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ORIGINAL CONTRIBUTIONS

Insomnia in Young Men and Subsequent Depression

The Johns Hopkins Precursors Study

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The Johns Hopkins Precursors Study, a long-term prospective study, was used to study the relation between self-reported sleep disturbances and subsequent clinical depression and psychiatric distress. A total of 1,053 men provided information on sleep habits during medical school at The Johns Hopkins University (classes of 1948–1964) and have been followed since graduation. During a median follow-up period of 34 years (range 1–45), 101 men developed clinical depression (cumulative incidence at 40 years, 12.2%), including 13 suicides. In Cox proportional hazards analysis adjusted for age at graduation, class year, parental history of clinical depression, coffee drinking, and measures of temperament, the relative risk of clinical depression was greater in those who reported insomnia in medical school (relative risk (RR) 2.0, 95% confidence interval (CI) 1.2–3.3) compared with those who did not and greater in those with difficulty sleeping under stress in medical school (RR 1.8, 95% CI 1.2–2.7) compared with those who did not report difficulty. There were weaker associations for those who reported poor quality of sleep (RR 1.6, 95% CI 0.9–2.9) and sleep duration of 7 hours or less (RR 1.5, 95% CI 0.9–2.3) with development of clinical depression. Similar associations were observed between reports of sleep disturbances in medical school and psychiatric distress assessed in 1988 by the General Health Questionnaire. These findings suggest that insomnia in young men is indicative of a greater risk for subsequent clinical depression and psychiatric distress that persists for at least 30 years. *Am J Epidemiol* 1997;146:105–14.

depression; insomnia; prospective studies; risk factors; sleep

Depression is a common cause of morbidity and substantial disability in the general population. Approximately 10 percent of all Americans will suffer from major depression at some point in their lives (1). Community studies have shown that depressive disorders and symptoms account for more disability and impaired functioning than do many chronic medical conditions (2). The total annual cost of depression in the United States has been estimated to be as high as $43.7 billion in 1990 (3). Identification of early risk factors would provide an opportunity to target preventive efforts at high-risk individuals.

Insomnia, which is reported by approximately 10–35 percent of the population in any 1-year period, has been associated with an increased risk of depression in both epidemiologic and clinical studies (4–11). Moreover, insomnia is a well-known feature of major depression and is one of the nine diagnostic criteria listed in *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (12). Clinical studies have

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Abbreviations: CI, confidence interval; GHQ, General Health Questionnaire; RR, relative risk.

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shown that psychiatric disorders are the most common cause of chronic insomnia in clinic populations (13, 14). Depressed persons appear to have substantial sleep impairment assessed both by self-report and by objective measurements (15–18).

It is difficult, however, to disentangle whether insomnia is a precursor or sequela of depression. The association of insomnia with depression may be due to the coexistence of insomnia with other risk factors for depression, such as female gender, age, history of depressive illness in first-degree relatives, prior episodes of major depression, substance use, or psychosocial stresses (19). Studies thus far have been either cross-sectional or prospective with relatively short follow-up periods of no more than 7 years (7–11). As a result, it is unclear how long the period of increased risk from sleep disturbance may persist. The Johns Hopkins Precursors Study, a longitudinal study of former medical students of The Johns Hopkins University with up to 45 years of follow-up, affords the unique opportunity to study prospectively the relation of sleep patterns in young adulthood to subsequent mental health. We postulated that the risk of depression during follow-up would be greater in individuals who reported insomnia and other sleep disturbances.

MATERIALS AND METHODS

Study population

The Johns Hopkins Precursors Study was designed by Dr. Caroline Bedell Thomas in 1946. In medical school, participants underwent a standardized medical examination and completed questionnaires about their personal and family history, health status, sleep patterns, and health behaviors (20, 21). The cohort has been followed after graduation by annual mailed questionnaires, with an average response rate of 90 percent (range 87–94 percent) over every 5-year period. Self-reports of various measures of personal health and disease by the physicians in this cohort have been demonstrated to be extremely accurate (22). It was not customary to obtain informed consent during the period in which the baseline data were collected. After the establishment of the Joint Committee on Clinical Investigation at The Johns Hopkins University, the protocol for follow-up was reviewed and approved.

The study sample consists of 1,271 (95 percent of those eligible) members of the graduating classes of 1948–1964. Excluded from this analysis were the small number of women (n = 111), those who did not provide information on sleep habits (n = 88), individuals who reported depression before graduation (n = 10), and those who died while in medical school or were lost to follow-up (n = 9), leaving 1,053 men for analysis.

Measures of sleep

The primary independent variable was insomnia. Information on sleep habits in medical school was obtained using a Habit Survey Questionnaire (20). Questions addressing sleep quality included "Do you ever have insomnia?," "Do you sleep well?," "Do you sleep soundly or lightly?," and "Do you have difficulty sleeping when under stress?" Questions regarding sleep quantity included "How many hours of sleep do you require to feel your best?" and "How many hours of sleep do you average a night?"

Covariates

Factors that were hypothesized to increase vulnerability to psychiatric distress and were found to be related to depression in this cohort were included as covariates, including age, parental history of depression, temperament types, and coffee consumption in medical school (23–26). Unlike other studies (27–30), tobacco and alcohol use at baseline were not related to mental health in this cohort (data not shown). Parental psychiatric history was assessed at baseline and during follow-up by annual questionnaires. From the Habit Survey Questionnaire administered in medical school, a temperament measure was previously constructed using latent class analysis of responses to stress (31). Temperament was characterized into three types: tension-in (described as uneasy, anxious, with loss of appetite and difficulty sleeping when under stress); tension-out (anxious, angry, with increased activity when under stress); and stable (more self-contained and solid when under stress). This measurement of temperament has been shown to predict total mortality in this cohort (31).

Outcome measures

The primary outcome for this analysis was incidence of clinical depression after graduation from medical school through December 31, 1993. Clinical depression was assessed by annual mailed questionnaires inquiring about medical and psychiatric conditions in checklist format and by medical records submitted by participants or their health care providers. Information on treatment was also assessed throughout follow-up. Use of antidepressant medication within the past year was specifically surveyed in 1985 and 1991; lifetime history of receiving care from a mental health specialist for "an emotional problem" was assessed in 1988. Symptoms of depression occurring before graduation were assessed by history and physical examination during medical school, review of student health records including information about treatment and hospitalization for depression, and exit

interviews before graduation specifically asking about symptoms of depression. Individuals with a history of depression during medical school were excluded from the study. However, those who committed suicide were included in the case definition of depression regardless of previous history of diagnosed depression. Suicide was ascertained by contacting family members, classmates, and friends; obtaining death certificates; scanning obituaries; and searching the National Death Index.

Self-reports of clinical depression were confirmed by a committee of five physician reviewers. Strict adherence to criteria of *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, was not possible. In rare cases when the respondent did not report his diagnosis of clinical depression, a physician note that documented an episode of clinical depression was the basis for reviewers assigning a diagnosis of depression. Depressive episodes that were related to grief or that lasted less than 2 weeks were excluded. All analyses were repeated after reclassifying eight men who committed suicide without confirmed depression as not depressed and after restricting the outcome to those who reported a history of receiving pharmacotherapy or professional mental health care for depression.

To assess psychiatric distress, the secondary outcome, the 20-item General Health Questionnaire (GHQ) was administered in 1988. The GHQ is a widely used and valid screening instrument to detect current, nonspecific psychiatric distress in clinical and community-based samples (32). The GHQ uses a broad array of items to measure psychiatric distress in the "past several weeks." Responses were scored by the standard method (33), with a score of four or more indicating psychiatric distress. This cutpoint yields a sensitivity and specificity of approximately 85 percent for detecting an episode of major depression compared with a structured clinical interview by a psychiatrist (34).

Analysis

Sleep disparity was defined as the difference between sleep requirement and sleep duration and was categorized as either deficit (requirement > duration), excess (requirement < duration), or none. Continuous sleep variables with responses defined as hours were dichotomized at their median value for analysis since their distributions were clustered around the median. Associations of sleep variables with each other were examined with chi-square analyses. Coffee drinking was categorized as zero, one, two, and three or more cups per day (35). Class year was defined as the graduating year of the class in which the participant originally matriculated.

The relation of each sleep variable with subsequent incidence of clinical depression was examined using Kaplan-Meier analyses. The log rank test was used to assess statistical significance. Cox proportional hazards analysis was used to estimate relative risk and 95 percent confidence intervals and to determine whether associations with depression were independent of other covariates. A separate multivariate model was created for each sleep variable. Because difficulty sleeping under stress was one component of the temperament scale, multivariate analysis for that sleep characteristic did not include temperament. Time-dependent variables were employed to test the proportionality assumption. To determine whether associations of sleep disturbances with depression merely reflect the coexistence of these conditions, analyses were repeated after censoring cases that occurred within the first 20 years of follow-up, approximately half of the duration of follow-up. Relative risks of high GHQ score and 95 percent confidence intervals for each sleep variable were calculated. Odds ratios from multiple logistic regression analysis were used to determine whether associations of sleep disturbances with psychiatric distress were independent of other covariates. Two-tailed test alpha levels of <0.05 were used to define statistical significance.

RESULTS

Study sample

The characteristics of the study sample at baseline are presented in table 1. Values are given for the total cohort of 1,053 men and for the 1,024 men who answered the question about insomnia in medical school. Although 45 percent reported difficulty sleeping under stress while in medical school, most participants slept well, soundly, and without insomnia; approximately two thirds required more sleep than they actually obtained. These characteristics were identical in the 695 cohort members who completed the GHQ in 1988 (data not shown). Approximately 74 percent of the respondents answered the questions on sleep habits during the first 2 years of medical school, the preclinical years. There was no difference in the prevalence of sleep disturbances or sleep quantity between those who answered the questionnaire during the first 2 years and those who answered the questionnaire during the clinical years. Because several of the questions were about similar characteristics of sleep, responses tended to be highly associated. For example, men who reported insomnia were more likely to report poor quality of sleep, difficulty sleeping under stress, sleep-

TABLE 1. Characteristics of the total study sample in medical school according to whether participants had insomnia, The Johns Hopkins Precursor Study, 1948–1964†

	Total (n = 1,053)				Insomnia (n = 137)				No insomnia (n = 887)			
	Mean	(SD)	No.	%	Mean	(SD)	No.	%	Mean	(SD)	No.	%
Age at graduation (years)	26.3	(2.3)			26.0	(1.9)*			26.4	(2.4)		
Race												
Caucasian			1,035	98.3			133	97.1			873	98.4
Non-Caucasian (Asian)			18	1.7			4	2.9			14	1.6
Sleep variables												
Difficulty under stress												
Yes			472	44.8			93	67.9***			373	42.1
No			581	55.2			44	32.1			514	57.9
Poor quality												
Yes			92	8.8			37	27.0***			55	6.2
No			953	91.2			100	73.0			831	93.8
Light sleep												
Yes			208	19.9			37	27.4*			166	18.8
No			835	80.1			98	72.6			718	81.2
Duration (hours/day)												
≤7			681	65.6			104	75.9**			560	63.9
>7			357	34.4			33	24.1			317	36.1
Requirement (hours/day)												
≤8			860	82.9			104	76.5*			736	83.9
>8			177	17.1			32	23.5			141	16.1
Disparity												
Deficit			683	66.2			111	81.6***			561	64.3
Excess			60	5.8			8	5.9			49	5.6
None			289	28.0			17	12.5			263	30.1

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$.
† A total of 1,024 men answered the question about insomnia.

ing lightly, a sleep deficit, needing more than 8 hours of sleep per night, and getting 7 hours or less per night.

Median follow-up for the 1,053 men was 34 years (range 1–45). The average age of the cohort alive in 1993 (n = 941) was 62.6 years (range 52–91). One hundred one men reported an episode of depression during follow-up (cumulative incidence 12.2 percent) with a median age at onset of 47 years. Eighty-seven (86.1 percent) of the men reporting clinical depression also reported either taking antidepressant medication or receiving professional mental health care for their depression. The incidence of depression displayed no secular trend. Thirteen men committed suicide after graduation; of this group, five (38.5 percent) had reported a previous history of depression.

Clinical depression

In table 2, the cumulative incidence and relative risk estimates of depression according to sleep characteristics are presented. Self-reported insomnia, difficulty sleeping under stress, poor sleep quality, and sleep duration of 7 hours or less per night were associated with a greater incidence of subsequent depression (figure 1 and table 2). The curves for those with and without sleep complaints continued to separate throughout follow-up. However, the majority of men who developed depression did not report insomnia or other sleep disturbances in medical school. The relative risk of depression was higher for those who reported insomnia compared with those who did not and higher for those with difficulty sleeping under stress compared with those who had no difficulty, even after adjustment for other factors associated with depression. Both insomnia (relative risk (RR) 1.9, 95 percent confidence interval (CI) 1.2–3.2, $p < 0.01$) and difficulty sleeping under stress (RR 1.7, 95 percent CI 1.1–2.5, $p < 0.05$) remained associated with depression when included in the same multivariate model. When cases of depression within the first 20 years of follow-up were censored (n = 47), only those with insomnia (RR 2.1, 95 percent CI 1.0–4.1, $p < 0.05$) in medical school continued to have a greater risk of depression.

The overall relative risk of developing depression was also greater for those with poor quality of sleep in medical school compared with those not reporting poor sleep quality and for those who slept 7 hours or less per night compared with those who slept more

TABLE 2. Cumulative incidence and crude and adjusted relative risks (RRs) of clinical depression over 44 years of follow-up from Cox proportional hazards analysis, The Johns Hopkins Precursor Study, 1948–1964

Sleep variable	No.	Cumulative incidence at 40 years' follow-up (%)	Crude RR	95% CI†	Adjusted‡ RR	95% CI
Insomnia						
Yes	137	31.6***	2.2	1.4–3.6***	2.0	1.2–3.3***
No	887	10.4	1.0		1.0	
Difficulty under stress						
Yes	472	17.7**	1.9	1.3–2.8**	1.8	1.2–2.7**
No	581	8.4	1.0		1.0	
Poor quality						
Yes	92	20.3*	1.9	1.1–3.3*	1.6	0.9–2.9
No	953	11.6	1.0		1.0	
Light sleep						
Yes	208	15.3	1.3	0.8–2.0	1.2	0.8–1.9
No	835	11.6	1.0		1.0	
Duration (hours/day)						
≤7	681	14.4*	1.6	1.0–2.5*	1.5	0.9–2.3
>7	357	8.7	1.0		1.0	
Requirement (hours/day)						
≤8	860	12.6	1.0	06.–1.7	0.9	0.6–1.6
>8	177	11.4	1.0		1.0	
Disparity						
Deficit	683	13.8	1.2	0.8–2.0	1.2	0.7–1.9
Excess	60	7.2	0.8	0.3–2.2	0.7	0.3–2.1
None	289	10.2	1.0		1.0	

* $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$.

† CI, confidence interval.

‡ Adjusted for age at graduation, class year, parental history of depression, measures of temperament, and coffee drinking (cups per day) in Cox proportional hazards analyses.

§ Adjusted for the covariates listed above excluding temperament.

than 7 hours. However, these relations did not reach statistical significance after censoring cases of depression within the first 20 years of follow-up or after adjustment for covariates, although the magnitude of the risk estimates remained similar. Soundness of sleep, sleep requirement, and sleep disparity were not related to risk of depression in either univariate or multivariate analysis.

Results were very similar when the outcome was limited to only those men who had received treatment for their depression ($n = 87$), when these associations were controlled for smoking and alcohol use in medical school, and when men who reported in medical school feeling depressed during times of stress were excluded ($n = 211$). When the eight men who committed suicide without a previously reported history of depression were excluded from the case definition of depression, poor sleep quality (RR 1.8, 95 percent CI 1.0–3.2), insomnia (RR 1.9, 95 percent CI 1.2–3.2), and difficulty sleeping under stress (RR 1.8, 95 percent CI 1.2–2.7) were also related to a greater risk of depression. When complaints of insomnia, difficulty sleeping under stress, and poor sleep quality were considered together, the cumulative incidence and relative risk of depression increased progressively for those reporting none (6.3 percent; RR 1.0), one (16.9 percent; RR 1.8, 95 percent CI 1.1–3.0), and two or more complaints (26.7 percent; RR 2.6, 95 percent CI 1.4–4.6).

Psychiatric distress measured by the General Health Questionnaire

A total of 695 men (72.1 percent of those alive) completed the GHQ in 1988. One hundred four (15.0 percent) of the men had had psychiatric distress in the past several weeks (GHQ scores ≥ 4); this prevalence was similar to the cumulative incidence of self-reported clinical depression in these men in 1993 (11.6 percent, $n = 67$). In addition, those who reported depression during follow-up had a higher prevalence of psychiatric distress in 1988 (34.3 percent) com-

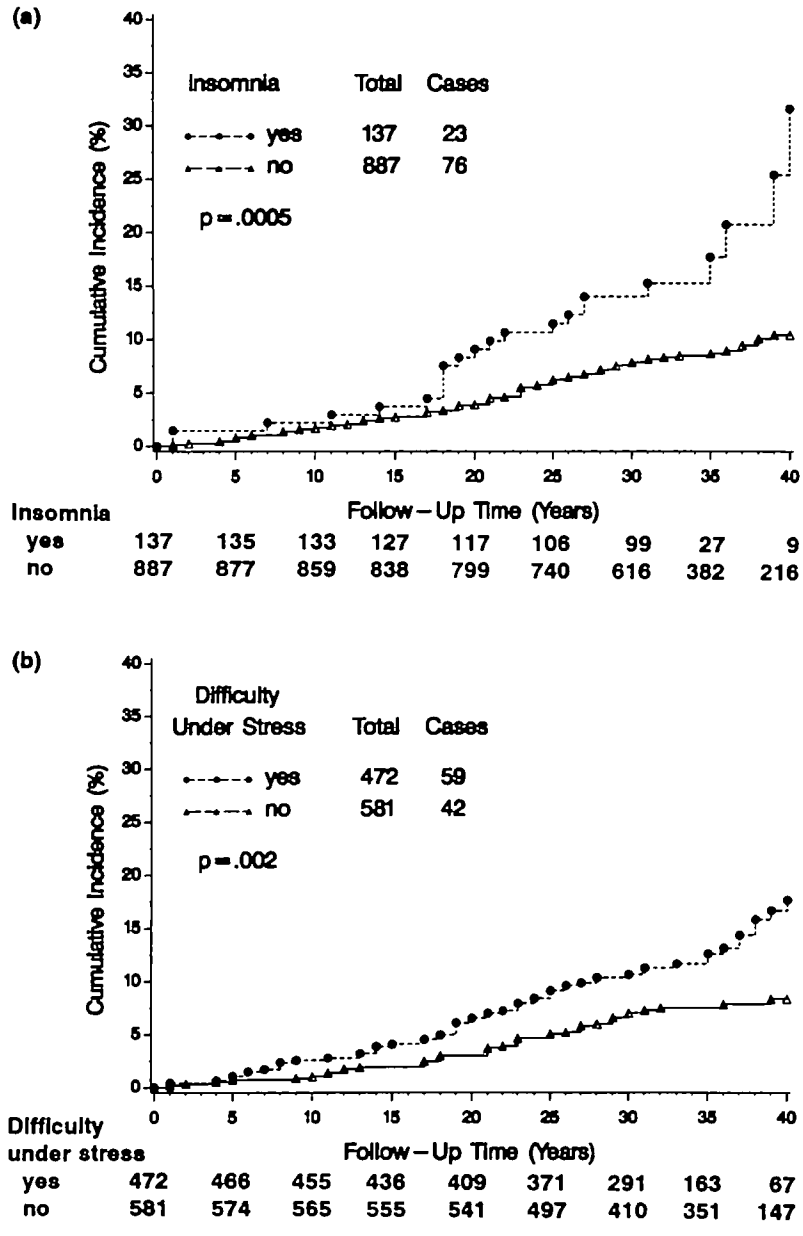

FIGURE 1. Cumulative incidence of depression in 1,045 men according to sleep complaints in medical school. a, insomnia (●) versus no insomnia (△). b, difficulty sleeping under stress (●) versus no difficulty (△). The numbers below each Kaplan-Meier plot are the numbers of men included in the analysis at each time point.

pared with those who did not report depression (12.9 percent, $p < 0.0001$). As shown in table 3, the odds ratio of having acute psychiatric distress in 1988 was twice as high in those who had insomnia in medical school compared with those who did not, even after adjusting for graduation age, parental history of depression, temperament type, and coffee consumption (odds ratio 2.0, 95 percent CI 1.1–3.4). The pattern of associations of difficulty sleeping under stress and poor quality of sleep with psychiatric distress was similar to that for depression, although neither of these associations reached statistical significance.

DISCUSSION

This report provides evidence that self-reported sleep quality in young adults predicts episodes of depression through midlife. Of the characteristics assessed, self-reported insomnia and difficulty sleeping under stress appear to be of greatest potential importance. It is unlikely that either sleep complaint was acting merely as a symptom of depression in medical school because these sleep disturbances in young adulthood predicted the development of depression more than 20 years later, independent of other poten-

TABLE 3. Crude relative risks (RRs) and adjusted odds ratios (ORs) of psychiatric distress (high GHQ† score, 1988) in midlife, The Johns Hopkins Precursor Study, 1948–1964

Sleep variable	No.	GHQ score ≥ 4		Crude		Adjusted‡	
		No	%	Crude RR	95% CI†	Adjusted‡ RR	95% CI
Insomnia							
Yes	94	22*	23.4	1.7	1.1–2.7*	2.0	1.1–3.4*
No	583	79	13.6	1.0		1.0	
Difficulty under stress							
Yes	301	53	17.6	1.4	1.0–1.9**	1.4	0.9–2.2§
No	394	51	12.9	1.0		1.0	
Poor quality							
Yes	60	14	23.3	1.7	1.0–2.8**	1.7	0.9–3.2
No	630	89	14.1	1.0		1.0	
Light sleep							
Yes	143	23	16.1	1.1	0.7–1.7	1.1	0.6–1.8
No	545	79	14.5	1.0		1.0	
Duration (hours/day)							
≤7	442	67	15.2	1.1	0.7–1.5	1.0	0.6–1.6
>7	244	35	14.3	1.0		1.0	
Requirement (hours/day)							
≤8	571	82	14.4	0.8	0.5–1.2	0.7	0.4–1.2
>8	114	21	18.4	1.0		1.0	
Disparity							
Deficit	455	73	16.0	1.5	0.9–2.4	1.4	0.8–2.4
Excess	41	8	19.5	1.8	0.9–3.9	1.9	0.7–4.7
None	186	20	10.8	1.0		1.0	

* $pH < 0.05$; ** $p < 0.10$.
† GHQ, General Health Questionnaire; CI, confidence interval.
‡ Adjusted for age at graduation, parental history of depression, measures of temperament, and coffee drinking (cups per day) in multiple logistic regression analyses.
§ Adjusted for the covariates listed above excluding temperament.

tial risk factors such as family history, age, temperament type, and tobacco and alcohol use. Moreover, the strong association of insomnia and difficulty sleeping under stress with incident depression persisted when suicides or men who did not report treatment for depression were excluded. In addition, insomnia continued to predict depression even for cases occurring after more than 20 years of follow-up. It is possible that insomnia at baseline was a proxy measure for depression at baseline or that men who report sleep disturbances are more likely to report depression or seek treatment for depressive symptoms. However, these men were thoroughly evaluated at baseline, and those with depressive symptoms at that time were excluded. Furthermore, only insomnia was related to midlife psychiatric distress as assessed with a standardized questionnaire, the GHQ, emphasizing the predictive power of this particular symptom.

The relation between insomnia and incident depression was quite specific, as other sleep characteristics displayed weaker associations with the development of clinical depression many years later. Sleeping poorly also carried a similarly elevated risk in univariate analysis and most likely represents another facet of the same underlying phenomenon as insomnia. The relation between poor sleep quality and depression was no longer present when earlier cases of depression were censored or after adjustment in multivariate analysis. This weaker association, compared with insomnia, may be due to a weaker biologic relation to depression or less precise assessment. However, when all three complaints (insomnia, difficulty under stress, and poor quality) were added together, those with more sleep disturbances had a stepwise greater risk of depression than those with fewer disturbances, suggesting a causal relation.

In terms of duration of sleep, those who slept 7 hours or less per night had a slightly greater risk of developing depression. However, this relation did not reach statistical significance in multivariate adjustment or after censoring cases within the first 20 years. Moreover, it was not related to GHQ score in midlife. Optimum amount of sleep was not related to either depression or GHQ score. Therefore, it appears that sleep quality, rather than quantity, is more important for subsequent mental health.

Among the previous studies of the relation between sleep disturbances and mood disorder, only a few have been prospective. Ford and Kamerow (7) found that persons who complained of insomnia at baseline and 1 year later had a greater risk of developing new depression over a subsequent 1-year follow-up period compared with those who did not report insomnia and those whose insomnia resolved. Livingston et al. (8) and Breslau et al. (9) found very similar results in community populations of elderly people and of young adults, respectively, with 2–3 years of follow-up. Vollrath et al. (10) also observed that persons who reported occasional or continued insomnia had higher rates of new depression 2–7 years later than those with no insomnia, but not statistically significantly so. The present study confirms the powerful effect of insomnia on subsequent incidence of depression over 29–45 years of follow-up.

Potential limitations of this study should be discussed. First, our results were strictly generalizable to men of high socioeconomic status. However, our rates of sleep disturbances and depression are similar to rates found in general community samples. For example, the prevalence of insomnia in our study, 13.4 percent, was within the range of 12.2–18.7 percent found in a community-based sample in Zurich (10) and similar to 10.7 percent found in young adults from the community sample in the Epidemiologic Catchment Area Study (7). Likewise, the prevalence of depression (9.6 percent) and of psychiatric distress (15.0 percent) were within the range of the lifetime prevalence of affective disorders (5.2 percent) and of dysphoric symptoms (23.5 percent) for men in community studies (36); in fact, the cumulative incidence of depression in our study (12.2 percent) was almost exactly that found in white men between 45 and 54 years of age in the National Comorbidity Survey (12.7 percent) (37). Thus, even though physicians might be less likely to report depression or depressive symptoms, this does not appear to be the case. Even if prevalence estimates are not generalizable, however, the relative risk estimates are likely to be generalizable because of the biologic basis of the association. In addition, potential biases, such as socioeconomic factors, which may increase or decrease the incidence of depression, would tend to affect those with and those without insomnia to a similar degree. Moreover, these results may actually underestimate the magnitude of the association since those with preexisting prolonged or severe depression presumably would be excluded from a sample of medical students. Since this analysis included only men, however, these results cannot be applied to women.

Second, as in most observational studies about sleep, insomnia and the other sleep disturbances were based only on subjective assessment by the respondent. For instance, not all men who reported difficulty sleeping under stress also reported ever having insomnia during medical school. It is possible that respondents did not consider a few nights of difficulty sleeping in the context of an obvious stress to be equivalent to insomnia, a more persistent sleep disturbance. Furthermore, although subjective and objective sleep assessments appear to measure different phenomena, previous studies have shown that there is an imperfect, but strong, relation between subjective evaluation of sleep and objective polysomnograph measurements (38–40).

Third, our definition of clinical depression was not based on standard criteria, such as the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition. Conducting a complete psychiatric interview would have been impossible since participants live throughout the United States and around the world. Since this cohort, mostly composed of practicing physicians, would be familiar with criteria for clinical depression, the self-reports of depression should be more valid than reports from the general population. The similarity in the estimates of the prevalence of psychiatric distress in 1988 and the cumulative risk of depression in 1993 suggests no underreporting of depression. The information regarding pharmacologic or professional treatment of depressive episodes further supports the validity of the self-reports. When analysis was restricted to only those who had been treated for depression (86.1 percent), the relation between insomnia and depression remained consistent.

Finally, because depression was assessed using specific questions regarding the presence of depression or emotional problems, some participants with subclinical depression at baseline who were unaware that they had depression may have been included. Moreover, some men may not have been willing to report their depression because of the social stigma attached to mental illness. This misclassification would tend to increase the strength of the observed association. It is unlikely, however, that undiagnosed depression would explain the association of insomnia with depression given the relatively constant risk over the long follow-up. In addition, the association persisted when cases in the first 20 years are excluded and when those most vulnerable to depression, i.e., those who reported in medical school feeling depressed during times of stress, are excluded.

Future research is required to elucidate the exact mechanism for how insomnia may lead to subsequent depression or psychiatric distress. Sleep studies have

demonstrated that certain sleep electroencephalogram patterns are very characteristic of, and even specific to, patients with depression (10, 14, 41). Deliberate sleep-wake manipulations have been reported to have antidepressant effects and have been used with favorable results as therapy for depression (42). Recent evidence from longitudinal treatment studies and from family studies suggests that sleep disturbances reflect vulnerability for depression and that sleep electroencephalogram abnormalities are present even after resolution of the depressive episode (43–47). This vulnerability is probably related to common neurobiologic regulatory systems for sleep and mood, which involve several neurotransmitter systems (48, 49).

Identification of individuals at high risk for depression is useful for designing and evaluating strategies to prevent the onset of depression and to improve outcomes for those with depression. As demonstrated in this study, sleep disturbances assessed with brief self-administered questionnaires may indicate an elevated risk for depression in the long term. Whether information on sleep habits can be translated into improvements for treatment of depression or potentially effective prevention strategies needs to be determined.

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REFERENCES

1. Regier DA, Boyd JH, Burke JD, et al. One-month prevalence of mental disorders in the United States. Arch Gen Psychiatry 1988;45:977–86.
2. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes study. JAMA 1989;262:914–19.
3. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. J Clin Psychiatry 1993;54: 405–18.
4. Karacan I, Thornby JI, Anch M, et al. Prevalence of sleep disturbance in a primarily urban Florida county. Soc Sci Med 1976;10:239–44.
5. Bixler EO, Kales A, Soldatos CR, et al. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979;136:1257–62.
6. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment: prevalence and correlates. Arch Gen Psychiatry 1985;42:225–32.
7. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 1989;262:1479–84.
8. Livingston G, Blizard B, Mann A. Does sleep disturbance predict depression in elderly people?: a study in inner London. Br J Gen Pract 1993;43:445–8.
9. Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411–18.
10. Vollrath M, Wicki W, Angst J. The Zurich study. VIII. Insomnia: association with depression, anxiety, somatic syndromes, and course of insomnia. Eur Arch Psychiatr Neurol Sci 1989;239:113–24.
11. Hohagen F, Rink K, Kappler C, et al. Prevalence and treatment of insomnia in general practice: a longitudinal study. Eur Arch Psychiatry Clin Neurosci 1993;242:329–36.
12. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.
13. Coleman RM, Roffwarg HP, Kennedy SJ, et al. Sleep-wake disorders based on a polysomnographic diagnosis: a national cooperative study. JAMA 1982;247:997–1003.
14. Buysse DJ, Reynolds CF III, Hauri PJ, et al. Diagnostic concordance for DSM-IV sleep disorders: a report from the APA/NIMH DSM-IV field trial. Am J Psychiatry 1994;151: 1351–60.
15. Waxman HM, McCreary G, Weinrit RM, et al. A comparison of somatic complaints among depressed and non-depressed older persons. Gerontologist 1985;25:501–7.
16. Benca RM, Obermeyer WH, Thisted RA, et al. Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 1992;49:651–68.
17. Reynolds CF III, Kupfer DJ. Sleep research in affective illness: state of the art circa 1987. Sleep 1987;10:199–215.
18. Ware JC, Morewitz J. Diagnosis and treatment of insomnia and depression. J Clin Psychiatry 1991;52(suppl):55–61.
19. Depression Guideline Panel. Depression in primary care. Vol 1: detection and diagnosis. Rockville, MD: US Department of Health and Human Services, Agency for Health Care Policy and Research, 1993. (AHCPR publication no. 93–0550).
20. Thomas CB, Pederson LA. Sleep habits of healthy young adults with observations on levels of cholesterol and circulating eosinophils. J Chron Dis 1963;16:1099–114.
21. Klag MJ, Ford DE, Mead LM, et al. Serum cholesterol in young men and subsequent cardiovascular disease. N Engl J Med 1993;328:313–18.
22. Klag MJ, He J, Mead LA, et al. Validity of physicians' self-reports of cardiovascular disease risk factors. Ann Epidemiol 1993;3:442–7.
23. Chang PP, Ford DE, Graves PL, et al. Predictors in male medical students for subsequent psychiatric distress and clinical depression. J Gen Int Med 1994;9(suppl 2):26.
24. Shirlow MJ, Mathers CD. A study of caffeine consumption and symptoms: indigestion, palpitations, tremor, headache and insomnia. Int J Epidemiol 1985;14:239–48.
25. Leibenluft E, Fiero PL, Bartko JJ, et al. Depressive symptoms and the self-reported use of alcohol, caffeine, and carbohydrates in normal volunteers and four groups of psychiatric outpatients. Am J Psychiatry 1993;150:294–301.
26. Rodin J, McAvay G, Timko C. A longitudinal study of depressed mood and sleep disturbance in elderly adults. J Gerontol 1988;42:45–53.
27. Anda RF, Williamson DF, Escobedo LG, et al. Depression and the dynamics of smoking: a national perspective. JAMA 1990; 264:1541–5.
28. Glassman AH, Helzer JE, Covey LS, et al. Smoking, smoking cessation, and major depression. JAMA 1990;264:1546–9.
29. Madden JS. Alcohol and depression. Br J Hosp Med 1993;50: 261–4.
30. Davidson KM, Ritson EB. The relationship between alcohol dependence and depression. Alcohol Alcohol 1993;28: 147–55.
31. Graves PL, Mead LA, Wang NY, et al. Temperament as a potential predictor of mortality: evidence from a 41-year prospective study. J Behav Med 1994;17:111–26.

32. Goldberg D, Williams P. A user's guide to the General Health Questionnaire. Berkshire, United Kingdom: Nfer-Nelson Publishing-Company Ltd., 1988.
33. Goldberg DP. The detection of psychiatric illness by questionnaire: a technique for the identification and assessment of nonpsychotic psychiatric illness. Maudsley monograph no. 21. London, United Kingdom: Oxford University Press, 1972.
34. Ford DE, Anthony JC, Nestadt JR, et al. The General Health Questionnaire by interview: performance in relation to recent use of health services. Med Care 1989;27:367–75.
35. LaCroix AZ, Mead LA, Liang KY, et al. Coffee consumption and the incidence of coronary heart disease. N Engl J Med 1986;315:977–82.
36. Robins LN, Regier DA. Psychiatric disorders in America: the Epidemiologic Catchment Area Study. New York, NY: The Free Press, 1991.
37. Blazer DG, Kessler RC, McGonagle KA, et al. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. Am J Psychiatry 1994;151:979–86.
38. Spielman AJ, Tannerbaum R, Saskin P, et al. A comparison between objective and subjective latency in patients with chronic insomnia. Sleep Res 1980;9:225–31.
39. Coates TJ, Killen JD, George J, et al. Estimating sleep parameters: a multitrait-multimethod analysis. J Consult Clin Psychol 1982;50:345–52.
40. Frankel BL, Coursey RD, Buschbinder R, et al. Recorded and reported sleep in chronic primary insomnia. Arch Gen Psychiatry 1976;33:615–23.
41. Kupfer DJ, Frank E, Grochocinski VJ, et al. Electroencephalographic sleep profiles in recurrent depression: a longitudinal investigation. Arch Gen Psychiatry 1988;45:678–81.
42. Gillin JC. The sleep therapies of depression. Prog Neuropsychopharmacol Biol Psychiatry 1983;7:351–64.
43. Kupfer DJ, Foster FG, Reich L, et al. EEG sleep changes as predictors in depression. Am J Psychiatry 1976;133:622–6.
44. Kupfer DJ, Spiker DG, Coble PA, et al. Sleep and treatment prediction in endogenous depression. Am J Psychiatry 1981: 138:429–34.
45. Heiligenstein JH, Faries DE, Rush AJ, et al. Latency to rapid eye movement sleep as a predictor of treatment response to fluoxetine and placebo in nonpsychotic depressed outpatients. Psychiatry Res 1994;52:327–39.
46. Giles DE, Jarrett RB, Rush AJ, et al. Prospective assessment of electroencephalographic sleep in remitted major depression. Psychiatry Res 1993;46:269–84.
47. Giles DE, Kupfer DJ, Roffwarg HP, et al. Polysomnographic parameters in first-degree relatives of unipolar probands. Psychiatry Res 1989;27:127–36.
48. Sandor P, Shapiro CM. Sleep patterns in depression and anxiety: theory and pharmacological effects. J Psychosom Res 1994;38(suppl 1):125–39.
49. Idzikowski C. Insomnia and depression—sleep EEG changes. J Psychosom Res 1994;38(suppl 1):27–40.