Insomnia with Short Sleep Duration and Mortality: The Penn State Cohort

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Study Objectives: Because insomnia with objective short sleep duration is associated with increased morbidity, we examined the effects of this insomnia subtype on all-cause mortality.

Design: Longitudinal.

Setting: Sleep laboratory.

Participants: 1,741 men and women randomly selected from Central Pennsylvania.

Measurements: Participants were studied in the sleep laboratory and were followed-up for 14 years (men) and 10 years (women). "Insomnia" was defined by a complaint of insomnia with duration ≥ 1 year. "Normal sleeping" was defined as absence of insomnia. Polysomnographic sleep duration was classified into two categories: the "normal sleep duration group" subjects who slept ≥ 6 h and the "short sleep duration group" subjects who slept < 6 h. We adjusted for age, race, education, body mass index, smoking, alcohol, depression, sleep disordered breathing, and sampling weight.

Results: The mortality rate was 21% for men and 5% for women. In men, mortality risk was significantly increased in insomniacs who slept less than 6 hours compared to the "normal sleep duration, no insomnia" group, (OR = 4.00, CI 1.14-13.99) after adjusting for diabetes, hypertension, and other confounders. Furthermore, there was a marginally significant trend (P = 0.15) towards higher mortality risk from insomnia and short sleep in patients with diabetes or hypertension (OR = 7.17, 95% CI 1.41-36.62) than in those without these comorbid conditions (OR = 1.45, 95% CI 0.13-16.14). In women, mortality was not associated with insomnia and short sleep duration.

Conclusions: Insomnia with objective short sleep duration in men is associated with increased mortality, a risk that has been underestimated.

Keywords: Insomnia, short sleep duration, mortality, population-based study

Citation: Vgontzas AN; Liao D; Pejovic S; Calhoun S; Karataraki M; Basta M; Fernández-Mendoza J; Bixler EO. Insomnia with short sleep duration and mortality: the Penn State Cohort. *SLEEP* 2010;33(9):1159-1164.

MANY STUDIES HAVE ESTABLISHED THAT INSOMNIA, THE MOST COMMON SLEEP DISORDER, IS HIGHLY COMORBID WITH PSYCHIATRIC DISORDERS AND IS a risk factor for the development of depression, anxiety, and suicide.[1,2] In contrast to sleep disordered breathing (SDB), the second most common sleep disorder, chronic insomnia has not been associated with significant medical morbidity, e.g., cardiovascular disorders.[3,4]

Recently, we demonstrated that insomnia with objective short sleep duration is associated with a high risk for hypertension and type 2 diabetes.[5,6] These data suggest that objective sleep measures in insomnia provide an index of the severity of the disorder and that the more severe form of insomnia is most likely associated with morbidity and possibly mortality. This hypothesis is further supported by physiological studies which demonstrated that activation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic system, including increased heart rate, 24-hour metabolic rate, and impaired heart rate variability, is present in insomniacs who meet both subjective and objective polysomnographic criteria.[7-12] Given the association of hypertension, diabetes, and HPA axis and sympathetic system activation with increased mortality,[13] we expect insomnia with objective short sleep duration to be associated with increased rates of death.

Previous studies on the association of insomnia with mortality have been inconsistent.[14-20] The most recent ones that included very large samples of a wide age range reported no association or even a negative association between insomnia and mortality.[19,20] A limitation of all these studies is that the presence of sleep disturbances was based on subjective questionnaires, did not include any criteria of frequency or severity, and did not control for polysomnographically documented obstructive sleep apnea, a sleep disorder whose association with medical morbidity and mortality is well established.[21] Thus, the question whether insomnia is associated with an increased risk for death remains open to further investigation.

The objective of this study was to examine the joint effects of chronic insomnia and objective sleep duration on mortality risk in a large prospective population-based sample from Central Pennsylvania (Penn State Cohort), after controlling for various confounders including sleep apnea.

METHODS

Population

The data presented here were collected as part of a two-phase protocol whose primary purpose was to establish the age distribution of sleep disordered breathing.[22,23] In the first phase of the study, a sample of adult men and women (aged ≥ 20 years) was randomly selected from local telephone households in 2 counties of Central Pennsylvania (Dauphin and Lebanon) using the

Submitted for publication November, 2009
Submitted in final revised form March, 2010
Accepted for publication April, 2010
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Mitofsky–Waksberg 2-stage random digit dialing procedure.[24] A within-household selection procedure described by Kish was used to select the specific man or woman to be interviewed.[25] Telephone interviews were conducted with 4,364 age-eligible men and 12,219 age-eligible women residing in the sample households, for a total sample of 16,583 with a response rate of 73.5% and 74.1%, respectively. The questionnaire employed in this interview included basic demographic and sleep information.

In the second phase of this study, a subsample of 741 men and 1,000 women selected from those subjects previously interviewed by telephone were studied in our sleep laboratory. The response rate for this phase was 67.8% and 65.8% for men and women, respectively. We contrasted those subjects who were recorded in the laboratory with those who were selected but not recorded in terms of age, self-reported BMI, reported use of medication for hypertension or diabetes, and prevalence of sleep disorders. There were no significant differences between these 2 groups on any of these variables. Each subject selected for laboratory evaluation completed a comprehensive sleep history and physical examination. All subjects were evaluated for one night in the sleep laboratory in sound-attenuated, light- and temperature-controlled rooms. During this evaluation, each subject was continuously monitored for 8 h using 16-channel polygraphs, including electroencephalogram, electrooculogram, and electromyogram. Bedtimes were adjusted to conform to subjects' usual bedtimes, and subjects were recorded between 22:00-23:00 and 06:00-07:00. The sleep records were subsequently scored independently according to standardized criteria.[26] Percent sleep time is total sleep time (duration of sleep) divided by recorded time in bed and multiplied by 100. Respiration was monitored throughout the night by use of thermocouples at the nose and mouth and thoracic strain gauges. All-night recordings of hemoglobin oxygen saturation (SpO_2) were obtained with an oximeter attached to the finger.

Key Measurements

As part of this protocol we assessed for the presence of all sleep disorders. The presence of sleep disorders was based on a standardized questionnaire completed by the subjects on the evening of their sleep laboratory visit. This questionnaire consists of 53 questions (7 demographic, 20 sleep related, and 26 general health questions). In addition, women responded to 8 questions related to menstrual history, menopause, and hormone therapy. Sleep related questions were qualified in terms of severity on a scale of 0-4 (0 = none, 1 = mild, 2 = moderate, 3 = severe) and duration. Health complaints were also qualified in terms of severity and type of treatment on a scale of 0-7 and duration. The presence of "insomnia" was defined by a complaint of insomnia with a duration of at least 1 year. "Normal sleeping" was defined as the absence of insomnia.

From the objectively recorded sleep time data, we regrouped the entire study sample into 2 ordinal groups: the top 50% of persons above the median percent sleep time (normal sleep duration group), and the 50% of persons in the bottom half (short sleep duration group). We then rounded the cut-off points to meaningful numbers and thus created the following 2 sleep duration groups: the normal sleep duration group consisted of those who slept ≥ 6 h, and the short sleep duration group of those who slept < 6 h.

To control for possible confounding variables influencing the relation between insomnia and mortality, in the subsample of 1,741 we ascertained whether the respondent was currently treated for depression (including a history of suicidal thoughts or attempts), hypertension, or diabetes. Hypertension was defined as a diastolic blood pressure > 90 mm Hg or a systolic blood pressure > 140 mm Hg at the time of the sleep laboratory evaluation, or the use of antihypertensive medication. Diabetes was defined as being treated for diabetes or having a fasting blood sugar > 126 mg/dl from blood drawn the morning after the subjects slept in the sleep laboratory. Additional information obtained during the polysomnographic evaluation included history of smoking (current use of any type of tobacco product) and alcohol use (> 2 alcohol drinks per day) and objective sleep data including sleep apnea and periodic limb movement assessment. For the purpose of this study, sleep apnea was defined as an obstructive apnea or hypopnea index ≥ 5 (OHI ≥ 5). The condition of periodic limb movement was considered present when there were five or more movements per hour of sleep. A leg movement was scored when it lasted > 0.5 sec, < 5.0 sec, and in intervals of < 90 sec between movements.[27] Body mass index was based on measured height (cm) and weight (kg) during the subjects' sleep laboratory visit, and data are presented in terms of mean, percentile distribution, and prevalence within each category.

Mortality Follow-up

Deaths in the cohort occurring up to December 31, 2007 were identified by matching social security numbers with 2 death record services: the U.S. Social Security Death Index and the Pennsylvania State Bureau of Healthy Information and Policy Vital Records Section. Duration of follow-up was calculated from the time of the baseline evaluation to the date of death.

Statistical Analyses

The design of this study included oversampling of those at higher risk for sleep disordered breathing (SDB) and women with markedly higher levels of BMI to increase the precision of the risk estimates. Because of this sampling strategy, numeric sampling weights were developed for the analysis so that the estimates could be inferred to the original target population.[22,23] Specifically, 3 weights were created for the men. First, in the telephone sample, 32 of the 963 clusters of phone numbers in the first stage were "exhausted" before the target sample size was obtained. A compensatory weight was computed which corrected for this problem. A second weight was computed because the within-household screening deliberately introduced unequal probabilities of selection across the 3 age groups in order to oversample the middle-aged group. The final weight for the men was computed to account for the oversampling of subjects for the sleep laboratory study (Phase II); those with larger counts of the 4 possible risk factors (snoring, daytime sleepiness, obesity, and hypertension) had substantially higher probability of being selected. For the women, the only weight required was to account for the oversampling of subjects for the sleep laboratory study. To eliminate any possible sample bias due to oversampling different strata of the target population, we calculated 32 unique weights for the women and 16 unique weights for the men, corresponding to all possible combinations of the 5 risk factors for the women (menopause was the

fifth risk factor) and 4 for the men. Any individual weight that had too small of a cell size was combined with adjacent cells, so that less than 10% of the cells had a sample < 25 and no cell had a size < 10.[25] All statistical analyses were adjusted for the sampling weight to make appropriate inference to the target population.

Finally we used the BMI and race distributions by age decade from the NHANES III laboratory data as the standard[28] to adjust both the men and women in terms of BMI and race to be more representative of the national population.

Logistic regression models were used to assess the independent associations of the insomnia complaints and objective sleep duration with mortality. We did not use proportional hazard models since Kaplan-Meier survival curves comparing sleep complaints crossed each other. Furthermore, because the follow-up duration was different between men and women, we performed separate analyses within each gender. We calculated the odds ratios and the 95% confidence intervals (95% CI) from this model to estimate the risk of death associated with the four combinations of insomnia (yes/no) and objective sleep duration (< 6 h / ≥ 6 h), simultaneously adjusting for age, race, education, BMI, diabetes, smoking status, alcohol consumption, depression, SDB, and sampling weight. The reference group was persons with ≥ 6 h of objective sleep duration and no insomnia complaints.

Table 1—Demographic and clinical characteristics and mortality rates of Penn State Cohort: men

		Insomnia /sleep duration category			
	Total n = 741	≥ 6 h No insomnia n = 342	≥ 6 h Insomnia n = 22	< 6 h No insomnia n = 344	< 6 h Insomnia n = 33
Baseline characteristics					
Continuous variables, mean (SD)					
Age, y	50.2 (14.5)	44.3 (12.1)	41.5 (7.8)	56.1 (14.3)	56.7 (12.0)
Body mass index kg/m^2	27.3 (4.6)	26.9 (4.5)	27.4 (3.1)	27.6 (4.7)	28.6 (4.1)
Binary variables, n (%)					
Ethnicity, white	652 (88)	294 (86)	17 (76)	313 (91)	31 (94)
Current smoker	245 (33)	116 (34)	12 (54)	110 (32)	6 (17)
Hypertension	282 (38)	103 (30)	11 (50)	155 (45)	23 (71)
Diabetes	156 (21)	48 (14)	5 (23)	90 (26)	19 (57)
OHI ≥ 5	133 (18)	48 (14)	2 (9)	72 (21)	11 (32)
Depression	104 (14)	45 (13)	9 (42)	38 (11)	18 (53)
Deaths					
Total deaths, n (%)*	145 (21)	39 (9)	3 (13)	91 (31)	12 (51)
Follow-up duration, mean y (SD)	13.9 (3.5)	14.6 (2.7)	14.3 (2.9)	13.2 (4.1)	13.1 (3.3)

*Percent figures are adjusted for sampling weight.

Table 2—Demographic and clinical characteristics and mortality rates of Penn State Cohort: women

		Insomnia /sleep duration category			
	Total n = 1000	≥ 6 h No insomnia n = 437	≥ 6 h Insomnia n = 64	< 6 h No insomnia n = 419	< 6 h Insomnia n = 80
Baseline characteristics					
Continuous variables, mean (SD)					
Age, y	47.4 (12.6)	43.9 (12.5)	45.0 (8.3)	53.0 (12.2)	53.4 (8.4)
Body mass index kg/m^2	27.9 (6.4)	27.3 (6.5)	31.6 (7.4)	28.4 (5.9)	27.3 (5.8)
Binary variables, n (%)					
Ethnicity, white	830 (83)	363 (83)	40 (62)	369 (88)	64 (80)
Current smoker	190 (19)	101 (23)	13 (21)	55 (13)	12 (15)
Hypertension	320 (32)	92 (21)	22 (34)	193 (46)	55 (69)
Diabetes	80 (8)	22 (5)	5 (7)	50 (12)	8 (10)
OHI ≥ 5	40 (4)	9 (2)	1 (2)	34 (8)	6 (7)
Depression	210 (21)	79 (18)	31(49)	80 (19)	24 (30)
Deaths					
Total deaths, n (%)*	103 (5)	23 (2)	2 (3)	71 (10)	7 (3)
Follow-up duration, mean y (SD)	10.3 (1.2)	10.4 (1.1)	10.5(0.9)	10.2 (1.3)	10.6 (0.7)

*Percent figures are adjusted for sampling weight.

RESULTS

The demographic and clinical characteristics, as well as number (%) of deaths, are presented in Table 1 for men and Table 2 for women. After about 10 years of follow-up for women and 14 years for men, 248 out of the 1,741 individuals at baseline were deceased. The mortality rate adjusted for sampling weight for men was 21% (145/741) and 5% (103/1,000) for women. Because the follow-up period was different between men and women, we analyzed the two cohorts separately, and the results are presented separately.

Men

The 14-year adjusted mortality rate was 9.1%, 12.6%, 31.0%, and 51.1% in normal sleep duration and no insomnia, normal sleep duration with insomnia, short sleep duration with no insomnia, and short sleep duration with insomnia groups, respectively. Mortality risk was significantly increased only in insomniacs who slept < 6 h, OR = 4.33, CI 1.25-15.04 (Table 3). The risk for death remained significant even after further adjusting for hypertension and diabetes (OR = 4.00, CI 1.14-13.99). The P-value for the interaction between insomnia and sleep duration with diabetes and hypertension status was 0.15, not statistically significant. However, since it showed a trend toward significance, we explored whether comorbidity of hypertension and/or diabetes with insomnia at

Table 3—Mortality risk by insomnia/ objective sleep duration category in men: adjusted odds ratios

	Model 1 Odds Ratio 95% CI			Model 2 Odds Ratio 95% CI		
≥ 6 h No Insomnia	1.00			1.00		
≥ 6 h Insomnia	0.85	0.08	9.44	0.74	0.07	8.37
< 6 h No insomnia	1.32	0.78	2.24	1.34	0.79	2.28
< 6 h Insomnia	4.33	1.25	15.04	4.00	1.14	13.99

Model 1: Adjusted for age, race, education, BMI, smoking status, alcohol use, depression, SDB, and sampling weight.
Model 2: Adjusted for age, race, education, BMI, smoking status, alcohol use, depression, SDB, sampling weight, hypertension, and diabetes.

Table 4—Mortality risk with insomnia/objective sleep duration by hypertension/ diabetes status at baseline: men

	Baseline Hypertension or Diabetes Status					
	NO Odds Ratio 95% CI			YES Odds Ratio 95% CI		
≥ 6 h No Insomnia	1.00			1.00		
≥ 6 h Insomnia	1.15	0.03	45.48	0.59	0.02	16.63
< 6 h No insomnia	0.98	0.44	2.19	1.94	0.91	4.16
< 6 h Insomnia	1.45	0.13	16.14	7.17	1.41	36.62

Both models adjusted for age, race, education, BMI, smoking status, alcohol use, depression, SDB, and sampling weight. The P-value for interaction between insomnia and sleep duration with hypertension/ diabetes status was 0.15, which is not statistically significant.

Table 5—Mortality risk by insomnia/ objective sleep duration in women: adjusted odds ratios

	Model 1 Odds Ratio 95% CI			Model 2 Odds Ratio 95% CI		
≥ 6 h No Insomnia	1.00			1.00		
≥ 6 h Insomnia	7.04	0.06	818.30	1.10	0.08	15.55
< 6 h No insomnia	0.50	0.05	5.55	1.41	0.47	4.19
< 6 h Insomnia	1.64	0.01	254.71	0.36	0.03	4.33

Model 1: Adjusted for age, race, education, BMI, smoking status, alcohol use, depression, SDB, and sampling weight.
Model 2: Adjusted for age, race, education, BMI, smoking status, alcohol use, depression, SDB, sampling weight, hypertension, and diabetes.

baseline increased the mortality risk compared to insomniac patients who did not have diabetes/hypertension at baseline. The odds ratio was significantly increased in the insomniacs with < 6 h of sleep and who were diabetic or hypertensive at baseline (OR = 7.17, CI 1.40-36.62) compared to the normal sleep duration and no insomnia group (Table 4). In contrast, in insomniacs with short sleep duration but without diabetes or hypertension at baseline, the mortality risk was not increased compared to the reference group (OR = 1.45, CI 0.13-16.14). The wide confidence intervals were due to the low number of deceased insomniacs with or without short sleep duration.

Women

In women, the 10-year adjusted mortality rate was 2.3%, 2.5%, 10.2%, and 2.5% in normal sleep duration and no insomnia, normal sleep duration with insomnia, short sleep duration and no insomnia, and short sleep duration with insomnia groups, respectively. The mortality risk was not significantly increased in the short sleep duration with insomnia group after adjusting for age, race, education, BMI, smoking status, alcohol use, depression, SDB, diabetes, hypertension, and sampling weight (Table 5).

CONCLUSIONS

This is the first study to demonstrate that in men, chronic insomnia with objectively measured short sleep duration is associated with increased mortality. This increased risk is independent of comorbid conditions frequently associated with mortality, such as age, race, obesity, alcohol consumption, smoking, sleep disordered breathing, or depression. Furthermore, our findings suggest that objective measures of sleep duration in insomnia may be a useful marker of the biological severity and medical impact of the disorder. We tested the hypothesis that the association between mortality and insomnia and short sleep duration might be attributable to chronic comorbidity, especially hypertension and type 2 diabetes. However, the odds ratio (4.33) from a model not adjusted for hypertension and type 2 diabetes was not attenuated in the model adjusted for hypertension and diabetes (OR = 4.00). Thus, these data did not support that the association between mortality and insomnia and sleep duration was largely attributable to these two chronic conditions.

Several studies have examined the association of sleep disturbances or insomnia with mortality risk with inconsistent findings.[14-20] Studies on two large cohorts, 1 million American Cancer Volunteers[19] and 13,000 well-characterized participants in the Atherosclerosis Risk in Communities (ARIC)[20] reported no association or even reduced mortality rate of individuals complaining of sleep difficulty. Limitations of these studies included a liberal definition of insomnia, and lack of information about duration of insomnia complaints as well as lack of objective measures of sleep. Those studies that reported a positive association of insomnia complaints were rather small, and focused on the elderly,[14,17] whereas a Swedish study that included middle-aged men and women after controlling for various confounders reported an increased risk for coronary artery disease associated death but not for "all-cause mortality" in men.[18] Importantly in all these studies the possible confounding effect of sleep disordered breathing could not be controlled for, since no polysomnographic data were obtained.

In previously published studies, based on the same cohort, we reported a significant association between insomnia with objective short sleep duration and hypertension and type 2 diabetes.[5,6] Given the known association of these two conditions with increased mortality, we explored whether these two factors are mediators of the increased mortality risk associated with insomnia. Controlling for diabetes and/or hypertension reduced the mortality risk by only a small percentage. This finding suggests that conditions other than diabetes or hypertension mediate the increased all-cause mortality risk of insomnia in men. An alternative explanation is that the small effect of hypertension/

diabetes on the association of insomnia with all-cause mortality may be related to the relatively small number of deceased subjects in our study.

We further examined whether the presence of diabetes or hypertension at baseline modifies the effect of insomnia on the risk for death. Indeed the impact of insomnia with short sleep duration was much stronger in those with diabetes and hypertension at baseline versus those who were healthy. The large magnitude of difference between the two odds ratios (1.45 vs. 7.17) presented in Table 4, although the P-value for the interaction between insomnia and sleep duration with diabetes and hypertension status was 0.15 (not statistically significant, largely due to small sample size and lack of statistical power) may indicate an important potential effect modification by hypertension and diabetes on the insomnia and mortality relationship, implying that persons with insomnia and short sleep duration may have a much higher risk of dying if they also have hypertension and diabetes. From a clinical standpoint, this finding suggests that treatment of insomnia in individuals with impaired physical health should be a medical priority.

Previous studies have reported an association between self-reported sleep duration (but not objective sleep duration) and mortality risk.[29-32] In our study we found no association between objective short sleep duration and mortality. The inconsistencies between self-reported and objective sleep duration have been well-described in large epidemiological studies (SHHS, CARDIA, Penn State Cohort).[6,33,34] In all three studies the average self-reported sleep duration is about seven hours whereas the average objective sleep duration is about six hours. Thus, it is possible that the answer to the question "how many hours do you usually sleep" is influenced by several other factors such as age, sex, sleep disturbance, and psychosocial factors besides objective sleep duration. Future studies are needed to address this epistemological challenge.

Our study, due to the relatively small number of deceased subjects did not have the statistical power to explore whether more severe short sleep duration, i.e., sleep duration < 5 hours is associated with increased mortality. Even with our current definition of short sleep duration, i.e., < 6 hours, the four insomnia-sleep duration subgroups stratified by gender were based on a small number of deaths (Table 1 and 2). As a consequence, the resulting odds ratios all had large 95% confidence intervals. Finally, the mortality risk was increased in men but not in women, which might be related to the fact that women were followed-up for a shorter period and that a smaller number were deceased at the time of the follow-up compared to the men. The question whether women compared to men are subject to the same death risk associated with insomnia or if there is a specific-gender association would require a larger study with a longer follow-up period.

The findings of this study suggest that polysomnographic measurements may provide a reliable index of the severity of chronic insomnia and the associated biological and medical significance. Given that the use of the sleep laboratory to predict the medical severity of chronic insomnia is costly and impractical, the validity and usefulness of other simpler methods, such as actigraphy, should be tested.

The data on the association of insomnia with hypertension, diabetes and mortality, as well as previous reports on insomnia and the stress system[7-9] and the autonomic system,[10-12] provide the basis for a meaningful subtyping of chronic insomnia based on objective duration of sleep. One subtype is associated with physiological hyperarousal (short sleep duration, activation of the stress system) and significant medical morbidity (hypertension, diabetes and/or neurocognitive deficits)[5,6,35] and mortality. The other subtype is not associated with physiological hyperarousal, i.e., normal sleep duration, normal activity of the stress system, and lack of significant medical sequelae. The diagnostic validity and utility of this subtyping should be tested in future studies.

The objective sleep duration in this study was based on one night of polysomnography, which may not be representative of the subjects' habitual sleep duration. However, in our previous studies, the association between objective sleep duration and hypercortisolemia was based on a 4 consecutive night sleep laboratory protocol, which should better represent the typical sleep profile of the subjects.[7,8] Objective sleep duration was used as an internally valid marker of the severity of insomnia and not as a recommended optimum sleep duration for the general population, which is beyond the scope of our study. The consistency of the findings on the role of objective sleep duration in predicting insomnia severity between the physiological studies with multiple night recordings[7,8] and the current epidemiological study based on a single night recording increases our confidence about the replicability and generalizability of the present findings. Future studies should explore the association between insomnia, sleep duration, and mortality using multiple night recordings.

In conclusion, insomnia with short sleep duration in men is associated with a significant risk for death, in a degree comparable to the other most common sleep disorder, sleep disordered breathing.[21] Given the high prevalence of the disorder in the general population and the widespread misconception that this is a disorder of the "worried well," its diagnosis and appropriate treatment should become the target of public health policy. Objective measures of sleep duration of insomnia may serve as clinically useful predictors of the medical severity of chronic insomnia and there is a need for validation of practical, easy to use, inexpensive methods, e.g., actigraphy, to measure sleep duration outside of the sleep laboratory. Finally, insomnia with objective short sleep duration may represent a subtype within chronic insomnia that may respond differentially to treatment.

ACKNOWLEDGMENTS

We thank Barbara Green for her overall preparation of this manuscript.

This research is funded in part by the National Institutes of Health grants RO1 51931, RO1 40916, and RO1 64415.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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