. Graded trends (*P*-trend $\leq$ 0.05) were observed with increasing number of symptoms, difficulty falling asleep, and difficulty returning to sleep. Given the small number of events using Zung $\geq$50 (depression cutpoint), a limitation that may bias multivariable estimates, continuous depression scores were analyzed; mean values were largely consistent with dichotomous findings. Insomnia symptoms or markers increased depression risk 2.2- to 5.3-fold. These results support prior findings based on self-reported insomnia and may extend similar conclusions to objective markers. Heightened recognition and treatment of insomnia may prevent subsequent depression.

depression; polysomnography; prospective studies; sleep; sleep initiation and maintenance disorders

Abbreviations: RR, relative risk; SD, standard deviation.

To date, studies of insomnia and depression have largely conceptualized insomnia as a clinical correlate or component of depression—that is, as a prodromic sign or symptom (1, 2), a precursor (3, 4), or its most persistent residual symptom after treatment (5). Insomnia's strong cross-sectional association and high comorbidity with depression and other mood disturbances have been well-established in epidemiologic studies (6–12). However, insomnia is increasingly being recognized as a possible contributor to the development of depression (13).

Elucidating insomnia's prospective relation to subsequent depression could lead to improved recognition, treatment, and prevention of depression, which is projected to rank as the second-leading cause of lost disability-adjusted life years after ischemic heart disease by 2020 (14). Both insomnia (15) and depression (16, 17) are highly prevalent, persistent, undertreated, and costly (18) disorders related to significant functional impairment and disability (17–19), including increased absenteeism (15, 20) and health-care utilization (9, 17, 19).

Prior prospective studies have found that self-reported insomnia predicts depression in varied populations (3, 12, 13, 21–29), including younger (12, 26, 27) and older (13, 28, 29) adults. However, with scant exceptions (12, 22, 25–28), most studies of insomnia and depression have been limited to shorter follow-up periods—1 year (3, 9, 10, 21, 23, 24) or 2 years (29, 30)—and all have been limited to self-reported assessment of insomnia. Furthermore, while electroencephalographic sleep abnormalities reflecting insomnia (31–34) have been cross-sectionally correlated with depression in

psychiatric populations, prospective relations of polysomnographic insomnia markers to depression have not been studied in clinical or population-based samples. Thus, insomnia's longitudinal consequences are still poorly understood (35).

We investigated whether objective markers and self-reported symptoms of insomnia would predict depression symptoms at 4-year follow-up in a large population-based sample that was free of depression at baseline. We hypothesized that polysomnographic markers of insomnia—namely, decreased sleep duration, poorer sleep continuity, longer sleep latency, and increased insomnia symptom frequency—would predict the incidence of depression in a graded (''dose-response'') fashion.

MATERIALS AND METHODS

Participants and data collection

The study procedures were approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. The sample comprised participants enrolled in the ongoing Wisconsin Sleep Cohort Study, previously described (36). Participants provided signed informed consent. A stratified random sample of previously surveyed Wisconsin state employees ($n = 2,884$) was invited to participate in a baseline overnight sleep study, and 53% ($n = 1,533$) agreed; the primary reported reason for nonparticipation was the burden of sleeping overnight in a sleep laboratory. Overnight protocols included nocturnal polysomnography at participants' usual sleep times; clinical assessments, including calculation of body mass index (weight (kg)/height $(m)^2$); administration of a depression scale; and completion of a questionnaire regarding health history, sleep habits, and insomnia symptoms. Approximately every 4 years after baseline studies, participants are invited to undergo follow-up examinations; by June 2008, there was an average follow-up participation rate of 80%.

Of 1,533 cohort participants, 787 were initially eligible for the present analyses, since they had completed overnight polysomnography between 1998 and 2002 and had undergone follow-up polysomnography 3–5 years later (average, 4 years) and had complete baseline and follow-up data on depression and self-reported insomnia for the period 1998–2006. Insomnia symptoms were first assessed during overnight protocols in 1998. For examination of incident depression, participants who had symptoms of depression (Zung score ≥ 50) or were taking antidepressant medication at baseline ($n = 192$) were excluded from the current analyses, which left 595 participants at risk for subsequent depression. Additionally, 40 participants who, at follow-up, were on antidepressant medication yet reported no depression symptoms (Zung score <50) were excluded from analyses, to limit potential bias related to overestimation of insomnia's association with depression. Thus, the final inception cohort for this analysis constituted 555 participants.

Insomnia

Self-reported symptoms. The health questionnaire included 4 items on insomnia: difficulty in getting to sleep (referred to as difficulty in falling asleep or initiating sleep), waking up repeatedly during the night (repeated nocturnal awakenings), waking up too early in the morning and being unable to get back to sleep (awakening too early), and waking up during the night and having a hard time getting back to sleep (difficulty getting back asleep). Response categories were never or rarely (once/month), sometimes (2–4 times/month), often (5–15 times/month), and almost always (16–30 times/month). Each item was dichotomized into often/almost always (≥ 5 times/month) versus sometimes/less (<5 times/month), and then a number-of-symptoms (0, 1, 2, 3, or 4) variable was created at the frequency of often/almost always. Another 4-level variable was created for individual symptom frequency: 0 represented having all symptoms never/rarely; 1, having the symptom of interest sometimes; and 2, having the symptom of interest often/almost always. The category ''any other symptom sometimes or more often'' differentiated the symptom of interest from other symptoms.

Polysomnographically assessed markers. Data on sleep latency, waking after sleep onset, sleep efficiency, and total sleep time were obtained during the overnight protocol by means of full 18-channel polysomnography (Grass Heritage PSG Digital Sleep System with model 15A54 amplifiers; Grass Technologies, West Warwick, Rhode Island) including electrooculography, electroencephalography, and electromyography. Sleep stage for each 30-second epoch was scored by technicians, according to conventional criteria (37). ''Sleep latency'' was defined as amount of time (minutes) from ''lights off'' to the first of 3 consecutive epochs of stage 1 sleep or the first epoch of any other stage of sleep; ''waking after sleep onset'' as the amount of time (minutes) spent awake after first sleep onset; ''total sleep time'' as the total amount of time spent sleeping (minutes); and ''sleep efficiency'' (%) as the proportion of total sleep time out of total duration of time in bed from ''lights out.''

Outcome: depression

On the same evening as the overnight studies, participants completed the Zung Self-Rating Depression Scale (38) and provided information on regularly taken medications, including antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, or other). Scores on the 20-item Zung scale range from 25 to 100. Scores less than 50 indicate ''normal'' (not depressed), and scores greater than or equal to 50 are considered indicative of depression (37). We used this standard cutpoint for our population-based sample rather than a higher threshold (perhaps better-suited for a clinical sample). The original instructions, ''how you have been feeling *in the past few days*,'' were modified, and participants were instructed, ''Please read each of the following statements and place an X in the box which best describes how you feel *in general* from day to day.'' For these analyses, we used a ''modified'' Zung scale that excluded 2 items (''I have trouble sleeping through the night'' and ''I get tired for no reason'') which may indicate insomnia and result in a built-in association between insomnia and depression. After exclusion of these items, the score was

rescaled for comparability to the original 20-item Zung scale, as previously reported (39).

Covariates included age, sex, clinically assessed body mass index, and variables from a self-administered health questionnaire: moderate/greater alcohol consumption ($\geq$2 daily drinks of beer, wine, or hard liquor vs. less); cigarette smoking (current, past, or never); caffeine consumption (0, 1–2, 3–4, or $\geq$5 caffeinated beverages daily); use of hypnotic agents; and self-report of any physician-diagnosed chronic illness (coronary artery disease, congestive heart failure, angina, hypertension, stroke, diabetes, asthma, emphysema, thyroid condition, epilepsy, arthritis, or back pain). Sleep-disordered breathing status was assessed by polysomnography and summarized as numbers of apnea events (complete cessation of nasal and oral airflow for $>$10 seconds) and hypopnea events (decrease in respiratory effort associated with a $>$4% drop in arterial oxygen saturation) per hour of sleep (apnea-hypopnea index). Using conventional cutpoints (37), apnea-hypopnea index was categorized as $<$5 (little or no sleep-disordered breathing), 5–$<$15 (mild), or $\geq$15 (moderate or worse).

Statistical analysis

In descriptive analyses, we examined average continuous baseline Zung scores in participants with Zung scores less than 50 to ensure that associations between insomnia and depression were not attributable to participants with insomnia symptoms or markers having subthreshold depression (higher scores near 50). Using analysis of variance, we tested for any (F test) or pairwise (t tests) significant differences between mean continuous Zung scores less than 50 (at baseline) and objectively measured (sleep latency and quartiles of total sleep time) and self-reported (number of symptoms) insomnia.

In unadjusted analyses, categorical differences were tested using the Pearson χ^2 test and the Mantel-Haenszel χ^2 trend test. Regression models were used to estimate adjusted relative risks and 95% confidence intervals for depression with respect to insomnia at baseline (1998–2002). Persons with incident depression symptoms were included in all analyses, irrespective of antidepressant use at follow-up. Depression at follow-up was only assessed at 4 years, on average. Analyses, carried out with Proc Genmod in SAS (SAS Institute Inc., Cary, North Carolina), assumed a Poisson distribution with robust error variances (40), a log-link function, and an unstructured variance-covariance structure. A P value less than or equal to 0.05 (2-sided) was considered significant.

Relations of polysomnographic markers to subsequent depression were initially assessed using quartile groupings obtained from the overall cohort (quartile cutpoints (25th percentile, median, 75th percentile): sleep latency (minutes)—4, 8, and 14; waking after sleep onset (minutes)—31, 48.5, and 78.5; sleep efficiency—78%, 85%, and 91%; total sleep time (minutes)—334, 374.5, and 409). Because linear relations were present only for total sleep time, we constructed binary variables for the remaining markers. For sleep latency and waking after sleep onset, the uppermost quartiles ($\geq$14 minutes and $\geq$79 minutes, respectively) represented marker presence; the other quartiles combined constituted the reference categories. Sleep efficiency was represented by the lowest quartile ($<$78%) and its referent by the upper quartiles combined. Given total sleep time quartiles' graded relation to depression and the significant ($P \leq 0.02$) linear relation observed when total sleep time was examined continuously, its quartiles were not combined.

Adjusted models included potentially confounding variables in 2 stages: 1) age, sex, and chronic health conditions; and 2) alcohol, smoking, caffeine, hypnotics, and body mass index. Two-way interactions of insomnia with age and sex were assessed.

Linear trends (with insomnia examined as a continuous variable) in the logarithms of relative risks were tested for significance in Poisson regression models. In individual insomnia symptom models, linear trends were tested for the reference, symptom-of-interest ''sometimes,'' and symptom-of-interest ''often/always'' categories (the ''other symptom'' category was excluded from trend tests) with adjustment for age, sex, and comorbidity but not full adjustment, because of nonconvergence of insomnia categories in these models.

In secondary analyses, after confirming the normality of continuous depression scores at follow-up and of depression's residuals, we conducted linear regression analysis to examine continuous depression scores (modified Zung scale) at follow-up for every insomnia variable modeled separately, with age, sex, and comorbidity adjustments as in the discrete-outcome (Zung score $\geq$50) models. Persons with depression (according to the modified Zung scale or antidepressant use) at baseline were excluded from these analyses; thus, all analyses were conducted in the same inception sample ($n = 555$). Overall F tests for insomnia variables were conducted first; if results were significant, individual t tests were conducted.

We examined sleep-disordered breathing as a potential confounder by adjusting for apnea-hypopnea index in regression models. Furthermore, we examined insomnia's association with depression symptoms after removing from the analyses participants with anxiety at baseline, defined by use of anxiolytic agents and/or a trait-anxiety score at or above the 75th percentile using the State-Trait Anxiety Inventory (41), which was self-administered during overnight studies. The cutpoint for anxiety (Trait Anxiety score $\geq$39) was defined by the overall cohort's 75th percentile. The correspondence of insomnia symptoms to polysomnographic measures was assessed for the same overnight study among 337 participants who reported that sleep obtained during their polysomnography study was typical of, or not much different from, their usual sleep.

RESULTS

The average follow-up period was 3.8 years (standard deviation (SD), 0.4). Of the initial subset ($n = 787$), 54% of participants were male; the mean age was 53.6 years (SD, 7.7; range, 33–71). Baseline characteristics are shown in Table 1. Relatively high proportions of self-reported insomnia symptoms (e.g., 34% for repeated nocturnal awakenings)

Table 1. Baseline Characteristics of Participants[a] ($n = 555$), Wisconsin Sleep Cohort Study, 1998–2002

Characteristic	No.	%	Mean (SD)
Age, years			54.0 (7.7)
Male sex	333	60.0	
Body mass index[b]			31.1 (6.7)
Current smoking	47	8.5	
Consumption of >4 caffeinated drinks/day	101	18.2	
Consumption of >1 alcoholic drink/day	29	5.2	
Use of hypnotic medication	11	2.0	
Zung depression score			36.7 (5.6)
Self-reported insomnia symptoms			
No. of insomnia symptoms experienced often or almost always			
0	307	55.3	
1	154	27.8	
2	59	10.6	
3 or 4	35	6.3	
Difficulty falling asleep (often/almost always)	54	9.7	
Repeated nocturnal awakenings (often/almost always)	188	33.9	
Difficulty getting back to sleep during the night (often/almost always)	93	16.8	
Early morning awakening (often/almost always)	101	18.2	
Polysomnographically assessed markers of insomnia			
Waking after sleep onset, minutes			68.4 (44.1)
Total sleep time, minutes			375.5 (62.8)
Sleep latency, minutes			11.6 (13.0)
Sleep efficiency, %			81.9 (10.8)
Chronic health conditions			
Asthma[c]	64	11.5	
Diabetes[c]	62	11.2	
Hypertension[c]	187	33.7	
Cerebrocardiovascular disease[c]	49	8.8	
Other conditions[d]	230	41.4	

Abbreviation: SD, standard deviation.

[a] The baseline sample excluded participants who reported depressive symptoms (defined as modified Zung depression scale score ≥50) or use of antidepressant medication.

[b] Weight (kg)/height (m)^2.

[c] Self-report of a physician's diagnosis.

[d] Self-report of a physician's diagnosis of epilepsy, emphysema, thyroid disease, arthritis, or back pain.

and polysomnographically defined markers were observed. Twenty-six participants (4.7%) in the final inception cohort had developed depression symptoms (Zung score ≥50) by follow-up.

Baseline mean depression scores (Zung score <50) in participants who developed (Zung score ≥50) or did not develop (Zung score <50) depression were similar: 40.0 (SD, 6.07) and 36.6 (SD, 5.5), respectively. Average scores changed (follow-up minus baseline) by +13.4 points versus only −0.01 points for participants developing, versus not developing, depression. Baseline average depression scores in participants without depression (Zung score <50) were not significantly different ($P = 0.74$) for decreasing total sleep time quartiles (Zung scores were 36 (quartile 4—longest, ''best'' total sleep time), 37 (quartile 3), 37 (quartile 2), and 34 (quartile 1—shortest, ''worst'' sleep time)) or increasing sleep latency (Zung scores were 37 (quartile 1—shortest, ''best''), 36 (quartile 2), 36 (quartile 3), and 37 (quartile 4—longest, ''worst'')). Despite statistical significance ($P < 0.0001$), average baseline Zung scores did not approach the 50 cutpoint for number of insomnia symptoms (36 for no symptoms, 37 for 1 symptom, 38 for 2 symptoms, and 38 for 3 or 4 symptoms).

Figure 1 shows the unadjusted incidence of depression by number of insomnia symptoms among participants who were free of depression symptoms and antidepressant use at baseline. Regardless of Zung depression scale (original or modified with 2 sleep-related items removed) and antidepressant use at follow-up, an increasing incidence of depression was observed across insomnia symptoms. This trend was significant for all categories (P-trend ≤ 0.02) except ''modified Zung score excluding antidepressant users at follow-up'' (P-trend = 0.06). Depression incidence for 3 or 4 symptoms was 3.2–3.6 times that for no symptoms (irrespective of exclusion of antidepressant users).

Insomnia symptoms

The number of symptoms occurring often/almost always (Table 2) was found to be associated with subsequent depression in a graded (''dose-response'') fashion (P-trend = 0.02) after adjustment for age, sex, and comorbidity; the relative risk for 3 or 4 symptoms was 3.23 ($P = 0.03$). Further adjustments attenuated this relation, though risk was still increased, and the overall trend remained significant (P-trend = 0.04).

Linear trends were observed for the relation of individual symptom frequency to incident depression symptoms (Figure 2) and were significant for increasing difficulty falling asleep (P-trend < 0.001) and increasing difficulty getting back asleep (P-trend = 0.02). After adjustment for age, sex, and comorbid conditions, increasing difficulty falling asleep and getting back asleep demonstrated significant graded trends for depression (P-trend = 0.01 and P-trend = 0.03, respectively) (Table 3). Repeated nocturnal and early morning awakenings demonstrated near-significant trends (P-trend = 0.07). Each symptom experienced ''often or always'' (versus all symptoms experienced ''never or rarely'') was related to a 3-fold or higher risk, though after full adjustment, risk was significant only for difficulty falling asleep (relative risk (RR) = 5.31; $P = 0.05$).

No significant at ($P \leq 0.05$) age or sex interactions were observed for individual symptoms or number of symptoms.

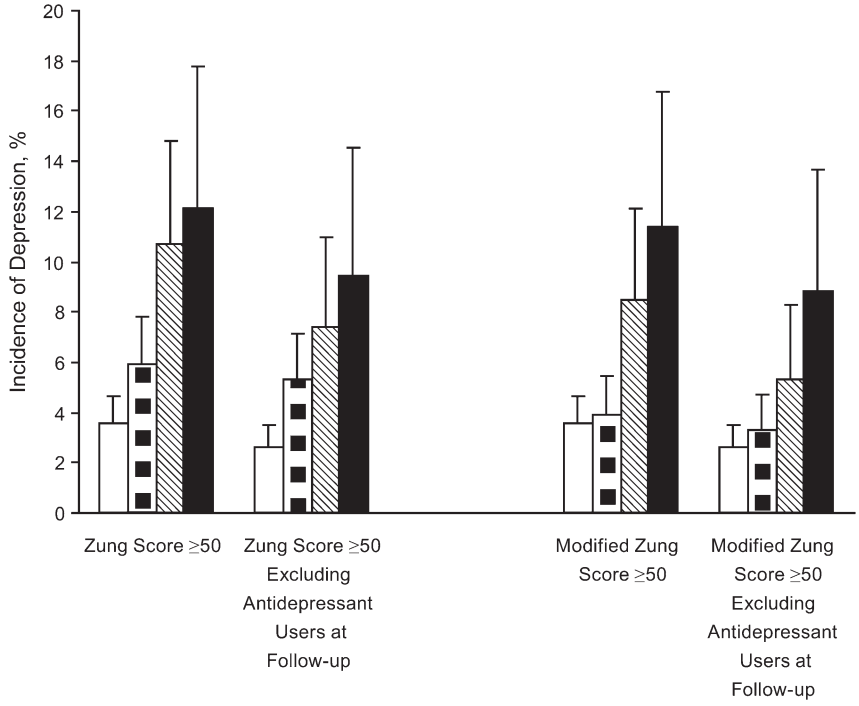

Figure 1. Incidence of depression symptoms (%) at 4-year follow-up (2002–2006), obtained using different classifications of depression, by number of insomnia symptoms at baseline (1998–2002) in Wisconsin Sleep Cohort Study participants (n = 542–685). White columns, no symptoms; columns, with squares, 1 symptom; striped columns, 2 symptoms; black columns, 3 or 4 symptoms. "Modified Zung score" refers to the Zung depression scale (38) rescored after exclusion of 2 items on insomnia and tiredness. P-trend values for the relation of number of insomnia symptoms to subsequent depression: for Zung score ≥50, P-trend = 0.006; for Zung score ≥50 excluding antidepressant users at follow-up, P-trend = 0.02; for modified Zung score ≥50, P-trend = 0.02; and for modified Zung score ≥50 excluding antidepressant users at follow-up, P-trend = 0.06. Bars, standard error.

Polysomnographic markers

Unadjusted depression risk was 2- to 3-fold higher for increased (uppermost quartile) sleep latency and waking after sleep onset and decreased (lowest quartile) sleep efficiency and total sleep time, versus the respective reference categories (Table 4). Significant associations persisted after additional adjustments, with the full adjustment expressed by significant relative risks between 2.2 and 4.7, and a graded pattern for total sleep time (P-trend = 0.03).

Secondary analyses

The significant relation of number of symptoms to incident depression, including its graded pattern (P-trend ≤ 0.05), was not altered by adding apnea-hypopnea index to the age-, sex-, and comorbidity-adjusted model (RR = 3.17, 95% confidence interval: 1.05, 9.61) or by excluding from the analyses participants with anxiety at baseline (RR = 3.70, 95% confidence interval: 1.22, 11.18).

Clinical polysomnographic cutpoints were examined in fully adjusted models. Sleep latency >30 minutes (vs. ≤30 minutes) (RR = 3.98) and sleep efficiency <80% (vs. ≥80%) (RR = 4.39) significantly ($P \leq 0.01$) predicted depression; total sleep time <360 minutes (vs. ≥360 minutes) (RR = 1.53) and waking after sleep onset >30 minutes (vs. ≤30 minutes) (RR = 1.10) did not.

Increasing mean sleep latency (polysomnographically assessed) was related to increasing frequency of self-reported difficulty falling asleep: 7.9 minutes—never (0 times/month), 9.3 minutes—rarely (once/month), 11.9 minutes—sometimes (2–4 times/month), 14.9 minutes—often (5–15 times/month), and 19.2 minutes—almost always (16–30 times/month). Increased mean waking after sleep onset (polysomnographically assessed) corresponded to increased self-reported frequency of nocturnal awakening: 7.9 minutes—never, 9.3 minutes—rarely, 11.9 minutes—sometimes, 14.9 minutes—often, and 19.2 minutes—almost always.

In our sample (n = 555), results based on mean continuous scores for depression at follow-up (Table 5) largely showed patterns similar to those based on a discrete outcome (Zung score ≥50), considered the clinical cutpoint (38). Mean depression values for 7 of 9 insomnia variables—number of symptoms, 4 individual symptoms, decreased sleep efficiency, and increased waking after sleep onset—were significantly increased upon follow-up and showed graded trends for all insomnia symptoms (P-trend ≤ 0.01). No associations were found for increased sleep latency and decreased total sleep time. Results remained unchanged after exclusion of antidepressant users from follow-up (n = 548).

Table 2. Relative Risk of Incident Depression[a] Symptoms at 4-Year Follow-up According to Number of Insomnia Symptoms[b] Reported at Baseline ($n = 555$), Wisconsin Sleep Cohort Study, 1998–2006

No. of Insomnia Symptoms[c]	Total No. of Participants	Incidence of Depression		Adjusted[d] RR[e]	95% CI	Fully Adjusted[f] RR[g]	95% CI
		No.	%				
0	307	11	3.58	1.00	Referent	1.00	Referent
1	154	6	3.90	1.12	0.43, 2.93	1.07	0.40, 2.90
2	59	5	8.47	2.62	0.92, 7.49	2.82	0.96, 8.21
3 or 4	35	4	11.43	3.23*	1.09, 9.57	2.49	0.83, 7.50

Abbreviations: CI, confidence interval; RR, relative risk.

* $P = 0.03$.

[a] Depression was defined as modified (without 2 sleep-related items) Zung depression scale score $\geq$50.

[b] Insomnia was defined as having any insomnia symptom (difficulty falling asleep, difficulty getting back to sleep after awakening during the night, waking up repeatedly during the night, or early morning awakening) at a frequency of "often or almost always" ($\geq$5 times/month).

[c] Participants who reported depressive symptoms (defined as modified Zung depression score $\geq$50) or use of antidepressant medication at baseline were excluded.

[d] Adjusted for age, sex, and chronic health conditions.

[e] $P = 0.02$ for linear trend in the logarithm of the relative risk.

[f] Adjusted for age, sex, chronic health conditions, alcohol consumption, cigarette smoking, caffeine consumption, use of hypnotic agents, and body mass index.

[g] $P = 0.04$ for linear trend in the logarithm of the relative risk.

DISCUSSION

Insomnia, whether assessed via polysomnographic markers or via self-report, was found to be a risk factor for depression symptoms at follow-up among participants who had been free of depression 4 years earlier in our population-based, observational study. Our study was unique in that we assessed both polysomnographic markers and self-reported symptoms of insomnia. Insomnia markers reflecting decreased sleep continuity and its symptoms, including number of symptoms and difficulty initiating sleep, predicted the occurrence of depression after adjustment for possible confounders. To our knowledge, significant graded associations between insomnia (increasing number of symptoms, difficulty initiating and maintaining sleep) and depression have not been previously reported. Our findings regarding self-reported insomnia's positive relation to depression are broadly consistent with results from most prospective epidemiologic studies conducted in various US and

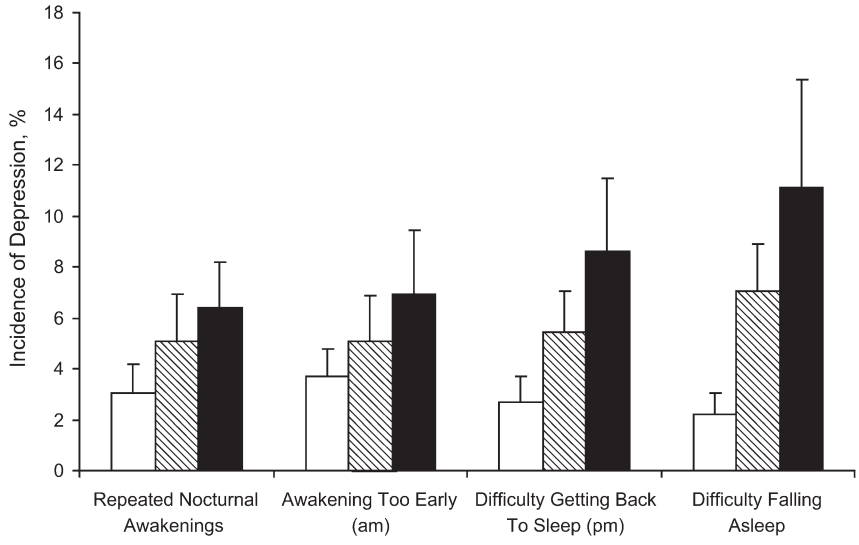

Figure 2. Incidence of depression symptoms (%) at 4-year follow-up (2002–2006) by frequency of insomnia symptoms at baseline (1998–2002) in Wisconsin Sleep Cohort Study participants ($n = 555$). White columns, never or rarely experienced symptom; striped columns, sometimes experienced symptom; black columns, often or almost always experienced symptom. "am," morning; "pm," night. Bars, standard error.

Table 3. Relative Risk of Incident Depression[a] Symptoms at 4-Year Follow-up According to Baseline Frequency of 4 Individual Insomnia Symptoms[b] ($n = 555$), Wisconsin Sleep Cohort Study, 1998–2006

Model, Insomnia Symptom, and Frequency[c]	Total No. of Participants	Incidence of Depression		Adjusted[d] RR	95% CI	Fully Adjusted[e] RR	95% CI
		No.	%				
Model 1: Difficulty falling asleep							
All symptoms "never/rarely"	100	2	2.00	1.00	Referent	1.00	Referent
Difficulty falling asleep "sometimes"	185	13	7.03	3.41	0.78, 15.00	3.08	0.74, 12.77
Difficulty falling asleep "often/always"	54	6	11.11	6.05**	1.18, 31.08	5.31*	1.05, 27.87
Any other symptom "sometimes/more often"	216	5	2.32	1.25	0.24, 6.62	1.22	0.24, 6.37
Model 2: Difficulty getting back/returning to sleep							
All symptoms "never/rarely"	100	2	2.00	1.00	Referent	1.00	Referent
Difficulty returning to sleep "sometimes"	202	11	5.45	2.95	0.63, 13.89	2.70	0.61, 11.94
Difficulty returning to sleep "often/always"	93	8	8.60	4.42	0.93, 20.90	4.06	0.87, 18.97
Any other symptom "sometimes/more often"	160	5	3.13	1.57	0.31, 8.00	1.45	0.28, 7.61
Model 3: Repeated nocturnal awakenings							
All symptoms "never/rarely"	100	2	2.00	1.00	Referent	1.00	Referent
Nocturnal awakenings "sometimes"	138	7	5.07	2.46	0.52, 11.68	2.21	0.46, 10.57
Nocturnal awakening "often/always"	188	12	6.38	3.40	0.74, 15.58	3.09	0.70, 13.58
Any other symptom "sometimes/more often"	129	5	3.88	2.10	0.40, 10.91	2.06	0.41, 10.28
Model 4: Early morning awakening							
All symptoms "never/rarely"	100	2	2.00	1.00	Referent	1.00	Referent
Early morning awakening "sometimes"	157	8	5.10	2.75	0.56, 13.48	2.42	0.52, 11.36
Early morning awakening "often/always"	101	7	6.93	3.79	0.78, 18.50	3.59	0.76, 16.84
Any other symptom "sometimes/more often"	197	9	4.57	2.26	0.49, 10.35	2.16	0.49, 9.66

Abbreviations: CI, confidence interval; RR, relative risk.

* $P = 0.05$; ** $P = 0.03$.

[a] Depression was defined as modified (excluding 2 sleep-related items) Zung depression scale score $\geq$50.

[b] Insomnia symptoms defined at a frequency of "never/rarely" refers to $\leq$1 occasion/month; "sometimes" refers to 2–4 times/month; "often/always" refers to $\geq$5 times/month; and "sometimes/more often" refers to $\geq$2 times/month. "Difficulty falling asleep" is also referred to as "difficulty initiating sleep." "Difficulty getting back to sleep" and "repeated nocturnal awakenings" are considered variables related to difficulty in maintaining sleep.

[c] Participants who reported depressive symptoms (defined as modified Zung depression score $\geq$50) or use of antidepressant medication at baseline were excluded.

[d] Adjusted for age, sex, and chronic health conditions.

[e] Adjusted for age, sex, chronic health conditions, alcohol consumption, smoking cigarettes, hypnotic use, caffeine consumption, and body mass index.

European populations (3, 12, 13, 21–24, 26–29), with a few exceptions (10, 25, 30) possibly due to the use of differing methods (e.g., insomnia definition or duration (12), sample characteristics, follow-up periods).

An important limitation of our study is that only 26 (4.7%) participants developed depression (defined as Zung score $\geq$50), since we emphasized specificity in our incident depression classification. Because the small number of outcome events (defined dichotomously) may have led to biased multivariable regression estimates and confidence intervals, we examined mean (continuous) depression values at follow-up to help address this limitation. Analyses based on mean scores were largely consistent with significant dichotomous results (based on the clinical cutpoint) and showed similar patterns. Fully adjusted multivariable regression results also resembled minimally adjusted or nonadjusted results. Nevertheless, larger study samples yielding a greater number of incident depression events may be warranted for confirmation of our findings.

The associations we found were not likely to have been due to subsyndromal depression in insomnia (scores near Zung's depression cutpoint). Average depression scores did not differ at baseline according to higher levels of, versus lower or absent, polysomnographic markers and were far from the depression cutpoint. For number of symptoms, depression scores were merely 2 points higher for 3 or 4 symptoms versus no symptoms, and far (12 points) from the 50 threshold. Moreover, average Zung scores less than 50 at baseline were similar for participants developing and not developing depression.

Although the definition of insomnia sometimes includes daytime consequences or impairment/interference (21, 42), our definition did not, which limited the potential for built-in associations. To avoid overestimating insomnia's association

Table 4. Relative Risk of Incident Depression Symptoms[a] at 4-Year Follow-up According to Insomnia Markers[b] Measured Polysomnographically at Baseline ($n = 555$), Wisconsin Sleep Cohort Study, 1998–2006

Insomnia Marker[c]	Total No. of Participants	Incidence of Depression		Adjusted[d] RR	95% CI[c]	Fully Adjusted[e] RR	95% CI[a]
		No.	%				
Sleep latency, minutes							
≥14 (≥75th percentile)	132	11	8.33	2.37**	1.10, 5.11	2.19*	1.02, 4.70
<14	422	15	3.55	1.00	Referent	1.00	Referent
Waking after sleep onset, minutes							
≥79 (≥75th percentile)	185	15	8.11	3.84***	1.84, 8.02	3.85***	1.81, 8.19
<79	370	11	2.97	1.00	Referent	1.00	Referent
Sleep efficiency, %							
<78 (<25th percentile)	169	15	8.88	4.40***	2.22, 8.77	4.65***	2.30, 9.43
≥78	386	11	2.85	1.00	Referent	1.00	Referent
Total sleep time, minutes							
<334 (<25th percentile)	121	7	5.79	2.69	0.98, 7.47	3.18***	1.04, 9.74
334–<374.5	139	7	5.04	1.90	0.66, 5.49	2.10	0.67, 6.56
374.5–<409	135	7	5.19	1.64	0.55, 4.93	1.82	0.56, 5.92
≥409	160	5	3.13	1.00	Referent	1.00	Referent
P for trend[f]				0.05		0.03	

Abbreviations: CI, confidence interval; RR, relative risk.

* $P = 0.05$; ** $P = 0.03$; *** $P \leq 0.001$.

[a] Depression was defined as modified (excluding 2 sleep-related items) Zung depression scale score ≥50.

[b] "Sleep latency" was defined as time (minutes) from "lights off" to the first of 3 consecutive epochs of stage 1 sleep or the first epoch of any other stage of sleep; "waking after sleep onset" was defined as amount of time (minutes) spent awake after first sleep onset; "sleep efficiency" was defined as proportion of total sleep time out of time spent in bed from "lights out"; and "total sleep time" was defined as total time spent sleeping, in minutes.

[c] Participants who reported depressive symptoms (defined as modified Zung depression score ≥50) or use of antidepressant medication at baseline were excluded.

[d] Adjusted for age, sex, and chronic health conditions.

[e] Adjusted for age, sex, chronic health conditions, alcohol consumption, cigarette smoking, use of hypnotic agents, caffeine consumption, and body mass index.

[f] *P* value for linear trend in the logarithm of the relative risk for total sleep time. Unlike the other polysomnographic measures, total sleep time had a linear relation to depression; thus, quartiles are shown and the variable was not dichotomized.

with depression, we used a modified depression scale excluding 2 sleep-related items, a method rarely used (10, 26). Estimates, though slightly attenuated, remained significant. Because antidepressants may be used for conditions beyond depression (43), we reanalyzed the data after excluding users of antidepressant medication (irrespective of depression symptoms) from follow-up; patterns and trends remained unchanged (Figure 1), even after adjustment. Relative risks were 2.8 ($P = 0.05$) for difficulty falling asleep, 4.8 ($P < 0.001$) for waking after sleep onset ≥79 minutes, and 2.9 ($P = 0.02$) for sleep latency ≥14 minutes.

When standard polysomnographic cutpoints considered clinically significant were analyzed, sleep efficiency <80% and sleep latency >30 minutes remained significantly associated with depression (Zung score ≥50); total sleep time <360 minutes and waking after sleep onset ≥30 minutes did not. The graded relation of total sleep time quartiles with depression was perhaps diluted by the binary cutpoint; waking after sleep onset was significant only at upper quartile values.

Several polysomnographic cutpoints used were more conservative than those typically utilized to define poor sleep (total sleep time <360–390 minutes, sleep efficiency <85%) (44). Our lowest quartiles of total sleep time (<334 minutes) and sleep efficiency (<78%) were similar to objective insomniacs' mean values in clinical settings (329 minutes and 75%, respectively) (45), suggesting that clinically relevant "objective" markers were assessed. Analyses further suggested that polysomnographic markers corresponded to self-reported difficulty in initiating and maintaining sleep.

Among our study's limitations, we were unable to examine whether depression was season-related (seasonal affective disorder) or to differentiate between first-onset and recurrent depression, since information on past depression was not available. Nevertheless, findings that insomnia predicts depression symptoms in persons without depression at baseline may be relevant for preventive purposes, irrespective of whether depression at follow-up is first-onset or

Table 5. Mean Scaled Zung Depression Score at 4-Year Follow-up According to Insomnia Symptoms and Polysomnographic Markers Measured at Baseline[a] ($n = 555$), Wisconsin Sleep Cohort Study, 1998–2006

Symptom or Marker	Adjusted[b] Mean Zung Depression Scale Score (Continuous Variable)	Overall *F* Test *P* Value	*t* Test *P* Value	*P* for Trend
No. of insomnia symptoms		<0.0001		<0.0001
0	36.57 (0.38)[c]		Referent	
1	37.15 (0.53)		0.3674	
2	40.28 (0.86)		<0.0001	
3 or 4	40.03 (1.11)		0.0031	
Individual insomnia symptoms				
Difficulty falling asleep		<0.0001		<0.0001[d]
All symptoms "never/rarely"	35.14 (0.66)		Referent	
Difficulty falling asleep "sometimes"	38.20 (0.49)		0.0002	
Difficulty falling asleep "often/always"	39.63 (0.89)		<0.0001	
Any other symptom "sometimes/more often"	37.03 (0.45)		0.0175	
Difficulty getting back/returning to sleep at baseline		0.0005		0.0015[d]
All symptoms "never/rarely"	35.12 (0.66)		Referent	
Difficulty returning to sleep "sometimes"	38.34 (0.46)		<0.0001	
Difficulty returning to sleep "often/always"	38.15 (0.68)		0.0014	
Any other symptom "sometimes/more often"	36.93 (0.53)		0.0300	
Repeated nocturnal awakenings		0.0004		<0.0001[d]
All symptoms "never/rarely"	35.12 (0.66)		Referent	
Nocturnal awakenings "sometimes"	36.87 (0.56)		0.0425	
Nocturnal awakening "often/always"	38.51 (0.48)		<0.0001	
Any other symptom "sometimes/more often"	37.82 (0.58)		0.0022	
Early morning awakening		0.0037		0.0088[d]
All symptoms "never/rarely"	35.13 (0.66)		Referent	
Early morning awakening "sometimes"	37.85 (0.53)		0.0014	
Early morning awakening "often/always"	37.66 (0.66)		0.0069	
Any other symptom "sometimes/more often"	37.87 (0.47)		0.0008	
Polysomnographic insomnia markers				
Sleep latency, minutes		0.3207	0.3207	—[e]
≥14 (≥75th percentile)	37.88 (0.59)			
<14 (referent)	37.17 (0.41)			
Waking after sleep onset, minutes		0.0015	0.0015	—[e]
≥79 (≥75th percentile)	38.68 (0.51)			
<79 (referent)	36.71 (0.35)			
Sleep efficiency, %		0.0004	0.0004	—[e]
<78 (<25th percentile)	38.93 (0.53)			
≥78 (referent)	36.68 (0.34)			
Total sleep time, minutes		0.7578	—[f]	0.38
<334 (<25th percentile)	37.67 (0.64)			
334–<374.5	37.38 (0.57)			
374.5–<409	37.57 (0.58)			
≥409 (referent)	36.88 (0.53)			

[a] Participants who reported depressive symptoms (defined as modified Zung depression score ≥50) or use of antidepressant medication at baseline were excluded.

[b] Adjusted for age, sex, and chronic health conditions.

[c] Numbers in parentheses, standard error.

[d] The *P* value for trend compares 3 categories: all symptoms "never/rarely," symptom-of-interest "sometimes," and symptom-of-interest "often/always" (any other symptom occurring "sometimes/more often" was excluded from trend tests).

[e] The *P* value for trend was redundant with the overall *F* test *P* value.

[f] Because the *P* value from the overall *F* test was not significant, pairwise *t* tests were not conducted.

recurrent. Furthermore, an interaction between insomnia and age was not observed, increasing the likelihood that a reasonably high proportion of newly developed (vs. recurrent) depression was identified at follow-up. Self-reported depression symptoms may also be more labile. Depression is dynamic and is characterized by symptomatic fluidity (16, 17), suggesting that our inability to differentiate between first-onset depression and recurrent depression may be less pertinent.

Both early and middle insomnia—difficulty in initiating and maintaining sleep, respectively—predicted depression symptoms. Similarly, Perlis et al. (13) found that chronic middle insomnia predicted depression. In contrast to our study, they found persistent delayed (early morning awakening) insomnia symptoms to be somewhat related to depression and persistent early insomnia to be unrelated (13). A clinical study by Fava et al. (46) suggested that delayed and initial insomnia are prodromal depression symptoms. Our findings that early and middle insomnia were most related to depression are thus partially consistent with prior studies; differences may relate to these studies' examining chronic insomnia or clinical populations.

The follow-up participation rate in the overall cohort has been 80%, on average. Proportions of insomnia and depression did not vary according to number of follow-up visits completed, suggesting an absence of selection bias. Despite the use of polysomnography, variability (night-to-night) and instrumentation errors were possible. However, the measurement error was probably nondifferential, thus likely underestimating our positive findings. A first-night effect (47) resulting in regression dilution bias is possible given 1 night of polysomnography. However, the fact that significant associations were found may highlight the strength of our findings.

The Zung scale has limitations; it is based on self-reporting and does not correspond directly to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (48). Nevertheless, its strengths include a high correlation with clinical evaluation (38, 49) and wide usage in research. Other potential limitations include confounding due to unmeasured factors like pain (24), though we adjusted for back pain. The external validity of our findings should be limited to the incidence of both first-onset and recurrent depression. Moreover, the findings may not be generalizable beyond a middle-aged population with similar characteristics or to persons assessed as depressed by a clinician.

Our study's strengths include the collection of longitudinal data from a large population-based sample, longer follow-up, high-quality polysomnographic and self-report assessments, consistent findings across insomnia measures, and consideration of multiple confounding factors. Because our baseline sample comprised mainly working persons and because we excluded depressed participants and adjusted for common comorbid conditions, baseline insomnia was probably unrelated to medical or psychiatric conditions. Significant results persisted after removal of participants with anxiety, suggesting that the association observed was not merely due to anxiety.

Conclusions

Despite its high prevalence, insomnia remains largely undiagnosed among patients seen in primary-care settings, due to factors ranging from inadequate training of primary care providers to concerns and misperceptions about sleep medications, lack of familiarity with behavioral techniques, and inadequate amounts of time spent with patients (50). Our findings suggest that insomnia may increase the risk of subsequent depression symptoms. If confirmed by future studies, our results suggest that recognition and treatment of insomnia by health-care providers may be critical for preventing or mitigating the occurrence of depression. Prevention of depression, even mild or subthreshold depression, has wide-ranging implications given its high (including invisible) costs (51), such as increased health-service utilization, its chronic recurrent nature, and undertreatment (16, 17).

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