

# Insomnia is associated with an increased risk of type 2 diabetes in the clinical setting

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## ABSTRACT

**Objective** To determine the possible association between insomnia and risk of type 2 diabetes mellitus (T2DM) in the naturalistic clinical setting.

**Research design and methods** We conducted a retrospective cohort study to examine the risk of developing T2DM among patients with pre-diabetes with and without insomnia. Participants with pre-diabetes (identified by a physician or via two laboratory tests) between January 1, 2007 and December 31, 2015 and without sleep apnea were followed until December 31, 2016. Patients were determined to have T2DM when two of the following occurred within a 2-year window: physician-entered outpatient T2DM diagnosis (International Classification of Diseases [ICD]-9 250.00; ICD-10 E11), dispensing of an antihyperglycemia agent, and hemoglobin A1c (A1c) >6.5% (48 mmol/mol) or fasting plasma glucose (FPG) >125 mg/dL. One hospital inpatient stay with an associated T2DM diagnosis was also sufficient for classification of T2DM.

**Results** Our cohort consisted of 81 233 persons with pre-diabetes, 24 146 (29.7%) of whom had insomnia at some point during the 4.3-year average observation period. After adjustment for traditional risk factors, those with insomnia were 28% more likely to develop T2DM than those without insomnia (HR 1.28; 95% CI 1.24 to 1.33). The estimate was essentially unchanged after adjusting for baseline A1c level (HR 1.32; 95% CI 1.25 to 1.40) or FPG (HR 1.28; 95% CI 1.23 to 1.33).

**Conclusions** Insomnia imparts an increased risk of T2DM comparable with that conferred by traditional risk factors (eg, overweight, non-white race, cardiovascular risk factors). This association could have clinical importance because it suggests a new potentially modifiable risk factor that could be targeted to prevent diabetes.

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a significant public health burden. If current trends continue, one in three Americans will develop T2DM by 2050.<sup>1</sup> Insomnia is emerging as a possible modifiable risk factor in the development of T2DM. In short-term laboratory studies, experimentally induced sleep deprivation led to hyperglycemia, which was subsequently reversed with normal sleep restoration.<sup>2–9</sup> These induced-insomnia

## Significance of this study

### What is already known about this subject?

- ▶ In short-term laboratory studies, experimentally induced sleep deprivation led to hyperglycemia, which was reversed with normal sleep restoration.
- ▶ Some epidemiologic studies have found that the quantity and quality of sleep are significant predictors of the risk of developing type 2 diabetes mellitus (T2DM).

### What are the new findings?

- ▶ Our study adds to this literature by examining whether and confirming that a clinical diagnosis of insomnia is a risk factor for diabetes.
- ▶ By establishing an association between clinically recognized insomnia and T2DM risk, we have expanded the at-risk category to include those with clinically diagnosed insomnia, which can be more easily applied in the healthcare setting than relying on sleep questionnaires.

### How might these results change the focus of research or clinical practice?

- ▶ Treatment of sleep problems holds promise as a strategy to prevent T2DM, but further research is needed to test its effectiveness.

studies have been necessarily limited to small samples and short duration and did not examine whether prolonged sleep disruption increased the risk of developing T2DM in otherwise healthy individuals. Relevant to this question, some, but not all, epidemiologic studies have found that the quantity and quality of sleep are significant predictors of the risk of developing T2DM.<sup>10</sup> The specific causal mechanisms are as yet undetermined, but sleep loss is hypothesized to increase the risk of developing diabetes via multiple pathways, including loss of pancreatic  $\beta$ -cell function,<sup>11</sup> altered adipokine profiles,<sup>12</sup> increased activation of the sympathetic nervous system,<sup>13</sup> increased inflammation,<sup>13</sup> increased cortisol levels,<sup>14</sup> increased food intake, weight gain, obesity, and decreased physical activity.<sup>15 16</sup>



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To further understand the association between insomnia and T2DM, we conducted a retrospective panel cohort study to examine the risk of developing T2DM among patients with pre-diabetes with and without insomnia. We hypothesized that the risk of T2DM would be higher among persons with insomnia, after controlling for other known or suspected T2DM risk factors.

## MATERIALS AND METHODS

### Setting

Kaiser Permanente Northwest (KPNW) is a not-for-profit, group-model integrated delivery system that provides comprehensive medical care to more than 600 000 individuals in the metropolitan area around Portland, Oregon.

### Identification of cohort or patients with pre-diabetes

KPNW uses healthcare utilization data to track and facilitate operations. An electronic medical record (EMR), in use since 1996, allows providers to record International Classification of Diseases (ICD) diagnosis codes at each patient contact and to update an electronic problem list, also with ICD codes. A single regional laboratory processes most KPNW outpatient laboratory tests, and the results are stored in a searchable database. A pharmacy is located at each medical clinic, and most members have a pharmacy benefit, ensuring almost complete capture of data on pharmaceutical dispenses. The EMR healthcare utilization data made it possible to determine patient eligibility for the study cohort. To be eligible for the study cohort, participants had to have had pre-diabetes (as defined by a physician diagnosis [ICD-9 790.29; ICD-10 R73.09] or two laboratory tests in the pre-diabetes range (fasting plasma glucose [FPG] from 100 to 125 mg/dL and/or hemoglobin A1c [A1c] from 5.70% to 6.49% [39–47 mmol/mol]) between January 1, 2007 and December 31, 2015. Participants' baseline ( $T_0$ ) was defined as the date of their first indicator of pre-diabetes. Participants had to be continuous members at least 1 year prior to  $T_0$  and 18 years or older at  $T_0$ . Participants with obstructive sleep apnea (ICD-9 327.23; ICD-10 G47.33), sleep-disordered breathing (ICD-9 327.2X; ICD-10 G47.30), restless leg syndrome (ICD-9 333.94; ICD-10 G25.81), and periodic leg movement disorder (ICD-9 327.5; ICD 10 G47.61) up to 1 year prior to  $T_0$ , or with T2DM (as described below) or bariatric surgery at any prior date were excluded.

### Follow-up of patients and identification of the development of T2DM

We followed participants with pre-diabetes from  $T_0$  until the earliest of the following events occurred: T2DM diagnosis, loss of Kaiser Permanente membership (>3 months break in coverage), death, bariatric surgery, or end of study follow-up (December 31, 2016). Patients were determined to have a T2DM diagnosis when two of the following occurred within a 2-year window: physician-entered outpatient T2DM diagnosis (ICD-9 250.00; ICD-10

E11), dispensing of an antihyperglycemia agent, A1c >6.5% (48 mmol/mol), and/or FPG >125 mg/dL. One hospital inpatient stay with an associated T2DM diagnosis was also sufficient for classification of T2DM.<sup>17</sup>

### Identification of insomnia and covariates

Participants were determined to have insomnia if they had a physician-entered diagnosis of insomnia (ICD-9 307.40, 307.45–9, 780.50, 780.53, 780.55–9, V69.4, 307.41, 307.42, 780.51, 780.52; ICD-10 F51.01) prior to the diagnosis of diabetes and/or used one or more medications predominantly prescribed for sleep problems in this health plan (eg, trazodone, eszopiclone, zaleplon, or zolpidem) in the 12 months prior to the diagnosis of diabetes.

We also collected data on potential covariates that might influence the development or detection of T2DM: age, body mass index (BMI), sex, race (black, Asian, white, other), ethnicity (Hispanic, not Hispanic), history of congestive heart failure (CHF) and myocardial infarction, hypertension (measured as  $\geq 140/90$  or by diagnosis code), elevated triglyceride levels (>150 mg/dL), and low high-density lipoprotein (HDL) levels (<40 mg/dL).<sup>18</sup>

### Statistical analyses

We calculated summary statistics describing the characteristics of eligible participants stratified by insomnia status. Continuous variables were summarized as mean $\pm$ SD and were compared using t-test (for data that were normally distributed) or Mann-Whitney U test (for data that were not normally distributed). Categorical variables were expressed as frequency and percentages and were compared using  $\chi^2$  test. We used multivariate time-varying covariates Cox regression models to estimate HRs and 95% CIs for the association between the risk of developing T2DM and insomnia, adjusting for various confounders. Insomnia was treated as the time-varying covariate as study participants could experience insomnia at any time during the follow-up period. Analyses were conducted using the SAS V.9.4 software.

## RESULTS

### Baseline characteristics

Our cohort consisted of 81 233 persons who had pre-diabetes between January 1, 2007 and December 31, 2015 and had data for all baseline covariates; 24 146 (29.7%) were classified as having insomnia at some point during the observation period (but before diagnosis of T2DM). The average observation window was 4.3 (SD 2.8) years. Participants had a mean age of 57.5 (SD 13.6) years at the time of initial identification with pre-diabetes (table 1). Compared with participants without insomnia indications, those with insomnia were older and were more likely to be above normal weight, female, white, not Hispanic, and current or previous smokers, and to have a history of CHF, hypertension, elevated triglycerides ( $\geq 150$  mg/dL), and low HDL (<40 mg/dL) (all  $p < 0.001$ ). Consistent with the American Diabetes Association guidelines, our

**Table 1** Baseline characteristics

	Total n=81 233	Insomnia n=24 146	No insomnia n=57 087	P value
Age				<0.0001
Mean (SD)	57.5 (13.6)	58.4 (13.1)	57.1 (13.8)	
BMI, kg/m <sup>2</sup> , n (%)				<0.0001
<25	14 238 (17.5)	4013 (16.6)	10 225 (17.9)	
≥25 to 29.9	26 694 (32.9)	7417 (30.7)	19 277 (33.8)	
≥30 to 39.9	31 943 (39.3)	9699 (40.2)	22 244 (39.0)	
≥40	358 (10.3)	3017 (12.5)	5341 (9.4)	
Sex, n (%)				<0.0001
Female	43 562 (53.6)	13 547 (56.1)	30 015 (52.6)	
Male	37 671 (46.4)	10 599 (43.9)	27 072 (47.4)	
Race, n (%)				<0.0001
White	65 803 (81.0)	20 761 (86.0)	45 042 (78.9)	
Asian	3979 (4.9)	724 (3.0)	3255 (5.7)	
Black	2208 (2.7)	572 (2.4)	1636 (2.9)	
Other	9243 (11.4)	2089 (8.7)	7154 (12.5)	
Ethnicity, n (%)				<0.0001
Not Hispanic	76 946 (94.7)	23 176 (96.0)	23 176 (94.2)	
Hispanic	4287 (5.3)	970 (4.0)	3317 (5.8)	
Smoking status, n (%)				<0.0001
Never	43 202 (53.2)	11 778 (48.8)	31 424 (55.0)	
Current	10 063 (12.4)	3172 (13.1)	6891 (12.1)	
Previous	27 519 (33.9)	9084 (37.6)	18 435 (32.3)	
Unknown	449 (0.6)	112 (0.5)	337 (0.6)	
Congestive heart failure, n (%)				<0.0001
No	79 915 (98.4)	23 613 (97.8)	56 302 (98.6)	
Yes	1318 (1.6)	533 (2.2)	785 (1.4)	
Myocardial infarction, n (%)				0.07
No	80 639 (99.3)	23 949 (99.2)	56 690 (99.3)	
Yes	594 (0.7)	197 (0.8)	397 (0.7)	
Hypertension, n (%)				<0.0001
No	35 159 (43.3)	9346 (38.7)	25 813 (45.2)	
Yes	46 074 (56.7)	14 800 (61.3)	31 274 (54.8)	
Elevated triglycerides (≥150 mg/dL), n (%)				<0.0001
No	38 478 (47.4)	10 976 (45.5)	27 502 (48.2)	
Yes	42 755 (52.6)	13 170 (54.5)	29 858 (51.8)	
Low HDL (<40 mg/dL), n (%)				<0.0001
No	4929 (60.7)	14 166 (58.7)	35 128 (61.5)	
Yes	31 939 (39.3)	9980 (41.3)	21 959 (38.5)	
Hemoglobin A1c	n=45 261	n=12 485	n=32 776	<0.0001
%, mean (SD)	5.8 (0.25)	5.8 (0.26)	5.9 (0.25)	
mmol/mol, mean (SD)	40 (2.73)	40 (2.84)	41 (2.73)	
Fasting glucose	n=50 443	n=16 714	n=33 729	0.87
mg/dL, mean (SD)	102.4 (9.62)	102.4 (9.45)	102.4 (9.70)	

BMI, body mass index; HDL, high-density lipoprotein.

**Table 2** Risk of developing T2DM according to insomnia status

Risk factor	Baseline model (n=79 608)	Model adjusted for baseline A1c (n=45 267)	Model adjusted for baseline FPG (n=50 443)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Insomnia	1.28 (1.24 to 1.33)	1.32 (1.25 to 1.40)	1.28 (1.23 to 1.33)
Baseline age (per 10-year increment)	1.11 (1.09 to 1.12)	1.04 (1.02 to 1.07)	1.08 (1.07 to 1.10)
Baseline BMI (vs 25 kg/m <sup>2</sup> )			
≥25 to 29.9	1.21 (1.13 to 1.28)	1.14 (1.04 to 1.25)	1.11 (1.03 to 1.19)
≥30 to 39.9	1.89 (1.78 to 2.01)	1.64 (1.50 to 1.79)	1.61 (1.51 to 1.73)
≥40	3.12 (2.91 to 3.35)	2.50 (2.25 to 2.77)	2.45 (2.26 to 2.65)
Male sex	1.02 (0.98 to 1.05)	1.13 (1.08 to 1.20)	0.90 (0.86 to 0.93)
Race (vs white)			
Asian	1.85 (1.71 to 2.01)	1.32 (1.17 to 1.50)	1.98 (1.81 to 2.17)
Black	1.36 (1.24 to 1.49)	0.90 (0.79 to 1.04)	1.66 (1.49 to 1.86)
Other	1.27 (1.20 to 1.35)	1.14 (1.03 to 1.25)	1.30 (1.21 to 1.39)
Hispanic	1.11 (1.02 to 1.21)	1.03 (0.90 to 1.17)	1.15 (1.04 to 1.27)
Smoking status (vs never)			
Current	1.36 (1.29 to 1.43)	1.26 (1.17 to 1.37)	1.29 (1.22 to 1.37)
Previous	1.09 (1.05 to 1.13)	1.18 (1.12 to 1.25)	1.05 (1.01 to 1.10)
Unknown	1.06 (0.86 to 1.31)	1.22 (0.85 to 1.77)	0.95 (0.75 to 1.20)
Congestive heart failure	1.76 (1.58 to 1.95)	1.55 (1.31 to 1.82)	1.69 (1.50 to 1.91)
Myocardial infarction	1.22 (1.03 to 1.44)	1.48 (1.17 to 1.88)	1.26 (1.04 to 1.53)
Hypertension	1.27 (1.23 to 1.32)	1.32 (1.25 to 1.40)	1.19 (1.14 to 1.24)
Low HDL	1.35 (1.30 to 1.39)	1.32 (1.25 to 1.39)	1.29 (1.24 to 1.34)
Elevated triglycerides	1.14 (1.10 to 1.18)	1.08 (1.02 to 1.14)	1.19 (1.14 to 1.24)
Baseline A1c (per 0.1% or 1 mmol/mol increase)	NA	1.26 (1.25 to 1.27)	NA
Fasting plasma glucose (per 10 mg/dL increase)	NA	NA	1.65 (1.61 to 1.68)

BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; NA, not applicable; T2DM, type 2 diabetes mellitus.

health system diagnoses pre-diabetes and diabetes with A1c or FPG levels; based on this, 45 267 (55.7%) persons had A1c levels and 50 443 (62.1%) had FPG at or prior to their pre-diabetes diagnosis. In this cohort, the mean A1c at baseline was 5.8% (40 mmol/mol) in those with insomnia vs 5.9% (41 mmol/mol) in those without; FPG was 102.4 mg/dL in both groups.

#### Risk of developing T2DM according to insomnia status and other traditional risk factors

A total of 14 626 (18.0%) of the sample developed T2DM over an average of 4.3 years of follow-up. Of those with insomnia, 4564 (18.9%) developed T2DM, compared with 10 062 (17.6%) of those without insomnia ( $p < 0.0001$ ). In a multivariable model adjusting for traditional T2DM risk factors (age, BMI, sex, race, ethnicity, and history of CHF or myocardial infarction, hypertension, high triglycerides, low HDL, and smoking status), those with insomnia were 28% more likely to develop T2DM than those without insomnia (HR 1.28; 95% CI 1.24 to 1.33) (table 2). As expected, traditional risk factors including older age, higher BMI, non-white race,

Hispanic ethnicity, current or previous smoking, history of CHF, history of myocardial infarction, hypertension, elevated triglycerides, and low HDL were also associated with an increased risk of developing T2DM. When we conducted sensitivity analyses, adding baseline A1c values (n=45 267) and FPG levels (n=50 443) to the model, the HR associated with insomnia was essentially unchanged (HR 1.32; 95% CI 1.25 to 1.40 and HR 1.28; 95% CI 1.23 to 1.33, respectively).

#### DISCUSSION

In our study of 81 233 persons with pre-diabetes, we found that participants with insomnia had about a 30% increased risk of developing T2DM even after adjusting for traditional risk factors including age, BMI, race, ethnicity, and cardiovascular risk factors. Because of the study's large size and because it was conducted in a real-world healthcare system, it adds important information to the growing body of literature suggesting the potentially important influence of sleep disruption on increased T2DM risk.

The degree of increased risk we report is similar to that conferred by traditional risk factors, such as being overweight or of minority (non-white) race or Hispanic ethnicity, or by cardiovascular risk factors such as hypertension, elevated triglycerides, and low HDL. This association could have clinical importance because it suggests a new risk factor that is potentially modifiable and could be targeted in the diabetes prevention effort unlike unmodifiable risk factors such as age, race, and ethnicity.

While current interventions (weight loss and/or exercise interventions) to address conventional T2DM risk factors such as high BMI or sedentary lifestyle can be successful, they are often difficult to implement because of low participant motivation, high dropout rates and, in the case of weight loss programs, an often-delayed effect of the intervention and high risk of return of excess weight.<sup>19</sup> In contrast, behavioral insomnia treatments are relatively brief and effective, are relatively easy to implement, and yield immediate positive benefit.<sup>20–22</sup> Further, sleep-deprived patients are typically very motivated to restore good-quality sleep, in part because restoration of normal sleep is intrinsically rewarding.

Our findings are consistent with experimental work in which researchers disrupt sleep in healthy volunteers. Such studies find that inadequate sleep duration (typically 4–5 hours per night for a 1-day to 14-day period) and disruption of sleep architecture (by circadian misalignment with resultant changes in rapid eye movement (REM) distribution) result in hyperglycemia and insulin resistance, which is reversed when sleep returns to normal.<sup>2–9</sup> Our study's findings are also consistent with previous epidemiologic studies which have found a 28%–84% increased risk of T2DM in those with short sleep duration or sleep difficulties.<sup>10 23</sup>

Our study adds to this literature by examining T2DM risk in participants with a clinical diagnosis of insomnia; previous cohorts have used sleep questionnaires and examined specific elements of sleep (ie, duration and sleep initiation). By examining the association between clinically recognized insomnia and T2DM risk, we have expanded the at-risk category to include those with clinical insomnia, which can be more easily applied in the healthcare setting than relying on sleep questionnaires.

There are several possible reasons why poor sleep might increase the risk of T2DM. Experimental sleep deprivation and epidemiologic studies suggest that disrupted or short-duration sleep could impair the profile of peptides that mediate energy homeostasis (eg, leptin, ghrelin, adiponectin), leading to increased appetite, including cravings for calorie-dense, high-carbohydrate food, and ultimately insulin resistance.<sup>12</sup> Other studies show that persons subjected to short-term experimental sleep deprivation and those with long-term short-sleep duration or sleep disturbances have elevated salivary and serum cortisol levels, particularly in the evening, when levels are normally quite low.<sup>14</sup> Elevated cortisol levels are associated with increased central fat distribution, which is strongly associated

with insulin resistance.<sup>24</sup> Increased inflammation and sympathetic activation could also contribute to the association between sleep disruption and diabetes risk. Both are activated with sleep disruption, and activation of both systems has been tied to insulin resistance and eventually T2DM.<sup>13 25–27</sup> Insomnia has also been shown to accelerate loss of  $\beta$ -cell function and increase  $\beta$ -cell apoptosis with increased loss of  $\beta$ -cell mass in laboratory models.<sup>11</sup> Finally, the fatigue associated with sleep loss may contribute to decreased amount and intensity of physical activity, which may contribute to the development of T2DM.<sup>15</sup>

This study has several strengths, including the large sample size with long follow-up and the use of multiple data sources (ICD-9 and ICD-10 codes, laboratory testing, and medication dispensing) to diagnose exposure and outcome data. However, the study is limited by the shortcomings of observational research. For example, measured insomnia may be the consequence of other unmeasured and thus uncontrolled factors (eg, work or personal stress, chronic pain). Further, all classifications of T2DM and insomnia were based solely on diagnoses, lab results, or medication dispenses recorded on the EMR, eroding our ability to discern the relationship between the two conditions. In particular, the prevalence of insomnia is likely underestimated in this cohort because sleep disorders are often underdiagnosed and/or insomnia symptoms are attributed to other conditions.<sup>28</sup>

T2DM is a major contributor to poor health and early death,<sup>29</sup> and additional strategies to prevent diabetes are greatly needed. Our research suggests that behavioral treatment of insomnia deserves further study as a way to decrease T2DM risk. If sleep treatment can be added to the armamentarium for preventing the devastating disease of T2DM, the health of millions of people could be improved.

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