

# Risk Factors for Excessive Sleepiness in Older Adults

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**Objective:** To determine risk factors for excessive daytime sleepiness in older adults.

**Methods:** This is a cross-sectional study assessing multiple risk factors for excessive daytime sleepiness in older subjects (mean age, 78 years; range 65–98 years) with (n = 149) and without (n = 144) complaints of frequent excessive daytime sleepiness. Assessment of risk factors included full in-laboratory sleep studies.

**Results:** Excessive sleepiness among the elderly is multifactorial. Multivariable modeling identified the following as simultaneously significant risk factors for excessive sleepiness: severe sleep-disordered breathing (apnea–hypopnea index, >30 episodes/hr), self-report of poor sleep quality, increased percentage of time in rapid eye movement sleep, pain at night at least three times per week, wheezing or whistling from chest at night, and medications with sleepiness as a side effect. Male sex also was associated with increased risk, whereas alcohol use (more than seven beverages per week) reduced the risk for sleepiness. Multiple risk factors were more commonly present in those with complaints of sleepiness. The presence of periodic limb movements, which are common in older adults, was not associated with sleepiness.

**Interpretation:** There is a distinct differential diagnosis of excessive daytime sleepiness in older adults. Many of the risk factors that we identified are treatable.

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Excessive daytime sleepiness in the elderly is common, affecting about 10 to 30% of adults older than 65 years.<sup>1–6</sup> Among the disorders that might be a risk factor, obstructive sleep apnea has the highest prevalence (see Lindberg and Gislason's article<sup>7</sup> for review). This prevalence increases with age<sup>8,9</sup> and is extremely common in otherwise well elderly.<sup>10,11</sup> But in the elderly, there is only a weak relation between the presence of sleep-disordered breathing and daytime complaints,<sup>11</sup> raising questions about the relevance of sleep-disordered breathing in this age group.<sup>12–15</sup> A weak relation between degree of sleep-disordered breathing and daytime complaints might arise because excessive sleepiness in older adults is multifactorial. Other potential causes are other sleep disorders, such as periodic limb movement disorder, which is also common in the elderly<sup>16</sup>; medical conditions that interrupt sleep (eg, chronic pain); or medications that have sleepiness as a side effect.<sup>17</sup>

To identify risk factors for excessive sleepiness in older adults and to identify their relative role, we performed a cross-sectional study in which we compared the presence of risk factors in subjects who had com-

plaints of excessive sleepiness to subjects without such problems. We analyzed the data arising from this study using case–control methodology. For ease of presentation, we refer to individuals with self-reported sleepiness as “cases” and those with no sleepiness as “control subjects.” Sensitivity analyses were then performed using “case–control” definitions that also included an objective criterion based on the Multiple Sleep Latency Test, a measure of sleep propensity.<sup>18,19</sup> Full in-laboratory sleep studies were performed for all subjects. Risk factors assessed included objective assessments of sleep disorders, self-reports of symptoms of sleep disorders, quantitative aspects of sleep characteristics, other factors that may interrupt sleep, medications with sleepiness as a side effect, comorbidities, and demographic and behavioral factors.

## Subjects and Methods

### *Study Design and Subjects*

Elderly adults (n = 293; 149 cases with sleepiness, 144 control subjects) were recruited from retirement communities supplemented by recruitment of community-dwelling African Americans. Individuals in these retirement communities

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Table 1. Summary of Descriptive Statistics of Risk Factors within Seven Domains Assessed for Associations with Excessive Daytime Sleepiness in Cases Relative to Control Subjects

Risk Factors	Cases (N = 149)	Control Subjects (N = 144)
Objective assessments of sleep disorders		
Mean apnea-hypopnea index score (SD)	17.7 (22.1)	11.9 (16.1)
Self-reports of sleep disorder symptoms and sleep quality		
Mean Pittsburgh Sleep Quality Index of overall sleep quality score (SD)	0.98 (0.70)	0.63 (0.62)
Quantitative aspects of sleep characteristics (architecture)		
Mean REM latency, min (SD)	101.1 (72.1)	112.8 (79.4)
Other factors (symptoms) that may interrupt sleep		
Pain or physical discomfort $\geq 3$ times/week, n (% of subjects)	25 (16.8)	5 (3.5)
Medications with sleepiness as a side effect		
US Pharmacopoeia more/less common vs rare/none, n (% of subjects)	107 (71.8)	80 (55.6)
Comorbidities		
Any heart disease, n (% of subjects)	54 (36.2)	36 (25.0)
Demographic and behavioral factors		
Mean age, yr (SD)	78.0 (6.3)	77.8 (6.4)
Male sex, n (%)	41 (27.5)	34 (23.6)
>7 alcoholic beverages per week, n (%)	17 (11.4)	32 (22.2)
Current smoker, n (%)	5 (3.4)	11 (7.6)

Only results for factors selected for inclusion in the initial multivariable model are included.  
SD = standard deviation; REM = rapid eye movement.

were approached about being involved in this study. Subjects initially responded to a brief questionnaire to assess whether they had excessive sleepiness and to assess exclusion criteria. Thus, individuals with excessive sleepiness and those with no excessive sleepiness came from the same source. All subjects were at least 65 years of age and currently free of clinically significant depression (ie, Geriatric Depression Score,  $<10^{20}$ ) and of dementia (ie, Short Blessed Examination Score,  $<7^{21}$ ). The Institutional Review Board of the University of Pennsylvania Medical Center approved the study protocol. All participating subjects provided written informed consent.

Individuals with excessive daytime sleepiness were those subjectively reporting problems with daytime sleepiness at least three to four times per week. Control subjects were selected as elderly individuals reporting neither problems with daytime sleepiness nor falling asleep in active or passive situations more than once or twice during the prior 1-month period. Individuals who met neither case nor control criteria were considered indeterminate and were not further studied. Enrolled subjects were also asked to complete the Epworth Sleepiness Scale,<sup>22-25</sup> a widely used standardized self-report instrument that assesses propensity for sleepiness; and, after a second overnight sleep study, subjects had objective daytime sleep propensity assessed four times by the Multiple Sleep Latency Test every 2 hours from 9 AM to 3 PM.<sup>18,19</sup>

#### Assessment of Potential Risk Factors

Potential risk factors for excessive sleepiness were organized into seven domains: (1) objective assessments of sleep disorders (five variables measuring severity of sleep-disordered breathing, inability to initiate or to sustain sleep, and periodic leg movements [PLMs]); (2) self-reports of sleep disorder symptoms and sleep quality (six variables reflecting general sleep quality, sleep apnea, insomnia, and restless leg syndrome); (3) quantitative aspects of sleep characteristics

(six variables measuring arousals during sleep, percentages of times in different sleep stages, and latency to rapid eye movement [REM] sleep); (4) other factors that may interrupt sleep (seven variables reflecting frequency of pain during sleep, nocturia, heartburn, indigestion, wheezing, chest pain, and environmental noise); (5) use of medications with sleepiness as a common side effect (one variable); (6) comorbidities (eight categories; see further discussion later in this article); and (7) demographic and behavioral factors (five variables reflecting demographics, obesity, smoking, and drinking status). Thus, based on clinical considerations, we limited attention to 38 variables reflecting these 7 domains. Then, to further reduce the likelihood of false-positive findings, we specified, based on consideration of known pathogenesis, an initial multivariable model that included one factor from each of the first six domains and all factors in the demographic and behavioral factors domain with the exception of obesity, which is associated with sleep apnea (see list of variables selected in Table 1). All remaining factors were then assessed as potential confounding variables and as secondary risk factors. In addition, multivariable models included a factor to account for the stratified sampling of elderly individuals from retirement communities versus elderly community-residing African Americans. The following sections provide details regarding the potential risk factors for sleepiness in the elderly assessed in this study.

**OBJECTIVE ASSESSMENTS OF SLEEP DISORDERS.** All participants underwent two full overnight polysomnographic sleep studies using standardized techniques with airflow being assessed by thermistors (see Gurubhagavatula and colleagues' article<sup>26</sup> for techniques used in our laboratory). (This study was initiated before reports showing the superiority of nasal pressure recordings compared with thermistors.<sup>27</sup>) An overnight sleep study involves simultaneous

recording of sleep and breathing by electroencephalography, measuring airflow, effort, and oximetry. The first study was an acclimation night, whereas the second study was scored for risk factor assessment. Severity of sleep apnea was measured by the apnea–hypopnea index defined as the number of apneas plus hypopneas per hour of sleep. A hypopnea was defined as a clearly discernible decrease in airflow associated with a 4% desaturation, arousal, or both. The apnea–hypopnea index was analyzed as a continuous variable in the initial multivariable model rather than as a dichotomous or categorical risk factor. This avoided the loss of statistical power associated with dichotomizing inherently continuous variables<sup>28</sup> and reduced type I error for other risk factors that require control of the apnea–hypopnea index as a confounding factor.<sup>29</sup> Odds ratios (ORs) for continuous risk factors are more interpretable when they reflect increased risk for clinically meaningful increases in their magnitudes. The standard deviations (SDs) of the apnea–hypopnea indices in subjects with sleepiness and in control subjects were 22.1 and 16.1 events/hr, respectively. Thus, the OR for apnea–hypopnea index was defined for a 20 events/hr increase (ie, approximately 1 SD), a clinically significant increase consistent with sample variability. Consensus guidelines recently have been developed that define mild, moderate, and severe disease as 5 to <15, 15 to <30, and  $\geq 30$  events/hr, respectively.<sup>10</sup> The effects of sleep apnea severity on risk relative to less than five events per hour were also assessed for these categories in supporting analyses.

Insomnia was defined objectively as sleep efficiency during the sleep study. This was computed as total sleep time divided by total time in bed expressed as a percentage. Sleep efficiency during the sleep study was assessed as a continuous variable and using a conventional dichotomous criterion (<80 vs  $\geq 80\%$ ).

Severity of PLMs was measured based on standard definitions.<sup>16,30</sup> Tibialis electromyogram bursts were scored if they were 0.5 to 5.0 seconds in duration, they had an interevent interval of 5 to 12 seconds, and there were 3 or more consecutive movements. The leg movements index was defined as the number of such movements per hour of sleep. This study preceded more recent definitions for epidemiological purposes.<sup>31</sup> The distribution of the PLM index was extremely skewed as reflected in the much larger mean values compared with median values (mean and median values [in brackets] among individuals with sleepiness and control subjects were 15.1 [1.0] and 14.2 [2.0], respectively, whereas SDs were 26.3 and 23.0, respectively). As a consequence, ORs defined for increases in the PLM index were not adequately interpretable. Therefore, the OR was defined for having a PLM index value larger than the pooled 75th percentile value (18 events/hr). Mean (and median) PLMs with arousal per hour among individuals with sleepiness and control subjects were 2.6 (0.0) and 2.4 (0.3), respectively. A pooled 75th percentile threshold value for PLMs with arousal was similarly defined (2.2 events/hr).

**SELF-REPORTS OF SLEEP DISORDER SYMPTOMS AND SLEEP QUALITY.** Four specific indices from the Pittsburgh Sleep Quality Index<sup>32</sup> were selected that provide self-assessments of one's overall sleep quality, ability to initiate sleep (ie, sleep

latency), usual sleep duration, and habitual sleep efficiency. This index has been used to compare healthy older adults with younger adults.<sup>33</sup> The global summary score could not be used because it includes a daytime dysfunction component. Therefore, the Pittsburgh Sleep Quality Global self-report of overall sleep quality score was selected for inclusion in the initial model. Respondents rate overall sleep quality in the last month according to the following scale: very good, fairly good, fairly bad, and very bad, which we scored as 0, 1, 2, and 3, respectively. The magnitude of risk was assessed for a one-point increase. For self-report of sleep apnea, we selected what is called Index 1 from the Multivariable Apnea Prediction questionnaire.<sup>34</sup> This index is a validated measure of the frequency of symptoms associated with sleep apnea; it is constructed from items reflecting the frequency of loud snoring, snorting and gasping, and breathing problems or struggling for breath. To assess self-report of restless legs, we used another question from this instrument,<sup>34</sup> ie, the frequency of the symptom “your legs feel jumpy or jerk.” This is a surrogate for restless legs syndrome but is not validated. These questions, and additional items described later from the Penn Sleep Survey, are of the form, “On average, how many day/nights during the last month have you had or been told you do the following while asleep or trying to sleep?” Answers are: never; rarely (<1 time/week); one to two, three to four, or five to seven times/week. Indices reflecting excessive sleepiness from the Pittsburgh Sleep Quality Index<sup>32,33</sup> and the Multivariable Apnea Prediction<sup>34</sup> were not assessed as risk factors, but instead were included in the analyses of concurrent validity of the “case–control” definitions.

**QUANTITATIVE ASPECTS OF SLEEP CHARACTERISTICS.** To assess the severity of sleep fragmentation, we defined an arousal index as the number of arousals per hour of sleep.<sup>35</sup> The arousal index is known to be associated with the apnea–hypopnea index because respiratory events during sleep often terminate with arousal. Therefore, it was not chosen for inclusion in the initial multivariable model. Other variables used to characterize sleep architecture included the percentages of time spent in stage 1, stage 3/4 (slow-wave sleep), and REM sleep. Because shortening of REM latency and hypersomnia have been described in depression (see Riemann and colleagues' article<sup>36</sup> for review), including subthreshold depression<sup>37</sup> both decreased REM latency (ie, assessed as a continuous variable defined by a SD = 75-minute decrease) and a latency to REM sleep that was less than 90 minutes, were included as candidate risk factors. For reasons outlined earlier for other variables, we included in the initial model REM latency expressed as a continuous variable.

**OTHER FACTORS (SYMPTOMS) THAT MAY INTERRUPT SLEEP.** The Penn Sleep Survey contains questions that assess how frequently symptoms that have potential for interrupting sleep occur (measured in nights/week) based on the scale defined earlier. The following were included in analyses: wheezing or whistling from chest, chest pain while in bed, using the toilet more than two times in a night, pain or physical discomfort, noise, heartburn during sleep time, and

indigestion during sleep time. Pain at night was selected for inclusion in the initial multivariable model.

**MEDICATIONS WITH SLEEPINESS AS A SIDE EFFECT.** Current medication use was assessed by direct observation of participants' medication containers. Medications were classified as to how commonly sleepiness is a side effect, using criteria from the United States Pharmacopoeia (more common, less common, rarely, none). The initial multivariable model defined exposure as taking any medication with more common or less common likelihood of sleepiness versus medications for which sleepiness has not been identified as a side effect.

**COMORBIDITIES.** During physical assessments, subjects were asked about current and lifetime status regarding 22 specific medical conditions. The lifetime status items were collapsed for analyses into the following categories: diabetes, chronic obstructive pulmonary disease (including emphysema and bronchitis), any heart disease (including high blood pressure, angina, heart attack, arrhythmia, and heart failure), any nasal problem (including sinus disease, hay fever, and deviated septum), thyroid disease, stroke, depression, and arthritis. Any heart disease was selected for inclusion in the initial model, because a previous study has shown an association between presence of heart disease and excessive sleepiness.<sup>38</sup>

**DEMOGRAPHIC AND BEHAVIORAL FACTORS.** Age, sex, body mass index (BMI), current smoking status, and current drinking status were obtained from questions included in the Penn Sleep Survey. Drinking status was analyzed as whether the subject currently consumed seven or more alcoholic beverages per week. All of the demographic and behavioral factors were included in the initial multivariable model with the exception of BMI because it has a known association, as a risk factor, for sleep apnea.

### *Statistical Analysis*

Subjects with excessive sleepiness and control subjects were descriptively compared using  $\chi^2$  tests, *t* tests, and rank-based procedures. Magnitudes of unadjusted associations with potential risk factors for sleepiness were assessed by ORs and 95% confidence intervals (CIs). Risk was expressed for 1-SD increases or decreases for some continuous variables to facilitate comparisons of effect sizes among risk factors. In some instances, the chosen units were defined to be close to the SD, but rounded to clinically meaningful and simpler values. ORs for ordinal risk factors were expressed as 1-unit increases or decreases. Frequencies of symptomatic complaints were dichotomized according to whether the reported occurrence was five or more, three or more, or one or more times/week, or whether they ever occurred even if less than once per week. To enhance stability of the statistical estimation procedure, we eliminated from inclusion in the multivariable modeling those variables for which there were less than five observations in any of the four cells that comprised a cross-tabulation with case-control status.

Multivariable models were developed to simultaneously assess the association between case-control status and the selected factors from among 38 variables spanning the 7 do-

main. The initial multivariable model included one variable from each of the first six domains and all variables in the demographic and behavioral factors domain with one exception, ie, obesity (BMI) (see Table 1). This strategy was chosen for two reasons. First, it reduces the likelihood of false-positive findings. Second, a multivariable model that includes all candidate risk factors without regard to multicollinearity can produce estimates of exposure effects that may be highly unstable or biased. A strategy to avoid the untoward effects of this multicollinearity is to control for a selected subset of the candidate factors.<sup>39</sup> However, the validity of the risk estimates from the selected model requires that the omitted variables are not confounders. Thus, all factors not included in the initial model were assessed as potential confounding variables and as secondary risk factors. A factor was considered an important confounding variable if its inclusion changed the OR of an already included variable by more than 15%.<sup>40</sup> These evaluations resulted in a final multivariable model. In addition, multivariable models included a factor to account for the stratified sampling of community-residing African Americans. Model fit was tested using a Hosmer-Lemeshow test.<sup>41</sup> A discrimination index<sup>42</sup> (*c*-statistic), equivalent to the area under the receiver operating characteristic curve, computed from model predicted relative likelihoods, was derived to provide a measure of the discriminatory capacity of the model that does not depend on sampling by sleepiness status. This measure has a simple probabilistic interpretation as the probability that a randomly selected individual with sleepiness has a larger model-predicted relative likelihood than a randomly selected individual without sleepiness. In addition, a proportion of variance explained measure ( $R^2$ ) analogous to that typically used in multiple linear regression was determined.<sup>43</sup> Age, sex, and race were assessed for effect modification by adding appropriate cross-product interaction terms to the initial multivariable model.<sup>44</sup> A *p* value less than 0.10 was used to assess the statistical significance of interaction terms because of the low statistical power associated with tests for interaction. Sensitivity analyses were performed on the definition used to classify cases and control subjects by reestimating the final main-effects model including only cases with mean sleep latencies less than 10 minutes and control subjects with values greater than or equal to 10 minutes, ie, normal. The primary focus of this analysis was to compare magnitudes of OR estimates for each risk factor (and not their statistical significance or width of their CIs) to determine whether their relative importance changed when simultaneously requiring both subjective and objective criteria to define case-control status.

## **Results**

### *Demographic Comparisons between Individuals with Sleepiness (Cases) and Control Subjects*

Individuals with sleepiness (cases; *n* = 149) and control subjects (*n* = 144) did not significantly differ with respect to sex (male subjects: 27.5 vs 23.6%), race (white subjects: 72.5 vs 73.6%), marital status (married with current spouse: 37.8 vs 41.0%), education (4 years college or more: 43.9 vs 49.0%), or age (cases:

Table 2. Unadjusted Odds Ratios and Those from Initial Multivariable Model for Factors Chosen from Each Domain and for Demographic and Behavioral Variables

Domains/Risk Factors	Unadjusted	Initial Multivariable Model	
	OR (95% CI)	OR (95% CI)	<i>p</i>
Objective assessments of sleep disorders			
Apnea-hypopnea index (20 events/hr increase)	1.4 (1.1–1.8)	1.4 (1.1–1.9)	0.02
Self-reports of sleep disorder symptoms and sleep quality			
Pittsburgh Sleep Quality Index of overall sleep quality (1 point increase)	2.2 (1.5–3.2)	2.1 (1.4–3.1)	0.0002
Quantitative aspects of sleep characteristics (architecture)			
REM latency (75 minute increase)	1.2 (0.93–1.5)	1.3 (1.0–1.8)	0.03
Other factors (symptoms) that may interrupt sleep			
Pain or physical discomfort $\geq 3$ times/week	5.6 (2.3–17.0)	5.7 (2.1–18.5)	0.002
Medications with sleepiness as a side effect			
US Pharmacopoeia more/less common vs rare/none	2.0 (1.3–3.3)	1.9 (1.1–3.2)	0.02
Comorbidities			
Any heart disease	1.7 (1.0–2.8)	1.2 (0.67–2.1)	0.57
Demographic and behavioral factors			
Age (5 year increase)	1.0 (0.86–1.2)	0.93 (0.74–1.2)	0.75
Male sex	1.2 (0.73–2.1)	1.6 (0.90–3.1)	0.11
>7 alcoholic beverages per week	0.45 (0.23–0.85)	0.44 (0.21–0.90)	0.03
Current smoker	0.42 (0.14–1.2)	0.60 (0.16–2.0)	0.38

OR = odds ratio; CI = confidence interval.

mean [SD] = 78.0 [6.3] years, range = 65–94 vs control subjects = 77.8 [6.4] years, range = 65–98). Individuals with sleepiness did, however, have a significantly larger mean BMI (cases: mean [SD] = 27.0 [4.6] kg/m<sup>2</sup>; control subjects: 25.8 [4.7] kg/m<sup>2</sup>; *p* = 0.02).

#### Validation of Case–Control Status Using Various Measures of Sleepiness

Concurrent validity of case–control status was assessed using multiple validated measures of subjective and objective sleepiness. The mean (SD) Epworth Sleepiness Scores were 11.1 (4.7) in cases and 5.1 (3.7) in control subjects (*p* < 0.0001). Likewise, cases and control subjects exhibited significant differences in Pittsburgh Sleep Quality Daytime Dysfunction scores (cases: mean [SD] = 0.93 [0.70]; control subjects: 0.29 [0.53]; *p* < 0.0001) and for the daytime sleepiness symptom-frequency index contained in the Multivariable Apnea Prediction questionnaire (cases: mean [SD] = 0.91 [0.63]; control subjects: 0.13 [0.35]; *p* < 0.0001). Objectively, the propensity to fall asleep was significantly greater in cases. The mean (SD) sleep latency values on daytime naps among cases and control subjects were 9.3 (4.8) and 11.9 (4.9) minutes, respectively (*p* < 0.0001).

#### Assessment of Risk Factors

Table 1 summarizes descriptive results for the 10 risk factors selected for inclusion in the initial multivariable model. Table 2 shows the unadjusted associations and adjusted OR with 95% CIs for the same 10 risk fac-

tors. The following sections describe in more detail the results for each risk factor.

**OBJECTIVE ASSESSMENTS OF SLEEP DISORDERS.** On average, cases exhibited significantly more respiratory disturbances during sleep (see Table 1). Controlling for the other risk factors in the model, the odds of excessive daytime sleepiness in an individual with an apnea-hypopnea index value that is 20 events/hr larger than another individual was estimated to be 1.4 times larger than the individual with the smaller number of respiratory events during sleep (95% CI, 1.1–1.9; *p* = 0.02; see Table 2). To provide information relevant to currently used categories of apnea severity in clinical practice,<sup>10</sup> the apnea-hypopnea index was replaced by apnea severity category as a categorical variable. It remained statistically significant (degrees of freedom = 3; *p* = 0.02). The percentages of elderly subjects reporting excessive daytime sleepiness who had severe, moderate, mild, and no apnea were 20.8% (*n* = 31), 15.4% (*n* = 23), 24.8% (*n* = 37), and 38.9% (*n* = 58), respectively. In contrast, these percentages were 9.7% (*n* = 14), 16.7% (*n* = 24), 31.9% (*n* = 46), and 41.7% (*n* = 60) among elderly subjects reporting no excessive daytime sleepiness. The adjusted OR comparing each level of severity with those with less than 5 events/hr were 0.7 for mild apnea (95% CI, 0.4–1.3; *p* = 0.27), 0.8 for moderate apnea (95% CI, 0.4–1.7; *p* = 0.50), and 2.6 for severe apnea (95% CI, 1.1–6.0; *p* = 0.03), respectively. Thus, among elderly individuals, and based on these categories, only severe sleep ap-

nea is an independent contributor to excessive daytime sleepiness.

**SELF-REPORTS OF SLEEP DISORDER SYMPTOMS AND SLEEP QUALITY.** Self-report of reduced sleep quality was also found to be a strong risk factor for subjectively reported excessive daytime sleepiness in the elderly. The adjusted OR (95% CI) in the initial multivariable model was 2.1 (1.4–3.1;  $p = 0.0002$ ) for each one-point increase in this four-point ordinal measure. The percentages of cases reporting very bad, fairly bad, fairly good, and very good sleep quality over the prior month were 2.7% ( $n = 4$ ), 15.4% ( $n = 23$ ), 59.1% ( $n = 88$ ), and 22.8% ( $n = 34$ ), respectively. In contrast, these percentages were 0.0%, 7.6% ( $n = 11$ ), 47.9% ( $n = 69$ ), and 44.4% ( $n = 64$ ) among control subjects.

**SLEEP CHARACTERISTICS.** Reduced REM latency was associated with increased risk in the initial multivariable model (adjusted OR for 75-minute decrease [ie, the SD of this measure] was 1.3, 95% CI, 1.0–1.8). That is, the odds of excessive daytime sleepiness was estimated to increase by a factor of 1.3-fold comparing an elderly individual who experienced REM sleep 75 minutes earlier than another individual, but was otherwise equivalent regarding the other factors listed in Table 2.

**OTHER FACTORS (SYMPTOMS) THAT MAY INTERRUPT SLEEP.** Pain or physical discomfort at night at least three times per week was found to be a strong risk factor for subjectively reported excessive daytime sleepiness in the elderly. Among cases and control subjects, 16.8 and 3.5%, respectively, reported pain or physical discomfort at least three nights per week. The adjusted OR (95% CI) in the initial multivariable model was 5.7 (2.1–18.5;  $p = 0.002$ ).

**US PHARMA COEIA MORE/LESS COMMON VERSUS RARE/NONE.** Medications with sleepiness as a side effect were more commonly used in cases (see Table 1) and were found to be significantly associated with risk for sleepiness (see Table 2). When we considered medications with sleepiness as at least a less common side effect, the adjusted OR (95% CI) was 1.9 (1.1–3.2;  $p = 0.02$ ). The percentages of cases using any medication where sleepiness side effects were “more common,” “less common,” “rare,” and “none” were 31.5% ( $n = 47$ ), 40.3% ( $n = 60$ ), 11.4% ( $n = 17$ ), and 16.8% ( $n = 25$ ). In contrast, these percentages were 21.5% ( $n = 31$ ), 34.0% ( $n = 49$ ), 18.1% ( $n = 26$ ), and 26.4% ( $n = 38$ ) among control subjects. When the dichotomous factor was replaced by a four-level factor with “none” as the reference, there was no difference between ORs associated with medications in which

sleepiness side effects were “more common” versus “less common” relative to a reference of “none.” Therefore, the dichotomous risk factor was retained in our final multivariable model (see later). Among medication classes, the largest ORs were associated with use of anti-infect/antiparasitic agents (OR, 5.7; 95% CI, 1.2–26.0) and nose and sinus agents (OR, 3.3; 95% CI, 1.1–10.5). Although these associations are likely due to sleepiness being a side effect of the drugs, it cannot be ruled out that the association with anti-infect/antiparasitic agents is related to an underlying inflammation leading to sleepiness.

**COMORBIDITIES.** The factor selected for inclusion in the initial multivariable model, any heart disease, was found to be a significant risk factor in bivariate analysis. However, in the initial multivariable model, the presence of heart disease was no longer a significant risk factor (see Table 2). We investigated the cause of this confounding and found that it was primarily caused by use of medications with sleepiness as at least a less common side effect and pain or physical discomfort at night at least three times per week. Controlling for only these two factors reduced the crude OR by 26% from 1.7 to 1.4. Controlling also for apnea-hypopnea index further reduced the OR to 1.3. Therefore, we conclude that the observed unadjusted elevated risk was due to confounding by these three underlying factors, and hence removed any heart disease from our final multivariable model.

**DEMOGRAPHIC AND BEHAVIORAL FACTORS.** Age, male sex, and current smoking were not significant risk factors in either the bivariate analyses or in the initial multivariable model. In contrast, having more than seven drinks per week was found to be protective in both analyses, ie, reduced the risk for excessive sleepiness. The adjusted OR was 0.44 (95% CI, 0.21–0.90;  $p = 0.03$ ). BMI was not included in the initial multivariable model because of its known strong association with sleep apnea. However, when BMI was added to the model, the OR for the apnea-hypopnea index only decreased by 6% from 1.4 to 1.3 (95% CI, 1.0–1.8). The addition of BMI did not appreciably alter results for other risk factors.

The goodness of fit of the initial multivariable model was assessed using the Hosmer–Lemeshow test. The null hypothesis of adequate fits was not rejected ( $\chi^2 = 7.8$ ; degrees of freedom = 8;  $p = 0.45$ ). The initial model also exhibited moderately good discriminatory power as reflected in a discrimination index value of  $c = 0.734$ .

Table 3. Summary of Descriptive Statistics and Unadjusted Analyses of Risk Factors within Seven Domains Assessed for Associations with Excessive Daytime Sleepiness in Cases Relative to Control Subjects

Domains/Risk Factors	Cases (N = 149)	Control Subjects (N = 144)	Unadjusted OR (95% CI)
	Mean (SD) or n (%)	Mean (SD) or n (%)	
Objective assessments of sleep disorders			
Mean sleep efficiency, % (SD) (OR for SD = 12.8% decrease)	74.9 (13.7)	78.3 (11.3)	1.3 (1.0–1.8)
Self-reports of sleep disorder symptoms and sleep quality			
Mean PSQI sleep duration index (SD) (OR for one-point increase)	1.05 (0.91)	0.84 (0.85)	1.3 (1.0–1.7)
Mean PSQI habitual sleep efficiency (SD) (OR for one-point increase)	0.95 (1.09)	0.71 (1.05)	1.2 (1.0–1.5)
Mean apnea symptoms (SD) (OR for one-point increase)	0.39 (0.78)	0.22 (0.65)	1.4 (1.0–2.0)
Quantitative aspects of sleep characteristics (architecture)			
Mean arousal index, arousals/hr (SD) (OR for SD = 14.6 increase)	23.9 (16.8)	20.6 (11.9)	1.3 (1.0–1.6)
Other factors (symptoms) that may interrupt sleep			
Any wheezing or whistling from chest at night, (%)	24 (16.1)	10 (6.9)	2.6 (1.2–5.8)
Used toilet >2 times $\geq$ 3 times/week, n (%)	84 (56.4)	60 (41.7)	1.8 (1.1–2.9)
Comorbidities			
Any nasal problems, n (%)	95 (63.8)	69 (47.9)	1.9 (1.2–3.1)
Stroke, n (%)	22 (14.8)	10 (6.9)	2.3 (1.1–5.3)
Demographic and behavioral factors			
Mean BMI, kg/m <sup>2</sup> (SD) (OR for 5kg/m <sup>2</sup> increase)	27.0 (4.7)	25.8 (4.7)	1.3 (1.0–1.7)

Only results for factors that were not selected for inclusion in the initial multivariable model and that were statistically significant in bivariate analyses are included in this table.

OR = odds ratio; CI = confidence interval; SD = standard deviation; PSQI = Pittsburgh Sleep Quality Index; BMI = body mass index.

#### Determination of Risk Factors for Inclusion in Final Multivariable Model

Table 3 includes descriptive statistics and bivariate associations for the remaining variables that appeared as statistically significant risk factors in bivariate analyses. These, as well as all other variables, were assessed as potential confounding factors for variables included in the initial model. Notably, increased period leg movements with or without requiring arousals did not increase the risk for excessive daytime sleepiness in bivariate analyses, were not significant when added to the multivariable model, and their inclusion did not result in more than a 15% change on the ORs of variables already included in the model.

The mean arousal index was 16.6% higher among cases compared with control subjects ( $p = 0.05$ ), but was not statistically significant when added to the initial model due to its expected strong association with the apnea–hypopnea index (partial correlation between the apnea–hypopnea index and arousal index controlling for case–control status was  $r = 0.72$ ;  $p < 0.0001$ ). When the percentage of time spent in REM sleep was added to the initial model, it was statistically significant ( $p = 0.05$ ). Moreover, its addition decreased the OR for 75-minute reductions in REM latency by more than 15% and eliminated its statistical significance. Therefore, REM latency was replaced by percentage of sleep time in REM in the final model. In this model, a

1-SD (SD = 6.8%) increase in the percentage of sleep time in REM was associated with a 1.5-fold (95% CI, 1.1–1.9;  $p = 0.008$ ) increase in the odds of excessive daytime sleepiness. Adding time spent in other sleep stages did not appreciably change the ORs of already included variables, and they were not statistically significant. Inclusion of any wheezing or whistling from chest at night increased the magnitude of current smoking (away from 1.0) by 30%. Thus, this variable was retained in the final risk model. In contrast, when use of the toilet more than two times in a night for at least three nights a week was added to the initial model, its inclusion did not appreciably change the OR estimates of any included variable, and it was not statistically significant. None of the remaining sleep interruption factors were important confounders or significant risk factors when added to the initial model. Age ( $p = 0.38$ ) and current smoking ( $p = 0.21$ ) were not significant risk factors, and their removal did not change any of the other ORs by more than 6%. Therefore, these variables were removed from the final main-effects model.

#### Results of Final Multivariable Model

Based on these analyses, we formed the final multivariable model, the results of which are shown in Table 4. The goodness of fit of the final multivariable was also found to be adequate (Hosmer–Lemeshow test

Table 4. Final Multivariable Model and Sensitivity Analysis for Final Multivariable Model

Variables	Final Multivariable Model <sup>a</sup>		Sensitivity Analysis for the Final Multivariable Model <sup>b</sup>
	OR (95% CI)	<i>p</i>	OR (95% CI)
Apnea-hypopnea index (OR for 20-events/hr increase)	1.4 (1.1–1.9)	0.01	1.4 (1.0–1.9)
PSQI self-report of overall sleep quality (OR for one-point increase)	2.3 (1.6–3.6)	<0.0001	1.8 (1.1–3.0)
% Time in REM sleep (OR for 6.8% increase)	1.4 (1.1–1.9)	0.01	1.4 (1.0–2.0)
Pain or physical discomfort ≥3 times/week	5.9 (2.2–19.0)	0.001	19.2 (3.3–370.2)
Any wheezing or whistling from chest at night	3.2 (1.4–8.0)	0.001	5.1 (1.6–18.7)
US Pharmacopoeia more/less common vs rare/none	1.9 (1.1–3.3)	0.02	1.5 (0.8–3.1)
Male sex	1.9 (1.0–3.5)	<0.05	3.7 (1.6–9.0)
>7 alcoholic beverages per week	0.42 (0.20–0.86)	0.02	0.28 (0.10–0.72)

<sup>a</sup>Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) derived from final multiple logistic regression model identified by assessment of confounding and secondary risk factors. The model also included a factor to account for the stratified sampling of community-residing African Americans.

<sup>b</sup>In this subsample analysis, cases (n = 88) were required to have both subjective and objective evidence of daytime sleepiness, whereas control subjects (n = 97) were required to be free from daytime sleepiness using both subjective and objective criteria.

PSQI = Pittsburgh Sleep Quality Index; REM = rapid eye movement.

$\chi^2 = 8.2$ , degrees of freedom = 8;  $p = 0.41$ ). The discrimination index for the final model ( $c = 0.760$ ) was better than the value for the initial model. The final model total  $R^2$  (total variance explained) was 0.204. In the final model, the same risk factors that were significant were largely those found in the initial model (compare the final multivariable model in Table 4 with Table 2). The major differences were: inclusion of any wheezing or whistling from chest at night (a risk factor from the sleep interruption domain), replacement of latency to REM sleep with percentage of time spent in REM sleep, and male sex was now marginally significant. Degree of sleep-disordered breathing as a continuous variable remained significant in the final model with an OR of 1.4 (95% CI, 1.1–1.9). When we replaced the interval measure of the apnea-hypopnea index with the categories described earlier in the final multivariable model, the adjusted OR comparing each level of severity with those with less than 5 events/hr were 0.7 for mild (95% CI, 0.3–1.4;  $p = 0.22$ ), 0.8 for moderate (95% CI, 0.4–1.8;  $p = 0.61$ ), and 2.7 for severe (95% CI, 1.2–6.4;  $p = 0.02$ ), respectively. Thus, only severe sleep apnea was a risk factor for excessive sleepiness in the final model. As in the initial model, use of alcohol was associated with reduced risk for sleepiness.

#### Assessment of Effect Modification

Risk factors in the final model were assessed for effect modification by sex, race, and age based on a significance level of 0.10. The following interactions meeting these criteria were observed. The adjusted ORs for medications with sleepiness side effects were 4.4 (95% CI, 2.3–8.4) and 1.4 (95% CI, 0.8–2.7) among male

and female subjects. Similarly, the adjusted ORs for medications with sleepiness side effects among community-dwelling African Americans and non-African Americans residing in retirement communities were 0.8 (95% CI, 0.5–1.4) and 2.7 (95% CI, 1.4–5.2), respectively. It is not possible to distinguish whether this latter interaction is due to race or to residential status (community vs retirement community). The adjusted OR for each 6.8% increase in the percentage of time spent in REM among community-residing African Americans and non-African Americans in retirement communities were 2.1 (95% CI, 1.8–2.5) and 1.2 (95% CI, 0.9–1.7), respectively. Finally, it appeared that the excess risk among male individuals was moderated by age. The adjusted OR for male versus female 70-year-old individuals was only 0.8 (95% CI, 0.4–1.5). In contrast, this OR was estimated to be 2.2 (95% CI, 1.8–2.8) for 85-year-old individuals.

#### Sensitivity Analysis of Case-Control Definition by Incorporating Objective Sleepiness

Among cases, 88 (59.9%) had sleep latency values of less than 10 minutes (accepted normal value).<sup>19</sup> In contrast, among control subjects only, 46 (32.2%) had values less than 10 minutes. The OR (95% CI) for subjective sleepiness comparing latency less than 10 with latency of 10 minutes or more was 3.1 (1.9–5.1), with  $p$  less than 0.0001. Therefore, case-control definition sensitivity analysis was performed by reestimating the final main-effects model using the 88 cases with sleep latency less than 10 minutes and the 97 control subjects with latency of 10 minutes or more (see last column in Table 4). The OR for many risk

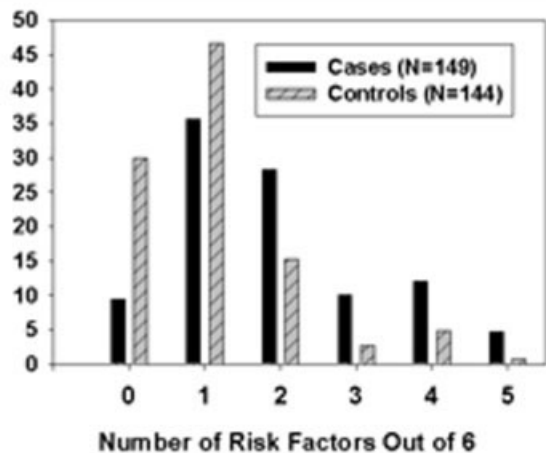


Fig. Percentages of cases (black bars;  $n = 149$ ) and control subjects (gray bars;  $n = 144$ ) with 0, 1, 2, 3, 4, 5, or 6 of the risk factors included in the final main-effects multivariable model excluding the alcohol and sex factors. The six risk factors used in this analysis are the first six factors in Table 4.

factors (eg, apnea–hypopnea index) were similar. Use of alcohol continued to reduce the risk for sleepiness. The magnitudes of the ORs increased substantially for frequent chronic pain, wheezing, and male sex. Only the OR for sleepiness as a side effect of medications was reduced in magnitude.

#### Presence of Multiple Risk Factors

Elderly cases, as well as elderly control subjects, were typically exposed to multiple risk factors. To illustrate, we counted the number of exposures found significant in the final multivariable model ( $n = 8$ ) but excluding the apparent protective effect of alcohol consumption and the effect of male sex. The remaining six factors assessed are the first six in Table 4. Exposure to sleep apnea was defined as apnea–hypopnea of 30 or more events/hr, because multivariable analyses based on categorical sleep apnea severity found that only elderly with apnea–hypopnea of 30 or more events/hr were at increased risk. This level of sleep apnea severity is consistent with the consensus definition for severe sleep apnea.<sup>10</sup> Moreover, data for efficacy of treatment are most compelling for this degree of apnea.<sup>45–47</sup> The REM effect was defined according to a reduced REM latency defined as less than 45 minutes, a value identified as significant in exploratory analyses. Ratings of “fairly bad” and “very bad” on the Pittsburgh Sleep Quality Global self-report of overall sleep quality score defined presence of this risk factor. The distributions of numbers of exposures are illustrated for cases and control subjects in the Figure. The mean (SD) number of exposures among cases and control subjects were 2.2 (1.4) and 1.3 (1.1), respectively ( $p < 0.0001$ ). Only 9.4% of older cases reporting excessive daytime sleepiness had no exposures compared with 29.9% of older subjects reporting no excessive daytime sleepiness.

A total of 55.0% of older cases reporting excessive daytime sleepiness were exposed to more than one of the six factors compared with only 23.6% of control subjects. The OR for elevated sleepiness comparing those with and without multiple exposures is 4.0 (95% CI, 2.4–6.5).

#### Discussion

We found that there were a number of factors associated with excessive sleepiness in older adults. Our results support the view that excessive sleepiness is multifactorial in the elderly, and the more risk factors that are present in a given individual the higher the risk for excessive sleepiness. Of the risk factors assessed, frequent chronic pain had the highest OR. Disturbed sleep and sleep fragmentation have been described in a number of conditions associated with pain.<sup>48,49</sup> However, it is also conceivable that sleepiness exacerbates pain, and our study design cannot rule out this alternative explanation. Self-report of wheezing or whistling from the chest at night was also a risk factor. Sleeping difficulty is more common in older individuals with chronic obstructive pulmonary disease or asthma than in control subjects.<sup>50</sup>

Our study demonstrated that sleep apnea is a significant independent contributor to the risk for excessive daytime sleepiness in the elderly. Associations between degree of sleep apnea and sleepiness have been shown in other large epidemiological studies.<sup>51</sup> In analyses, severity of sleep apnea was assessed initially as a continuous variable to maximize statistical power and to avoid type I error for other factors in the model requiring control for sleep apnea severity as a confounder. When we replaced the continuous measure of apnea–hypopnea index with suggested clinical categories,<sup>10</sup> elevated risk was observed only for those with severe sleep apnea ( $\geq 30$  events/hr). Thus, among elderly individuals, only severe sleep apnea is an independent contributor to excessive daytime sleepiness.

In contrast with findings concerning sleep apnea, our study found no evidence that PLMs during sleep are a risk factor. The clinical significance of these movements has long been debated with some arguing that they may lead to excessive sleepiness,<sup>30,52</sup> whereas others argue that they are not of clinical significance.<sup>53,54</sup> Our data support the latter point of view.

Decreased REM latency was a risk factor in initial bivariate analyses. Exploratory analyses found that less than 45 minutes versus 45 minutes or longer produced an OR of 2.2 (95% CI, 1.1–4.6;  $p = 0.03$ ). The final multivariable model included, however, percentage of time spent in REM sleep as a significant risk factor. The basis of reduced latency to REM sleep, and increased REM sleep as a percentage of total sleep, as a

risk factor for sleepiness is unknown but could reflect differences in latency to REM sleep found even in sub-threshold depression.<sup>37</sup> We excluded subjects with more major depression in our study.

We also found that certain diagnoses were associated with an increased risk for sleepiness, in particular, nasal problems, stroke, and in initial bivariate analyses, the presence of heart disease. Patients with heart disease were significantly more likely to use medications with sleepiness as a side effect, have frequent pain at night, and have increased sleep-disordered breathing. These associations therefore resulted in the presence of heart disease not being significant in our multivariable analyses. A previous study has shown an association between complaints of excessive sleepiness and incident cardiovascular mortality and morbidity,<sup>38</sup> whereas another cross-sectional study failed to show an association with cardiovascular diagnoses.<sup>5</sup> These differing results may reflect differences in the ability of previous studies to control for important confounders.

Medications with sleepiness as a side effect were also found to be a significant risk factor for sleepiness. This is not surprising. What is surprising is how frequently individuals with excessive sleepiness were still prescribed these medications. This suggests that when prescribed, physicians do not follow up with inquiries about sleepiness. It is known that only about 50% of geriatricians inquire about sleep complaints in their patients.<sup>55</sup>

A robust finding found in all analyses was that drinking seven or more alcoholic beverages a week reduced the risk for sleepiness. It is unclear why increased alcoholic beverage consumption was found to be associated with reduced risk, as alcohol consumption is sometimes implicated as a factor associated with sleep disruption (see Brower's article<sup>56</sup> for review). The most parsimonious explanation is that the elderly with awareness of excessive sleepiness learn to appreciate the negative impact of alcohol on their sleep, and hence reduce alcohol intake.

Our study design was a cross-sectional comparison of subjects who had frequent complaints of excessive sleepiness and those who had no such problem. Subjects who were intermediate between these groups were not studied. We used a case-control strategy to analyze the role of different risk factors. Hence, we called individuals with excessive sleepiness "cases" and those with no such problem "control subjects." The subjects were recruited largely from retirement centers for the elderly. Given the agreement with the leadership of the communities, we could only approach individuals who, after hearing about the study at community presentations or through another outlet, volunteered to participate. Thus, we are not able to determine whether the group with sleepiness who volunteered for this study is representative of all subjects with sleepiness in these

communities. There is no reason to believe otherwise, and an important strength of our design is that cases and control subjects came from identical communities. Risk factors were assessed concurrently with sleepiness status, although subjective symptom assessments generally asked about the preceding 30 days. Nonetheless, our study design did not permit definitive determination of the temporal relation between risk factors and excessive daytime sleepiness limiting our ability to determine the direction of causality. Although it is conceivable that, in our study, recall bias might have affected responses to the questionnaires we administered, many of the risk factors we assessed were not affected by such bias. In particular, sleep apnea, periodic limb movements, and so forth were determined by objective testing and medication use by direct observation of the pill bottles for subjects.

In conclusion, our studies show that excessive sleepiness, which is a common complaint in the elderly, has a number of identifiable and treatable risk factors. The role of multiple risk factors, often present simultaneously, is shown. Thus, elders with frequent daytime sleepiness were much more likely to have the presence of multiple risk factors compared with control subjects. This is the first study to address using case-control methodology, in any age group, the presence of multiple risk factors for sleepiness. Physicians evaluating elderly individuals need ask only one simple question to identify those with excessive sleepiness; ie, do you have a problem with sleepiness during the day and, if so, how frequently? If individuals have a problem with sleepiness three to four times/week or more, the physician then needs to consider the following questions: Is the patient suffering from uncontrolled nighttime pain? Does the patient have severe sleep apnea? Is the patient on medications causing sleepiness as a side effect? Future studies need to address treatment efficacy directed at different risk factors for sleepiness in older adults before full clinical guidelines can be developed. Our studies also support the concept that PLMs during sleep, found commonly in the elderly,<sup>16</sup> are an epiphenomenon and not by themselves of clinical significance to excessive daytime sleepiness.

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