Sleep Disturbances and Risk of Depression in Older Men

Misti Paudel, MPH; Brent C. Taylor, PhD, MPH1,2; Sonia Ancoli-Israel, PhD4; Terri Blackwell, MA6; Jeanne E. Maglione, MD, PhD4; Katie Stone, PhD4; Susan Redline, PhD3; Kristine E. Ensrud, MD, MPH1,2,3; for the Osteoporotic Fractures in Men (MrOS) Study Group

1Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN; 2Center for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, MN; 3Department of Medicine, University of Minnesota, Minneapolis, MN; 4Department of Psychiatry, University of California-San Diego, La Jolla, CA; 5California Pacific Medical Center Research Institute, San Francisco, CA; 6Division of Sleep Medicine, Brigham and Women’s Hospital and Beth Israel Deaconess Medical School, Harvard Medical School, Boston, MA

Introduction: Self-reported sleep disturbances are associated with an increased risk of depression in younger and older adults, but associations between objective assessments of sleep/wake disturbances via wrist actigraphy and risk of depression are unknown.

Methods: Depressive symptoms (Geriatric Depression Scale [GDS]), self-reported (questionnaires), and objective (actigraphy) sleep parameters were measured at baseline in 2,510 nondepressed men 67 y or older. Depressive symptoms were reassessed an average of 3.4 ± 0.5 y later.

Results: Of the 2,510 men without evidence of depression at baseline, 116 (4.6%) were depressed (GDS ≥ 6) at the follow-up examination. After adjusting for multiple potential confounders, including baseline depressive symptoms (GDS 0-5), there was evidence of an association between poor self-reported sleep quality and higher odds of being depressed at follow-up (multivariable odds ratio [MOR] = 1.53, 95% confidence interval [CI] 1.00-2.33). In age- and site-adjusted models, objectively measured reduced sleep efficiency (odds ratio [OR] = 1.88, 95% CI 1.13-3.13), prolonged sleep latency (OR = 1.77, 95% CI 1.04-3.00), greater nighttime wakefulness (OR = 1.48, 95% CI 1.01-2.18) and multiple long-wake episodes (OR = 1.69, 95% CI 1.15-2.47) were associated with increased odds of depression at follow-up, but these associations were attenuated and no longer significant after further adjustment for number of depressive symptoms at baseline. Self-reported excessive daytime sleepiness and objectively measured total sleep time were not associated with depression status at follow-up. Excluding baseline antidepressant users from the analyses did not alter the results.

Conclusions: Among nondepressed older men, poor self-reported sleep quality was associated with increased odds of depression several years later. Associations between objectively measured sleep disturbances (e.g., reduced sleep efficiency, prolonged sleep latency, greater nighttime wakefulness, and greater long-wake episodes) and depression several years later were largely explained by a greater burden of depressive symptoms at baseline.

Keywords: Actigraphy, depression, elderly, sleep quality

Citation: Paudel M; Taylor BC; Ancoli-Israel S; Blackwell T; Maglione JE; Stone K; Redline S; Ensrud KE; for the Osteoporotic Fractures in Men Study Group. Sleep disturbances and risk of depression in older men. SLEEP 2013;36(7):1033-1040.

INTRODUCTION

Prior studies have suggested that up to 50% of older adults endorse symptoms of poor or insufficient sleep, such as difficulty falling asleep, fragmented sleep, early morning awakening, and daytime sleepiness.1-4 Depression is also common among older adults, with an estimated prevalence of 8-16%.1,5-8 In older populations, both sleep disturbances and depression are associated with greater risk of adverse health-related outcomes, such as poor health status,2,6 disability,6 poorer physical functioning,9,10 falls, and fractures.11 However, the association between poor sleep and depression is complex, bidirectional in nature, and not thoroughly understood.2

The results of a recently published meta-analysis suggests that insomnia is associated with an approximately 2-fold increased risk of incident depression,5,12-14 whereas results from studies including older adults reported that the risk may be 3-fold.5,12,15-17 However, all of these previous studies relied on self-reported assessments of sleep disturbances and/or insomnia. Studies ex-

a

http://dx.doi.org/10.5665/sleep.2804

Submitted for publication June, 2012
Submitted in final revised form March, 2013
Accepted for publication March, 2013
Address correspondence to: Misti L. Paudel, MPH, Division of Epidemiology and Community Health, University of Minnesota-Twin Cities, 1100 Washington Ave S. Suite 201, Minneapolis, MN 55455; Phone: (612) 467-1649; Fax: (612) 725-2284; E-mail: ames0047@umn.edu


1033

Sleep Disturbances and Risk of Depression in Older Men—Paudel et al
latency. Our results were confirmed in a similar analysis using data from the Study of Osteoporotic Fractures in community-dwelling older women.22

In this study, we tested the hypothesis that objective sleep/wake disturbances, as well as self-reported sleep disturbances, are associated with incident depression in older men. We assessed several measures of self-reported and objective sleep disturbances and depressive symptoms at baseline in 2,510 community-dwelling, nondepressed men age 65 y and older enrolled in the MrOS Sleep study and then reassessed depressive symptoms an average of 3.4 y later.

METHODS

Participants

From March 2000 through April 2002, 5,994 men were recruited for participation in the baseline examination of the prospective Osteoporotic Fractures in Men (MrOS) Study.23 Men were recruited from population-based listings in six areas of the United States: Birmingham, Alabama; the Monongahela Valley near Pittsburgh, Pennsylvania; Minneapolis, Minnesota; Palo Alto, California; San Diego, California; and Portland, Oregon.24 Men with a history of bilateral hip replacement and men who were unable to walk without the assistance of another person were excluded.

From December 2003 through March 2005, active participants were invited to enroll in an ancillary study: MrOS Sleep. Of the 5,994 men enrolled in the overall MrOS Study, 3,135 (68%) were enrolled in the MrOS Sleep Study (> 100% of recruitment goal). Of the 2,859 men who did not participate in this ancillary study, 344 died before the sleep visit; 36 had already stopped participating in the study; 332 were not invited because recruitment goals had already been met; 150 were not eligible due to current continuous positive airway pressure or mouthpiece use, open tracheotomy, or use of oxygen therapy; and 1,997 refused participation. Of those who participated in MrOS Sleep, 2,989 men had at least 72 h (3 nights) of wrist actigraphy data, and measures of depressive symptoms at baseline. The 2,510 men who were categorized as nondepressed at baseline (GDS score < 6) and had repeat measures of depression were averaged over the total number of nights the actigraph was worn. Because most men did not complete the requested 5 nights of actigraphy data, we restricted our primary analyses to men who had at least 72 h of actigraphy recordings.

For primary analyses, sleep parameters were expressed as dichotomous variables based on consideration of clinical relevance of values for older adults, validated cut-points, and/or comparability to prior MrOS Sleep publications21,31-33: poor sleep efficiency (< 70% versus ≥ 70%), prolonged sleep latency (≥ 1 versus < 1 h), greater nighttime wakefulness (awakening after sleep onset ≥ 1.5 versus < 1.5 h), and multiple long-wake episodes (≥ 8 versus < 8). TST was expressed as a three-level predictor (< 5 h (short sleep duration), 5-8 h (normal sleep duration), > 8 h (long sleep duration)) based on clinical relevance and the presumption that there is a U-shaped association between TST and depression.24 In secondary analyses we expressed sleep/wake parameters as continuous variables.

We computed an objective sleep/wake disturbances summary score by counting the number of times a participant was classified as having a sleep/wake disturbance, as defined previously, on each on the actigraphy parameters. Scores ranged from 0 to 5.

Self-Reported Measures of Sleep and Daytime Sleepiness

Participants were asked to complete the PSQI and the ESS. The PSQI is a validated measure of self-reported sleep quality and sleep disturbances over the past month. The questionnaire is divided into sections that assess self-reported sleep quality, sleep latency, sleep duration, sleep efficiency, sleep distur-
bances, use of sleeping medications, and daytime dysfunction. Global PSQI scores range from 0 to 21, and a standard cutoff greater than 5 is indicative of poor sleep quality. This cutoff has a sensitivity of 89.6% and a specificity of 86.5% in distinguishing good sleepers from poor sleepers,\textsuperscript{35-37} and has been shown to have good reliability, internal consistency, and construct validity in the MrOS cohort.\textsuperscript{38} In primary analyses we expressed PSQI as a dichotomous predictor: > 5 versus ≤ 5, and in secondary analyses we expressed PSQI as a continuous variable.

The ESS is a self-administered questionnaire that classifies self-reported daytime sleepiness in people with sleep disorders. Patients are asked to rate how likely (from 1 to 3, with 1 being unlikely and 3 being highly likely) they are to doze off in eight typical daily situations. ESS scores range from 0 to 24, with a standard cutoff of > 10 indicative of excessive daytime sleepiness.\textsuperscript{39,40} The ESS has been validated in the MrOS cohort.\textsuperscript{39} In primary analyses we expressed ESS as a dichotomous cut-point: > 10 versus ≤ 10, and in secondary analyses we expressed ESS as a continuous variable.

Measurement of Depression

Depressive symptoms were evaluated at baseline and at the follow-up visit using the 15-item GDS. The GDS is designed specifically for elderly patients and consists of 15 yes or no questions assessing depressive symptoms. A standard cutoff of six or more symptoms is used to define clinically significant depression; this cutoff has a sensitivity of 91% and a specificity of 65% compared with diagnoses by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.\textsuperscript{41,42} For this analysis we assessed whether sleep disturbances at baseline were associated with incident depression at a follow-up examination, and therefore, men with depression at baseline (GDS ≥ 6) were excluded.

Other Measures

A trained technician interviewed participants at each examination. Information was obtained on health status,\textsuperscript{43} alcohol intake, caffeine consumption,\textsuperscript{44} smoking status, walking for exercise, and impairments in instrumental activities of daily living (IADL).\textsuperscript{45,46} Information from a previous visit was used to assess age, race/ethnicity, living situation, and education. Participants were asked to report all medications (prescription and nonprescription) used within the past 30 days. All prescription and nonprescription medications were entered into an electronic database and each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).\textsuperscript{47} Participants were asked about a history of physician-diagnosed stroke, parkinsonism, diabetes mellitus, chronic obstructive lung disease, congestive heart failure, chronic kidney disease, and myocardial infarction. Cognitive function was assessed using the Modified Mini-Mental State Examination.\textsuperscript{48} Body weight was measured using a balance beam or digital scale. Height was measured using a wall-mounted stadiometer. Height and weight were used to calculate body mass index (kg/m\textsuperscript{2}).

Statistical Analysis

Differences in baseline characteristics according to depression status at the follow-up examination were compared using analysis of variance for normally distributed continuous data, Kruskal-Wallis for skewed continuous data, and chi-square tests for categorical data.

For primary analyses, the associations between sleep disturbances at baseline and odds of being depressed at follow-up were examined using logistic regression in the entire cohort (n = 2,510), and in a subset of participants who reported not using antidepressants at the baseline examination (n = 2,352). Secondary analyses expressed sleep disturbance parameters as continuous variables and calculated odds ratios per standard deviation increase/decrease in sleep parameters.

Models included an age- and clinic site-adjusted base model, the base model further adjusted for number of baseline GDS symptoms, and the base model that further adjusted for multiple potential confounders. Covariates thought to be associated with depression or with sleep disturbances were considered for selection in multivariable models if they showed a significant association at P ≤ 0.10 in univariate analyses. Covariates included in multivariable-adjusted models were: age, clinic site, number of baseline GDS symptoms, health status, education, alcohol use, use of benzodiazepines at baseline, use of antidepressants at baseline (in the cohort that included baseline antidepressant users), cognitive function, walking for exercise, impairments in IADL, and selected medical conditions.

Several sensitivity analyses were conducted and included analyses examining change in GDS symptoms, and analyses excluding men who reported using antidepressants or benzodiazepines at the baseline examination. Because results of sensitivity analyses were consistent with the primary analysis, only results of the primary analysis are shown. Statistical analyses were conducted using SAS v9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of the Study Population

Of the 3,135 men who attended the sleep visit, the analytic cohort consisted of 2,510 men who had complete measures of self-reported and objective sleep and depression and who were classified as nondepressed (GDS < 6) at baseline. Of the 625 men who participated in the sleep examination but who were not included in the analytical cohort, 306 (49%) remained actively enrolled in the study beyond the sleep examination but did not have follow-up data, 272 (44%) died prior to the follow-up visit, 26 had been terminated from the study after the sleep visit, and 21 refused participation in the follow-up visit. On average, men who died or did not have follow-up data had a greater burden of depressive symptoms at baseline, compared with men who were included in the analytical cohort (1.89 versus 1.28 symptoms). Furthermore, compared with men included in the analytical cohort, the 306 surviving enrolled men not included in the analytical cohort were on average older (77.0 versus 75.9 y), and more likely to report poorer health status at baseline (25.6% versus 8.7%).

At the follow-up examination, 1,899 men were not depressed (zero to two depressive symptoms), 495 (19.7%) had some depressive symptoms (three to five), and 116 (4.6%) were depressed with six or more depressive symptoms. The mean and median (inter-quartile range) change in GDS score (computed as follow-up score − baseline score) was 0.44 and 0 (0-1) symp-
Sleep Disturbances and Risk of Depression in Older Men—Paudel et al

Longitudinal Association of Self-Reported Sleep Disturbances and Depression

In general, poor sleep quality (PSQI > 5) at baseline was associated with a 2.6-fold increased odds of depression at follow-up, in age- and site-adjusted models (OR = 2.55, 95% CI 1.72-3.77) (Table 2). Results were attenuated by approximately 39.6% after adjustment for number of baseline GDS symptoms, but remained significant. After further adjustment for health status, education, use of antidepressants or benzodiazepines at baseline, alcohol consumption, cognitive function, walking for exercise, IADL, and comorbidities, results were further attenuated, but persisted (OR = 1.53, 95% CI 1.00-2.33, P = 0.05). Results in analyses excluding baseline antidepressant users were similar (multivariable OR = 1.64, 95% CI 1.03-2.62, P = 0.037).

There was no association between excessive daytime sleepiness (ESS > 10) and odds of depression in age- and site-ad-

---

Table 1—Baseline characteristics of 2,510 participants according to depression status at follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All participants (n = 2,510)</th>
<th>Not depressed (n = 2,394)</th>
<th>Depressed (n = 116)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>75.9 ± 5.3</td>
<td>75.8 ± 5.3</td>
<td>77.9 ± 5.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Caucasian, %a</td>
<td>90.3</td>
<td>90.1</td>
<td>94.0</td>
<td>0.174</td>
</tr>
<tr>
<td>Excellent or good health status, %</td>
<td>89.4</td>
<td>90.0</td>
<td>77.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lives alone, %a</td>
<td>11.9</td>
<td>11.8</td>
<td>12.9</td>
<td>0.718</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>4.9</td>
<td>4.9</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>15.6</td>
<td>15.2</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>College or graduate school</td>
<td>79.5</td>
<td>80.0</td>
<td>69.8</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake, drinks/week, %</td>
<td></td>
<td></td>
<td></td>
<td>0.165</td>
</tr>
<tr>
<td>0-2</td>
<td>46.0</td>
<td>45.6</td>
<td>54.3</td>
<td></td>
</tr>
<tr>
<td>3-13</td>
<td>48.1</td>
<td>48.5</td>
<td>39.7</td>
<td></td>
</tr>
<tr>
<td>≥ 14</td>
<td>5.9</td>
<td>5.9</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>1.9</td>
<td>1.8</td>
<td>4.3</td>
<td>0.054</td>
</tr>
<tr>
<td>Caffeine intake, mg/day, mean ± SD</td>
<td>237 ± 245</td>
<td>237 ± 246</td>
<td>229 ± 207</td>
<td>0.728</td>
</tr>
<tr>
<td>Use of antidepressants at baseline, %</td>
<td>6.3</td>
<td>5.7</td>
<td>19.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Use of benzodiazepines at baseline, %</td>
<td>3.8</td>
<td>0.4</td>
<td>12.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Use of nonbenzodiazepine anxiolytic/hypnotic use at baseline, %</td>
<td>2.0</td>
<td>2.0</td>
<td>2.6</td>
<td>0.639</td>
</tr>
<tr>
<td>Modified Mini-Mental State Examination Score, range 0-100, mean ± SD</td>
<td>93.3 ± 5.4</td>
<td>93.4 ± 5.2</td>
<td>90.1 ± 7.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean ± SD</td>
<td>27.2 ± 3.7</td>
<td>27.2 ± 3.7</td>
<td>27.7 ± 4.5</td>
<td>0.163</td>
</tr>
<tr>
<td>Walks for exercise, %</td>
<td>48.3</td>
<td>48.6</td>
<td>40.5</td>
<td>0.088</td>
</tr>
<tr>
<td>Any instrumental activity of daily living impairment, %</td>
<td>16.9</td>
<td>15.9</td>
<td>36.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 1 selected medical conditions, %</td>
<td>33.6</td>
<td>32.7</td>
<td>52.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GDS at baseline, mean (SD)</td>
<td>1.21 (1.25)</td>
<td>2.60 (1.47)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>GDS at follow-up, mean (SD)</td>
<td>1.43 (1.35)</td>
<td>7.69 (2.13)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

ESS, Epworth Sleepiness Scale questionnaire; GDS, Geriatric Depression Scale; PSQI, Pittsburgh Sleep Quality Index questionnaire; SD, standard deviation. 

*Measurement taken at a previous clinic visit. *Kruskal-Wallis test used due to skewed distribution. *History of one or more selected medical conditions includes stroke, diabetes mellitus, parkinsonism, chronic obstructive lung disease, chronic kidney disease, congestive heart failure, and myocardial infarction.
adjusted models, or in multivariable adjusted models (Table 2). Results were similar in analyses excluding baseline antidepressant users.

Longitudinal Associations of Objective Sleep/Wake Disturbances and Depression

In age- and site-adjusted models, we observed statistically significant associations between objective sleep/wake summary score (per one-unit increase), sleep efficiency < 70% versus ≥ 70%, sleep latency ≥ 1 h versus < 1 h, awakening after sleep onset ≥ 1.5 h versus < 1.5 h, and eight or more versus fewer than 8 long wake episodes and greater odds of being depressed (Table 2). Results however were attenuated and no longer statistically significant after further adjustment for the number of baseline depressive symptoms, as well as after additional adjustment for multiple potential confounders (Table 2).

Table 2—Association between sleep/wake disturbances and odds of depression at follow-up

<table>
<thead>
<tr>
<th>Sleep/wake Disturbances</th>
<th>Prevalence</th>
<th>Depressed versus not depressed (Including baseline antidepressant users (n = 2,510))</th>
<th>Depressed versus not depressed (Excluding baseline antidepressant users (n = 2,352))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds ratio (95% confidence interval)</td>
<td>Odds ratio (95% confidence interval)</td>
</tr>
<tr>
<td><strong>Self-reported sleep/wake disturbances</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor sleep quality (PSQI &gt; 5 versus ≤ 5)</td>
<td>41.4%</td>
<td>2.55 (1.72-3.77) <strong>&lt; 0.001</strong></td>
<td>2.56 (1.66-3.95) <strong>&lt; 0.001</strong></td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>1.75 (1.16-2.65) 0.008</td>
<td>1.79 (1.14-2.82) 0.011</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.53 (1.00-2.33) 0.051</td>
<td>1.64 (1.03-2.62) 0.037</td>
<td></td>
</tr>
<tr>
<td>Excessive daytime sleepiness (ESS &gt; 10 versus ≤ 10)</td>
<td>11.5%</td>
<td>1.39 (0.82-2.35) 0.223</td>
<td>1.11 (0.59-2.08) 0.743</td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>0.99 (0.57-1.72) 0.980</td>
<td>0.78 (0.41-1.50) 0.463</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>0.92 (0.52-1.64) 0.778</td>
<td>0.77 (0.39-1.52) 0.442</td>
<td></td>
</tr>
<tr>
<td><strong>Objective sleep/wake disturbances</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary Objective Disturbance Score (0-5), per one-unit increase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>1.20 (1.07-1.36) 0.002</td>
<td>1.17 (1.02-1.34) 0.023</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.06 (0.93-1.21) 0.415</td>
<td>1.03 (0.89-1.20) 0.677</td>
<td></td>
</tr>
<tr>
<td>Poor sleep efficiency (&lt; 70% versus ≥ 70%)</td>
<td>9.8%</td>
<td>1.88 (1.13-3.13) 0.016</td>
<td>1.71 (0.96-3.06) 0.069</td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>1.45 (0.85-2.49) 0.173</td>
<td>1.32 (0.72-2.42) 0.378</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.22 (0.69-2.14) 0.493</td>
<td>1.11 (0.59-2.11) 0.741</td>
<td></td>
</tr>
<tr>
<td>Prolonged sleep latency (≥ 1 h versus &lt; 1 h)</td>
<td>9.3%</td>
<td>1.77 (1.04-3.00) 0.035</td>
<td>1.59 (0.86-2.92) 0.139</td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>1.44 (0.83-2.50) 0.195</td>
<td>1.31 (0.70-2.47) 0.400</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.22 (0.68-2.19) 0.508</td>
<td>1.16 (0.59-2.27) 0.665</td>
<td></td>
</tr>
<tr>
<td>Greater nighttime wakefulness (WASO ≥ 1.5 h versus &lt; 1.5 h)</td>
<td>30.4%</td>
<td>1.48 (1.01-2.18) 0.046</td>
<td>1.34 (0.87-2.06) 0.188</td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>1.23 (0.82-1.84) 0.313</td>
<td>1.12 (0.71-1.75) 0.629</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.09 (0.71-1.65) 0.702</td>
<td>0.97 (0.61-1.54) 0.741</td>
<td></td>
</tr>
<tr>
<td>Multiple long-wake episodes (≥ 8 versus &lt; 8)</td>
<td>31.2%</td>
<td>1.69 (1.15-2.47) 0.007</td>
<td>1.53 (1.00-2.33) 0.052</td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>1.37 (0.92-2.03) 0.122</td>
<td>1.26 (0.81-1.95) 0.310</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.17 (0.77-1.77) 0.471</td>
<td>1.08 (0.68-1.72) 0.739</td>
<td></td>
</tr>
<tr>
<td>Short versus normal sleep duration (TST ≤ 5 h versus 6-8 h)</td>
<td>11.5%</td>
<td>1.52 (0.90-2.56) 0.118</td>
<td>1.36 (0.75-2.48) 0.308</td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>1.20 (0.70-2.07) 0.513</td>
<td>1.08 (0.58-2.01) 0.814</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.06 (0.60-1.87) 0.848</td>
<td>0.94 (0.49-1.80) 0.846</td>
<td></td>
</tr>
<tr>
<td>Long versus normal sleep duration (TST &gt; 8 h versus 6-8 h)</td>
<td>7.0%</td>
<td>1.38 (0.72-2.66) 0.337</td>
<td>1.69 (0.84-3.38) 0.138</td>
</tr>
<tr>
<td>Age- and site-adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base model</td>
<td>1.42 (0.72-2.80) 0.306</td>
<td>1.76 (0.86-3.60) 0.121</td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1.27 (0.64-2.55) 0.493</td>
<td>1.71 (0.82-3.54) 0.150</td>
<td></td>
</tr>
</tbody>
</table>

*Objective sleep/wake disturbances measured using wrist actigraphy. Base model adjusted for age, clinic site and baseline GDS score. Multivariate model adjusted for age, clinic site, baseline GDS score, health status, education, use of benzodiazepines, use of antidepressants (in analyses including baseline antidepressant users), alcohol consumption, cognitive function, walks for exercise, impairments in activities of daily living and certain medical conditions. ESS, Epworth Sleepiness Scale; GDS, Geriatric Depression Scale; PSQI, Pittsburgh Sleep Quality Index; TST, total sleep time; WASO, wake after sleep onset.*
Tests for an interaction between subjective poor sleep quality and objective summary score were not statistically significant (P for interaction = 0.389). Furthermore, results were similar and remained nonsignificant in analyses that excluded baseline antidepressant users. We did not observe statistically significant associations between sleep duration categories and depression status at follow-up in any of the models.

**Additional Analyses**

When the sleep parameters were expressed as continuous variables, there was evidence of linear associations of increasing sleep latency, increasing numbers of long-wake episodes, and worsening PSQI with higher odds of depression at follow-up, in models adjusted for age, site, and baseline GDS score (Table 3). After further adjustment for multiple potential confounders, these associations were attenuated and were no longer significant. There was no evidence of linear associations of sleep efficiency, awakening after sleep onset, TST, and ESS with odds of depression at follow-up.

**DISCUSSION**

Poor self-reported sleep quality at baseline was independently associated with greater odds of incident depression at follow-up in older, community-dwelling men. Men with poor sleep efficiency, prolonged sleep latency, greater nighttime wakefulness, multiple long-wake episodes, and greater burden of objectively measured sleep/wake disturbances also had greater odds of being depressed at the follow-up examination. These associations were mostly explained by having a greater number of depressive symptoms at baseline among men with these sleep disturbances. Furthermore, we did not observe an association of objectively assessed TST or reports of daytime sleepiness with depression status at follow-up.

Although we were unable to identify other studies that have examined the longitudinal associations between actigraphy-assessed sleep/wake disturbances and risk of developing depression, our findings regarding self-reported sleep disturbances are generally consistent with previously published studies. A meta-analysis including longitudinal studies across a variety of age groups found that in comparison with participants without insomnia, nondepressed participants with insomnia or insomnia symptoms have a 2-fold increased risk of developing depression. Although we did not specifically assess insomnia in our study, our results also suggested that the odds of being depressed at follow-up ranged from 1.3 to 2.5-fold higher among men with poor sleep quality at baseline. Furthermore, we observed that greater burden of depressive symptoms at baseline and health-related factors partially explained the association between poor sleep quality and risk of depression at follow-up. Because we did not ascertain a self-reported history of depression in the study, we are unable to discern whether burden of depressive symptoms at baseline indicate participants who

### Table 3—Association between continuous sleep/wake parameters and odds of depression at follow-up

<table>
<thead>
<tr>
<th>Unit (per SD)</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not depressed (n = 2,394)</td>
</tr>
<tr>
<td><strong>Self-reported sleep/wake measures</strong></td>
<td></td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>Per 3.1 unit increase</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>Per 3.5 unit increase</td>
</tr>
<tr>
<td><strong>Objective Sleep/wake disturbances</strong></td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>Per 10.0% decrease</td>
</tr>
<tr>
<td>Sleep latency, 1 h</td>
<td>Per 30 min increase</td>
</tr>
<tr>
<td>Awake after sleep onset, 1.5 h</td>
<td>Per 42 min increase</td>
</tr>
<tr>
<td>Long-wake episodes, N</td>
<td>Per 3.2 additional episodes</td>
</tr>
<tr>
<td>Total sleep time, h</td>
<td>Per 1.2 h decrease</td>
</tr>
</tbody>
</table>

N = 2,510. Objective sleep/wake disturbances measured using wrist actigraphy. Adjusted for age, clinic site, baseline GDS score. Adjusted for age, clinic site, baseline GDS score, health status, education, use of benzodiazepines or antidepressants at baseline, alcohol consumption, cognitive function, walks for exercise, impairments in activities of daily living and certain medical conditions. GDS, Geriatric Depression Scale; SD, standard deviation.
were not ‘depressed’ according to a GDS score < 6, but who had a history of depressive illness. It is also possible that depressive symptoms at baseline were attributable to sleep disturbances at baseline because the association between sleep and depression may be bidirectional in nature. Furthermore, there was no evidence of linearity in multivariable adjusted models examining associations between self-reported sleep quality (using the PSQI) and odds of depression at follow-up. This suggests that a threshold rather than linear association exists between sleep quality and depression. We also did not find any evidence of an interaction between poor subjective sleep quality (PSQI > 5 versus ≤ 5) and objective sleep/wake disturbances summary score, which suggests that in this cohort, associations between objective sleep/wake measures did not differ by presence/absence of subjective poor sleep quality.

Prior studies using objective measures (PSG) of sleep have observed that dysregulations in REM sleep patterns are associated with recurrent depressive episodes18,19 and that disturbances in PSG parameters (such as reduced REM latency and slow wave sleep) are associated with a greater lifetime risk of depression.20 Our current analysis did not use PSG parameters.

Our findings also suggest that the associations between objectively assessed poor sleep efficiency, prolonged sleep latency, greater nighttime wakefulness, and multiple long-wake episodes, and increased odds of depression at follow-up are largely explained by a higher burden of depressive symptoms at baseline among older men with these sleep disturbances. The results of our previously published cross-sectional analyses21 showed independent associations between greater level of depressive symptoms (expressed as GDS 0-2; 3-5; ≥ 6) and higher odds of poor sleep quality, excessive daytime sleepiness, and objectively assessed prolonged sleep latency at baseline. The clinical implications of our findings, both cross-sectional and longitudinal, suggest that older men presenting with reports of disturbed sleep should be evaluated for prevalent depressive symptoms and depression. The underlying mechanisms explaining why poor self-reported sleep quality, but not objective assessments of sleep/wake disturbances, is an independent predictor of future depression are not understood. Future studies should continue to focus efforts on furthering our understanding of the mechanisms underlying sleep and depression pathways and the direction of the associations.

The strengths of this study include a large sample size; excellent follow-up (> 90%), participants from six different areas of the United States; and participant selection that was not contingent on presence of a sleep disorder, depression, or other medical conditions; a comprehensive set of measurements, including validated measures of both self-reported and objective sleep/wake parameters; and robustness of results to sensitivity analyses.

There are also several limitations to note. Because the cohort included only older, community-dwelling, primarily Caucasian men, these results may not apply to other populations. Also, these analyses rely on a self-reported questionnaire to assess depressive symptoms and depression. Although this scale has performed well in validation studies, it is not a clinical measure of depression; therefore, studies using clinical measures of depression would improve our understanding of the sleep/wake-depression association. Information on history of depression prior to baseline was not assessed, and we are unable to discern whether the men in our study have had prior depressive episodes. Furthermore, approximately 75% of the cohort experienced no change or only a one-unit change in GDS symptoms during follow-up. Although these men were generally healthy at baseline, there remains the question about how sensitive the GDS is to change in symptoms in older men. Future studies should further evaluate the sensitivity of the GDS to change, and confirm results using other measures of depression. Future studies should also examine longitudinal associations using alternative objective parameters (such as those obtained with PSG), as well as explore the interrelationships between objective and subjective measures of sleep. The follow-up time was relatively short, and some of the associations may reflect reverse causality.

There are also a few limitations to note regarding actigraphy. Actigraphy algorithms may be less reliable in people who have insomnia, and will result in overestimations of periods of sleep. It is also important to note that there was a modest correlation between actigraphy and PSG in our cohort (ICC = 0.32-0.57).26 We did not assess insomnia in our cohort, but are confident that if this bias exists, it likely has an attenuating effect on our results.

CONCLUSION

In summary, in a cohort of nondepressed, community-dwelling older men at baseline, poor subjective sleep quality was associated with depression at follow-up. Associations of objectively measured reduced sleep efficiency, prolonged sleep latency, greater nighttime wakefulness, and greater long-wake episodes with depression at follow-up were mostly explained by having a greater number of depressive symptoms at baseline in men with these sleep disturbances.

ACKNOWLEDGMENTS

The National Heart, Lung, and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study “Outcomes of Sleep Disorders in Older Men” under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839. The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health (NIH) funding. The following institutes provide support: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Center for Research Resources (NCRR), and NIH Roadmap for Medical Research under the following grant numbers: U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01 AG027810, and UL1 RR024140. This work was also supported with resources and the use of facilities at the Minneapolis VA Medical Center. The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Ancoli-Israel has been a consultant or served on the advisory board of Ferring Pharmaceuticals, GlaxoSmithKline, Merck, Neurocrine Biosciences, Pfizer, Respironics/Philips, Sanofi-Aventis, Somaxon, and that disturbances in PSG parameters (such as reduced REM latency and slow wave sleep) are associated with a greater lifetime risk of depression.20 Our current analysis did not use PSG parameters.

Our findings also suggest that the associations between objectively assessed poor sleep efficiency, prolonged sleep latency, greater nighttime wakefulness, and multiple long-wake episodes, and increased odds of depression at follow-up are largely explained by a higher burden of depressive symptoms at baseline among older men with these sleep disturbances. The results of our previously published cross-sectional analyses21 showed independent associations between greater level of depressive symptoms (expressed as GDS 0-2; 3-5; ≥ 6) and higher odds of poor sleep quality, excessive daytime sleepiness, and objectively assessed prolonged sleep latency at baseline. The clinical implications of our findings, both cross-sectional and longitudinal, suggest that older men presenting with reports of disturbed sleep should be evaluated for prevalent depressive symptoms and depression. The underlying mechanisms explaining why poor self-reported sleep quality, but not objective assessments of sleep/wake disturbances, is an independent predictor of future depression are not understood. Future studies should continue to focus efforts on furthering our understanding of the mechanisms underlying sleep and depression pathways and the direction of the associations.

The strengths of this study include a large sample size; excellent follow-up (> 90%), participants from six different areas of the United States; and participant selection that was not contingent on presence of a sleep disorder, depression, or other medical conditions; a comprehensive set of measurements, including validated measures of both self-reported and objective sleep/wake parameters; and robustness of results to sensitivity analyses.

There are also several limitations to note. Because the cohort included only older, community-dwelling, primarily Caucasian men, these results may not apply to other populations. Also, these analyses rely on a self-reported questionnaire to assess depressive symptoms and depression. Although this scale has performed well in validation studies, it is not a clinical measure of depression; therefore, studies using clinical measures of depression would improve our understanding of the sleep/wake-depression association. Information on history of depression prior to baseline was not assessed, and we are unable to discern whether the men in our study have had prior depressive episodes. Furthermore, approximately 75% of the cohort experienced no change or only a one-unit change in GDS symptoms during follow-up. Although these men were generally healthy at baseline, there remains the question about how sensitive the GDS is to change in symptoms in older men. Future studies should further evaluate the sensitivity of the GDS to change, and confirm results using other measures of depression. Future studies should also examine longitudinal associations using alternative objective parameters (such as those obtained with PSG), as well as explore the interrelationships between objective and subjective measures of sleep. The follow-up time was relatively short, and some of the associations may reflect reverse causality.

There are also a few limitations to note regarding actigraphy. Actigraphy algorithms may be less reliable in people who have insomnia, and will result in overestimations of periods of sleep. It is also important to note that there was a modest correlation between actigraphy and PSG in our cohort (ICC = 0.32-0.57).26 We did not assess insomnia in our cohort, but are confident that if this bias exists, it likely has an attenuating effect on our results.

CONCLUSION

In summary, in a cohort of nondepressed, community-dwelling older men at baseline, poor subjective sleep quality was associated with depression at follow-up. Associations of objectively measured reduced sleep efficiency, prolonged sleep latency, greater nighttime wakefulness, and greater long-wake episodes with depression at follow-up were mostly explained by having a greater number of depressive symptoms at baseline in men with these sleep disturbances.

ACKNOWLEDGMENTS

The National Heart, Lung, and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study “Outcomes of Sleep Disorders in Older Men” under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839. The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health (NIH) funding. The following institutes provide support: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Center for Research Resources (NCRR), and NIH Roadmap for Medical Research under the following grant numbers: U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01 AG027810, and UL1 RR024140. This work was also supported with resources and the use of facilities at the Minneapolis VA Medical Center. The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Ancoli-Israel has been a consultant or served on the advisory board of Ferring Pharmaceuticals, GlaxoSmithKline, Merck, Neurocrine Biosciences, Pfizer, Respironics/Philips, Sanofi-Aventis, Somaxon,
and had a grant from Litebook, Inc. Dr. Corey-Bloom has received research funds from Elan, SIENA, PRANA, and Teva. Dr. Redline has received research equipment and/or research support from Philips Respironics and ResMed Inc. and ResMed Foundation. The other authors have indicated no financial conflicts of interest.

REFERENCES

1. Ancoli-Israel S. Sleep and aging: prevalence of disturbed sleep and treat-
2. Ancoli-Israel S, Cooke JR. Prevalence and comorbidity of insomnia
and effect on functioning in elderly populations. J Am Geriat Soc
3. Neikrug AB, Ancoli-Israel S. Sleep disorders in the older adult - a mini-
4. Ohayon MM. Epidemiology of insomnia: what we know and what we still
5. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of de-
pression: a meta-analytic evaluation of longitudinal epidemiological stud-
6. Cole MG, Dendukuri N. Risk factors for depression among elderly com-
munity subjects: a systematic review and meta-analysis. Am J Psychiatry
2003;160:1147-56.
7. Pincus T, Summey JA, Soraci SA, Jr, Wallston KA, Hummon NP. As-
sessment of patient satisfaction in activities of daily living using a modified
8. Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints
and depression in an aging cohort: a prospective perspective. Am J Psychi-
9. Spira AP, Covinsky K, Rebok GW, et al. Poor sleep quality and func-
10. Callahan CM, Koenke K, Counsell SR, et al. Treatment of depres-
sion improves physical functioning in older adults. J Am Geriat Soc
Depression, falls, and risk of fracture in older women. Study of Osteo-
13. Ohayon MM, Roth T. What are the contributing factors for insomnia in the
14. Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relations-
hips for subsequent depression and therapeutic implications. Dialogues
and insomnia subtypes: a longitudinal study on the elderly in Japan. Sleep
2010;33:1693-702.
16. Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints
and depression in an aging cohort: a prospective perspective. Am J Psychi-
17. Livingston G, Blizard B, Mann A. Does sleep disturbance predict de-
pression in elderly people! A study in inner London. Br J Gen Pract
18. Kupfer DJ, Ehlers CL, Frank E, Grochocinski VJ, McEachran AB. EKG
19. Kupfer DJ. Sleep research in depressive illness: clinical implications--a
20. Giles DE, Kupfer DJ, Rush AJ, Roffwarg HP. Controlled comparison of
electrophysiological sleep in families of probands with unipolar depres-
symptoms and sleep disturbances in community-dwelling older men. J
22. Maglione JE, Ancoli-Israel S, Peters KW, et al. Depressive symptoms and
subjective and objective sleep in community-dwelling older women. J
23. Orwell E, Blank JB, Barrett-Connor E, et al. Design and baseline charac-
teristics of the osteoporotic fractures in men (MrOS) study--a large obser-
vational study of the determinants of fracture in older men. Contemp Clin

24. Blank JB, Cawthon PM, Carrion-Petersen ML, et al. Overview of recruit-
ment for the osteoporotic fractures in men study (MrOS). Contemp Clin
Trials 2005;26:557-68.
The role of actigraphy in the study of sleep and circadian rhythms. Sleep
26. Blackwell T, Ancoli-Israel S, Redline S, Stone KL. Factors that may in-
fluence the classification of sleep-wake by actigraphy: the MrOS Sleep
estimation from wrist movement quantified by different actigraphic mo-
29. Blackwell T, Ancoli-Israel S, Gehrmann PR, Schneider JL, Pedula KL,
Stone KL. Actigraphy scoring reliability in the study of osteoporotic frac-
30. Blackwell T, Ancoli-Israel S, Redline S, Stone KL. Factors that may in-
fluence the classification of sleep-wake by actigraphy: the MrOS Sleep
teristics and cognition in older community-dwelling men: the MrOS sleep
study. Sleep 2011;34:1347-56.
32. Ensrud KE, Blackwell TL, Redline S, et al. Sleep disturbances and
2009;57:2085-93.
34. Fava M. Daytime sleepiness and insomnia as correlates of depression. J
35. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure func-
tional status outcomes for disorders of excessive sleepiness. Sleep
1997;20:835-43.
36. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The
Pittsburgh Sleep Quality Index: a new instrument for psychiatric prac-
37. Buysse DJ, Reynolds CF III, Monk TH, Hoch CC, Yeager AL, Kupfer
DJ. Quantification of subjective sleep quality in healthy elderly men and
women using the Pittsburgh Sleep Quality Index (PSQI). Sleep
Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in older
40. Johns MW. Sensitivity and specificity of the multiple sleep latency test
(MSLT), the maintenance of wakefulness test and the epworth sleepiness
41. Sheikh J, Yesavage J. Geriatric Depression Scale: recent evidence and
42. Almeida OP, Almeida SA. Short versions of the geriatric depression scale:
a study of their validity for the diagnosis of a major depressive episode ac-
43. Ware J, Kosinski M, Keller SF, SF-12: How to score the SF-12 Physical
and Mental Health Summary Scores. 1998;
44. Barone JJ, Roberts HR. Caffeine consumption. Food Chem Toxicol
45. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. As-
seessment of patient satisfaction in activities of daily living using a modified
46. Fitti JE, Kovar MG. The Supplement on Aging to the 1984 National
47. Pahor M, Chrishilles EA, Guralnik JM, Brown SL, Wallace RB, Carbon-
bon P. Drug data coding and analysis in epidemiologic studies. Eur J
48. Teng EL,Chui HC. The Modified Mini-Mental State (3MS) examination.