

**Insomnia with Objective Short Sleep Duration is Associated with Type 2
Diabetes:
A Population-based Study**

Running title: Insomnia, objective sleep duration, diabetes

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Objective: We examined the joint effects of insomnia and objective short sleep duration, the combination of which is associated with higher morbidity, on diabetes risk.

Research Design and Methods: 1,741 men and women randomly selected from Central Pennsylvania were studied in the sleep laboratory. *Insomnia* was defined by a complaint of insomnia with duration of ≥ 1 year while *poor sleep* was defined as a complaint of difficulty falling asleep, staying asleep, or early final awakening. Polysomnographic sleep duration was classified into three categories: ≥ 6 hours of sleep (top 50% of the sample); 5-6 hours (approximately third quartile of the sample); and ≤ 5 hours (approximately the bottom quartile of the sample). Diabetes was defined either based on a fasting blood glucose > 126 mg/dl or using medication. In the logistic regression model we simultaneously adjusted for age, race, sex, body mass index, smoking, alcohol use, depression, sleep disordered breathing (SDB), and periodic limb movement.

Results: Chronic insomnia but not poor sleep was associated with a higher risk for diabetes. Compared to the normal sleeping and ≥ 6 hour sleep duration group, the highest risk of diabetes was in individuals with insomnia and ≤ 5 hour sleep duration group [OR (95% CI) 2.95 (1.2 – 7.0)], and in insomniacs who slept 5-6 hours [OR (95% CI) 2.07 (0.68 – 6.4)].

Conclusions: Insomnia with short sleep duration is associated with increased odds of diabetes. Objective sleep duration may predict cardiometabolic morbidity of chronic insomnia, whose medical impact has been underestimated.

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 (5). 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 (6-11). Given the association of the HPA axis and sympathetic system activation with the pathogenesis of metabolic disorders, including diabetes (12), we hypothesize that insomniacs with objective short sleep duration will be associated with type 2 diabetes.

Previous studies have shown that sleep disturbances or complaints are associated with increased incidence of type 2 diabetes (13-16). However, in these studies, the presence of sleep disturbances was based only on a subjective questionnaire and did not control for obstructive sleep apnea, a sleep disorder whose association with diabetes mellitus and insulin resistance is well-established (12). Thus, it is unknown whether insomnia per se is associated with an increased risk for diabetes.

To test this hypothesis, we examined the joint effects of the complaints of chronic insomnia and poor sleep (a milder form of insomnia), and objective sleep duration on the prevalence of diabetes in a large cross-sectional population-based sample from Central Pennsylvania (Penn State Cohort).

RESEARCH DESIGN AND METHODS

Population: The data were collected as part of a two-phase protocol whose primary purpose was to establish the age distribution of sleep disordered breathing (17,18). In the first phase of the study, a sample of adult men and women (age ≥ 20 years) was randomly selected from local telephone households in two counties of Central Pennsylvania (Dauphin and Lebanon) using the Mitofsky – Waksberg two-stage random digit dialing procedure. A within-household selection procedure described by Kish was used to select the specific man or woman to be interviewed. 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 sample of men was chosen by counting the number of four risk factors (snoring, daytime sleepiness, obesity, and hypertension) each interviewed subject reported. Subjects with higher counts of risk factors were oversampled (3%, 9%, 32%, 45%, and 70% for 0, 1, 2, 3, and 4 symptoms reported, respectively). The sample of women was chosen by counting the number of five risk factors (snoring, daytime sleepiness, obesity, hypertension, and menopause) reported by each interviewed

subject. Those with higher counts of risk factors were oversampled (2%, 4%, 10%, 27%, 51%, and 56% of those with 0, 1, 2, 3, 4, and 5 symptoms reported, respectively). The response rate for this phase was 67.8% and 65.8% for men and women, respectively. There were no significant differences between those subjects who were recorded in the laboratory with those who were selected but not recorded in terms of age, BMI, reported use of medication for hypertension or diabetes and prevalence of sleep disorders. Each subject selected for laboratory evaluation completed a comprehensive sleep history and physical examination, and was continuously monitored for one night for 8h using 16-channel polygraphs including electroencephalogram, electrooculogram, and electromyogram. Bedtimes were adjusted to conform to subjects' usual bedtimes, and subjects were recorded between 10:00-11:00 p.m. and 6:00-7:00 a.m. The sleep records were subsequently scored independently according to standardized criteria. 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 (SaO₂) were obtained with an oximeter attached to the finger.

Key measurements: Diabetes was defined as being medically treated for diabetes or having a fasting blood glucose greater than 126 mg/dl from blood drawn the morning after the sleep laboratory testing. Hypertension was defined as a diastolic blood pressure greater than 90 mm Hg or a systolic blood pressure greater than 140 mm Hg at the time of the sleep laboratory evaluation or the use of antihypertensive medication.

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 (for more details see reference 5). The presence of sleep difficulty was established on three levels of severity. First, *insomnia* was defined by a complaint of insomnia with a duration of at least 1 year. Second, *poor sleep* was defined as a moderate to severe complaint (based on a mild to severe scale) of difficulty falling asleep, difficulty staying asleep, early final awakening, or unrefreshing sleep. In order to create two mutually exclusive categories, the *insomnia* group could include those who reported one or more of the four symptoms of poor sleep, whereas none of the *poor sleep* group had a complaint of insomnia. Finally, *normal sleeping* was defined as the absence of either of these two categories.

From the objectively recorded sleep time data, we regrouped the entire study sample into three ordinal groups based on standard mathematical approaches using as cutoff points the 50th percentile and the 25th percentile: the top 50% of persons above the median percent sleep time ("normal sleep duration group"); the 25% of persons in the third quartile ("moderately short sleep duration group"); and the bottom 25% of persons ("severely short sleep duration group"). We then rounded the quartile cut-off points to practically meaningful numbers. Thus, we created the following three relative sleep duration groups: the "normal sleep duration group" consisted of those who slept > 6 hours, the "moderately short sleep duration group" of those who slept 5-6 hours, and the "severely short sleep duration group" of those who slept ≤ 5 hours.

To control for possible confounding variables influencing the relation between insomnia and diabetes, in the subsample of 1,741 we ascertained whether the respondent

was currently treated for depression (including a history of suicidal thoughts or attempts), had a history of smoking (current use of any type of tobacco product), a history of alcohol use (more than two alcohol drinks per day), and whether he/she had sleep apnea and periodic limb movements. For the purpose of this study, sleep apnea was defined as an obstructive apnea or hypopnea index of 5 or greater ($OHI \geq 5$) (5,17,18). The condition of periodic limb movement was considered present when there were five or more movements per hour of sleep while leg movements were scored according to standardized criteria (5). 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.

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 (5,17,18). Specifically, three 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 three age groups in order to oversample the middle age 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 four possible risk factors, i.e., 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 suggestion of possible sample bias, we calculated 32 unique weights for the women and 16 unique weights for the men corresponding to all possible combinations of the five risk factors for the women and four 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 less than 10.

Finally, we used the BMI and race distributions by age decade from the NHANES III laboratory data as the standard 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 three-level sleep difficulty complaints and objective sleep duration with diabetes. We adjusted for major confounding factors expected to affect this relationship (i.e., age, race, gender, BMI, smoking status, alcohol consumption, depression, and SDB). We further tested the interaction between sleep difficulty complaints and objective sleep duration using -2 log likelihood ratio test in logistic regression models. Because the interaction between sleep difficulty complaints and objective sleep duration was not significant, we entered these two variables into the model separately, except for the last model (Table 2, Model with ##, the last column in the table) in which the results were adjusted for each other. Finally, we performed final logistic regression models to include eight dummy variables to represent all nine possible combinations of sleep difficulty and sleep duration, and used persons without insomnia/poor sleep and with ≥ 6 hour of sleep duration as a common reference group (Table 3).

RESULTS

The demographic, clinical, and sleep characteristics of the entire sample and its subgroups, based on sleep difficulty, and the three levels of objective sleep duration and diabetes, are presented in Table 1.

Insomnia was associated with a significantly higher risk for diabetes (OR = 1.84, 95%CI 1.05 – 3.20, $P < 0.05$) in the first basic covariable adjusted model (Table 2). With the increases of the number of potential confounding factors in the model, the OR of insomnia and diabetes remained very similar (changed less than 8%, from 1.84 to 1.69), but the precision of the estimation worsened, reflected by increased width of 95%CI. Poor sleep was associated with a slight, nonsignificant increase of risk for diabetes. Finally, an objective sleep duration of 5-6 hours was associated with a slight, nonsignificant, increase of risk for diabetes (OR = 1.35, 95%, CI, 0.92 – 1.98).

The risk of diabetes was synergistically and significantly increased among persons with both insomnia, and short sleep duration (Table 3). The presence of both insomnia and an objective sleep duration ≤ 5 hours increased the risk for diabetes by about 300% (OR = 2.95, 95% CI 1.24 – 7.05) compared to the group who have no insomnia/poor sleep complaint and slept for more than 6 hours. Also, the joint effect of insomnia and a sleep duration of 5-6 hours increased the risk for diabetes by about 200% (OR = 2.07, 95% CI 0.68 – 6.37). The association in subjects with poor sleep and a short sleep duration was not significant.

Finally, objective short sleep duration in the absence of a sleep complaint was associated with a nonsignificant increased risk for diabetes. The ORs remained very similar to those reported in Table 3 after we adjusted for number of wakes, number of sleep stage changes, percent stage 1 sleep, and periodic limb movements.

In summary, insomnia is associated with a higher risk of diabetes in this population-based sample. Most importantly, insomnia in combination with objective short sleep duration is associated with a clinically significant risk of diabetes.

CONCLUSIONS

This is the first study to demonstrate that chronic insomnia associated with objectively measured short sleep duration is a clinically significant risk factor for type 2 diabetes. This increased risk is independent of comorbid conditions frequently associated with insomnia or diabetes, such as age, race, obesity, alcohol consumption, smoking, sleep disordered breathing, periodic limb movements, 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.

Several studies have examined the association of “sleep disturbances” with diabetes with inconsistent findings (13-16,19). Importantly, all of these studies did not obtain objective sleep data and did not control for sleep apnea, a major confounder, both for “sleep disturbance” and increased incidence of type 2 diabetes.

In our study, the group with the more severe insomnia, (i.e., complaint of insomnia for at least one year), was significantly associated with higher odds of diabetes in basically adjusted model. Most importantly, severe insomnia in combination with an objective sleep duration of less than five hours was associated with a 300% higher risk for diabetes than the subjects who did not have a sleep complaint and slept for ≥ 6 hours. The second highest risk was found in the group of insomniacs who slept 5-6 hours, although the association did not reach significance. These findings are consistent with the data on insomnia and hypertension, where the strongest associations were found

in these two groups (5). Further, these data are consistent with our hypothesis and previous physiological studies which showed that the HPA axis and sympathetic system activity is elevated in insomniacs with objective short sleep duration (6-11).

Insomnia based solely on clinical criteria and after adjusting for multiple variables was not associated with a significant risk for diabetes. This is consistent with the results of the Sleep Heart Health Study (20). Further, the milder form of insomnia i.e., poor sleep combined with short sleep duration was not associated with a significant risk for diabetes. This lack of significance may reflect, given the large confidence intervals, a relatively small number of patients with diabetes in each subgroup and/or lack of employment of more sensitive measures of glycemic status, i.e., standard oral glucose challenge in our study. An alternative explanation is that a larger degree of sleep disturbance is required to affect glycemic status compared to blood pressure, as is the case with sleep apnea where an association with diabetes has been reported only in the more severe apneics (21).

Experimental studies have shown that acute or short-term modest sleep loss is associated with impaired glycemic control (22) and inflammation, a condition which predisposes an individual to diabetes (23). In this study in a general population sample, we did not observe an association between objective sleep duration and diabetes. Several limitations may have resulted in this lack of significance, such as relatively small number of patients with diabetes in each of the nine subgroups (combination of insomnia complaints and objective sleep measures), lack of more sensitive measures of glycemic status, (i.e., OGTT), and a single night sleep recording, which may not be representative of the subjects' typical sleep patterns. Notably, all previous studies that have reported an association between sleep duration and

diabetes were based on subject self-report (22). Future studies, including both subjective and objective sleep measures, and more sensitive methods of glycemic status, should address the issue of long-term sleep restriction and diabetes.

The data on the association of insomnia with hypertension and diabetes, as well as previous reports on insomnia and the stress system (6-8) and the autonomic system (9-11), provide the basis for a meaningful subtyping of chronic insomnia based on objective duration of sleep. One subtype is associated with physiological hyperarousal, i.e., short sleep duration, activation of the stress system, and significant medical sequelae, such as hypertension and/or diabetes. 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 (6,7). It should be noted that our study investigated the relative sleep duration measured objectively (i.e., < 5 hours of objective sleep is relatively shorter than >6 hours of sleep). 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. Finally, the proposed criterion of >7 hours as the cutoff point for "normal" sleep duration is based on self-reported duration whereas, in

large epidemiologic studies, i.e., Sleep Heart Health Study or CARDIA, the average objective sleep duration is about 6 hours, which is very similar to that of our sample (24,25). This is independent of whether sleep was recorded at home (SHHS) (24) or for three consecutive nights with actigraphy (CARDIA) (25) or in the sleep laboratory (Penn State Cohort) (17,18). The consistency of the findings on the role of objective sleep duration in predicting insomnia severity between the physiological studies with multiple night recordings (6,7) 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 diabetes using multiple night recordings. Finally, our study is cross-sectional and does not provide causality in terms of the direction of the association. However, based on large amounts of clinical and research data, which have documented that insomnia is associated with physiologic hyperarousal (2,611), the most likely direction is that insomnia leads to diabetes.

In conclusion, insomnia with short sleep duration is associated with a significant

risk for diabetes in a degree comparable to the other most common sleep disorder, i.e., 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 phenotype within chronic insomnia that may respond differentially to treatment.

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sleeping	70	71	66	\	\	\	70	66	72
Poor sleep	22	22	24	\	\	\	20	26	22
Insomnia	8	7	10	\	\	\	11	8	6

* Adjusted for sampling weight. Where appropriate the standard deviation is presented in parenthesis.

Table 2. Multivariable adjusted odds ratio (95% CI) of diabetes associated with insomnia or objective sleep duration

	Adjusted* OR (95% CI)	Adjusted# OR (95% CI)	Adjusted### (OR (95% CI)
Sleep difficulty			
Normal sleeping	1.00	1.00	1.00
Poor sleep	1.31 (0.91, 1.90)	1.23 (0.84, 1.80)	1.22 (0.83, 1.78)
Insomnia	1.84 (1.05, 3.20)	1.70 (0.95, 3.02)	1.69 (0.95, 3.02)
Sleep duration			
>6 hours	1.00	1.00	1.00
5-6 hours	1.38 (0.94, 2.02)	1.37 (0.93, 2.00)	1.35 (0.92, 1.98)
≤5 hours	1.15 (0.77, 1.71)	1.11 (0.74, 1.65)	1.08 (0.72, 1.61)

* Adjusted for age, race, sex, BMI, and sampling weight.

Adjusted for age, race, sex, BMI, sampling weight, smoking, alcohol consumption, depression symptoms, and SDB.

The interaction between insomnia and sleep duration was not statistically significant. So, these two variables entered into the model separately, except for the last model, indicated by “###” above, in which the results were adjusted for each other.

Table 3. Multivariable adjusted odds ratio (95% CI) of diabetes associated with insomnia and objective sleep duration

Sleep difficulty	Sleep duration	Adjusted * OR (95% CI)
Normal sleeping	>6 hours	1.00
Normal sleeping	5-6 hours	1.45 (0.91, 2.30)
Normal sleeping	<5 hours	1.10 (0.68, 1.79)
Poor sleep	>6 hours	1.52 (0.87, 2.65)
Poor sleep	5-6 hours	1.55 (0.80, 3.01)
Poor sleep	<5 hours	1.06 (0.53, 2.15)
Insomnia	>6 hours	1.10 (0.40, 3.03)
Insomnia	5-6 hours	2.07 (0.68, 6.37)
Insomnia	<5 hours	2.95 (1.24, 7.03)

* Adjusted for age, race, sex, BMI, sampling weight, smoking, alcohol consumption, depression symptoms and SDB.
 The interaction between insomnia and sleep duration is not statistically significant, p=0.75.