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Sleep Characteristics are Associated with Risk of Treated Diabetes Among Postmenopausal Women

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Author Contributions

ESL contributed to the study conception, design, and interpretation of results, and developed the first draft of the manuscript. SZ and HH contributed to the study conception and design, researched and analyzed the data, contributed to interpretation of results, and reviewed/edited the manuscript. The remaining authors contributed to the study conception and design and reviewed/edited the manuscript. The final draft for submission was approved by all authors. ESL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

The full list of WHI investigators is available online at Https://www.whi.org/doc/WHI-Investigator-Short-List.pdf

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Abstract

Objective: Determine whether sleep characteristics are associated with incidence of treated diabetes in postmenopausal individuals.

Methods: Postmenopausal participants ages 50–79 reported sleep duration, sleep-disordered breathing, and/or insomnia at baseline and again in a subsample 3 years later. The primary outcome was self-reported new diagnosis of diabetes treated with oral drugs or insulin at any time after baseline. Multivariable Cox proportional hazards models were used.

Results: In 135,964 participants followed for 18.1 (±6.3) years, there was a non-linear association between sleep duration and risk of treated diabetes. Participants sleeping ≤5 hours at baseline had a 21% increased risk of diabetes compared to those sleeping 7 hours (adjusted hazard ratio [aHR] 1.21; 95% confidence interval [CI] 1.00,1.47). Those who slept for ≥9 hours had a nonsignificant 6% increased risk of diabetes compared to those sleeping 7 hours (aHR 1.06; 0.97, 1.16). Participants whose sleep duration had declined at 3 years had a 9% [aHR 1.09; 1.02, 1.16] higher risk of diabetes than participants with unchanged sleep duration. Participants who reported increased sleep duration at 3 years had a similar risk of diabetes [HR 1.01; 0.95, 1.08] to those with no sleep duration change. Participants at high risk of sleep-disordered breathing at baseline had a 31% higher risk of diabetes than those without [aHR 1.31; 1.26, 1.37]. No association was found between self-reported insomnia score and diabetes risk.

Conclusions: Sleep-disordered breathing and short or long sleep duration were associated with higher diabetes risk in a postmenopausal population.

Keywords

Diabetes; insomnia; sleep duration; menopausal women; sleep-disordered breathing

Introduction

Type 2 diabetes mellitus has severe effects on public health. Over 30 million US adults have diabetes, and 1.5 million new cases are diagnosed each year. While physical activity, weight loss, and drug therapy with metformin can prevent diabetes (1, 2), physical activity and weight loss are difficult to initiate and maintain (3), and metformin is less effective than lifestyle (1). There may be other modifiable risk factors for diabetes, including sleep duration, sleep quality, and sleep-disordered breathing (4, 5).

Menopause is associated both with increased risk of type 2 diabetes (6) and with sleep changes, which may be related to menopausal symptoms such as night sweats and mood swings. To examine whether sleep factors account for changes in type 2 diabetes risk in postmenopausal people, we examined the prospective impact of sleep factors on diabetes in the Women's Health Initiative (WHI) Study cohort. Because of its large sample size, long follow-up period, data on menopausal symptoms that can impact sleep, and prospective ascertainment of diabetes, WHI provides an ideal cohort to test the hypotheses that short sleep duration, sleep-disordered breathing, and self-reported insomnia are associated with increased risk of diabetes in postmenopausal people.

Methods

The WHI consisted of an observational study (OS) and randomized clinical trials (CT) evaluating how hormone therapy, diet modification, and calcium and vitamin D supplementation impacted health in postmenopausal women. The WHI enrolled 68,132 female participants ages 50 to 79 between 1993 and 1998 into at least 1 clinical trial (mean [±SD] follow-up 18.1 [±6.3] years) and 93,676 additional participants into the OS (7, 8). In 2005, over 115,400 participants provided written informed consent to ongoing follow-up. Institutional Review Board approval was obtained. Full details of data collection are available elsewhere (7). The present analyses use data from all CT and OS participants except those who reported a history of diabetes at baseline and those in the intervention arm of the Diet Modification Trial.

At baseline, all participants completed questionnaires regarding demographics; medical, family, and smoking history; age at menopause; and menopausal symptoms. Self-reported race categories were American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or more than one race. Ethnicity was reported as Hispanic or not Hispanic. Physical activity-related energy expenditure (MET-h/week) was calculated from the summed product of frequency, duration, and intensity of leisure activities. Height, weight, and waist circumference were measured by trained clinic staff; height and weight were used to determine body mass index (BMI, wt/ht^2). To determine diabetes at baseline, participants were asked, "*Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?*" At baseline, post-trial, and some follow-up visits, participants were asked to bring all current medications to be inventoried by clinic interviewers; after 2005, participants completed medication inventory by mail; drug codes were assigned using Medi-Span software (First databank, Inc., San Bruno, CA).

Information on sleep was collected from all participants at baseline (from 1993–1998) and again at Year 3 for a subsample of CT participants (N=46,190) and all OS participants (N=89,774). Sleep duration was measured with a single question (Table 1). Seven hours was considered the reference duration, with 6 hours or less considered "short duration" and 8 hours or more "long duration."

Risk of sleep-disordered breathing was assessed with questions about frequency of snoring and falling asleep during quiet activities over the past 4 weeks (Table 1). Responses, along with blood pressure and BMI, were used to calculate a sleep-disordered breathing risk score (9, 10), which was adapted from the Berlin Questionnaire (11, 12). Scores ≥2 were defined as high risk.

Perceived insomnia was assessed with validated the Women's Health Initiative Insomnia Rating Scale (WHIIRS; Table 1) (13–15). A higher score indicates more insomnia symptoms and poorer sleep quality over the past four weeks; scores 9 or higher were considered insomnia (14).

The primary outcome for this study was incident self-report of treated diabetes. Participants were asked annually through questionnaires, "*Since the date given on this form, has a doctor*

prescribed any of the following pills or treatments?" Choices included "*pills for diabetes*" and "*insulin shots for diabetes.*" Diagnosis was further identified through the medication inventory. Individuals were considered an incident case of treated diabetes if they reported receiving insulin shots, oral diabetes medication, or both for the first time during the follow-up period. This definition was validated, with good concordance between self-report of treated diabetes, the medication inventory, and fasting glucose values (16, 17).

Participants were followed from randomization (CT) or enrollment (OS) until they first reported diabetes treatment. Participants who did not develop treated diabetes were censored at last study follow-up (March 1, 2019) or death.

Statistical analysis

Means and standard deviations (SD) were calculated for baseline continuous variables stratified by insomnia and sleep duration. For baseline categorical variables, frequency distributions were examined. Given the large population, absolute standardized differences (18), in units of SD, are presented for all characteristics as they can be interpreted using Cohen's guidelines independent of sample size (19).

We fit multivariable time-varying Cox proportional hazards regression models to obtain unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) comparing the risk of diabetes by insomnia (Yes vs No), sleep-disordered breathing (Yes vs No), and sleep duration categories (short and long duration categories vs 7 hours) in separate models. We also examined associations between diabetes risk and sleep-disordered breathing and insomnia score as continuous measures. We did not examine sleep duration as a continuous variable, given the nonlinear association observed in our categorical analysis. Confounders included in the models were identified *a priori* based on known associations with both sleep and diabetes risk: age, race, ethnicity, physical activity level, alcohol use, smoking, education, history of hypertension, age at menopause, randomization to calcium and vitamin D supplementation arm in a WHI trial, OS or CT enrollment, hot flashes and night sweats at baseline, and family history of diabetes (20–23). Physical activity level, alcohol use, and smoking were treated as time-varying covariates. BMI was included in models assessing sleep duration and insomnia but not sleep-disordered breathing because the Berlin score is calculated from BMI. In a secondary analysis, we tested whether BMI, race, or ethnicity were effect modifiers of each association as they are associated with both sleep characteristics and diabetes risk (24, 25). Due to limited racial diversity in the cohort, our sample for the secondary analysis by race was restricted to Black, White, and Asian participants.

We conducted several sensitivity analyses. First, we repeated the primary analyses including those in Diet Modification Trial intervention arm and examined if there was an interaction between arm assignment for the trial and later sleep outcomes. Second, we limited our cohort to only those in the observational study. Third, we excluded women diagnosed with diabetes within 2 years of baseline to eliminate diabetes as a cause of sleep difficulties. Finally, in the subset of individuals who had sleep measures available at both baseline and 3 years, we compared those who had a change in their sleep duration or quality to those who did not.

Our analyses assumed data were missing at random. We used multiple imputation (using predictive mean matching in the 'mice' R package) to account for missing covariates by creating five imputed datasets (26). All analyses were performed using R statistical programming software, version 4.0.3 (27). All tests were two-sided and conducted at the alpha=0.05 level of significance. We did not adjust for multiple comparisons. Rather, we specified our primary objectives in this secondary analysis and all other analyses are conducted to provide additional context.

Results

Of the 161,808 participants, 6,303 were excluded because of a history of diabetes at baseline and 19,541 were excluded due to participation in the intervention arm of the Diet Modification Trial. This left an analytic cohort of 135,964 participants. Data from 82,210 individuals who provided information on sleep at year 3 and had not developed diabetes at that time were used to fit models examining changes in sleep quality. Participants were followed for a mean of 18.1 years (SD ±6.3).

Baseline characteristics by insomnia category and sleep duration are shown in Table 2 and Table S1, respectively. Participants with insomnia (WHIIRS scores ≥9) were more likely than those without to suffer from hot flashes, night sweats, and depressive symptoms, and to report sleeping fewer than 7 hours. Similarly, those who slept fewer than 7 hours were more likely to have insomnia and sleep-disordered breathing and have hot flashes, night sweats, and depressive symptoms than those who slept 7 hours or more. No other substantial differences in baseline characteristics were observed. Over 2,462,062 person-years of follow-up, 13,761 individuals reported new diabetes diagnoses (unadjusted incidence of diabetes of 6.3/1,000 person-years).

In Cox proportional hazards models, we found a non-linear association between diabetes risk and sleep duration ($p < 0.01$; Table 3). In unadjusted models, participants who slept for 5 hours or less per night were 50% more likely, and those who slept for 6 hours were 20% more likely, to develop diabetes than those who slept for 7 hours (HR 1.50; 95% CI 1.38,1.62 and HR 1.20; 95% CI 1.14,1.26, respectively). After adjustment, participants sleeping 5 hours or less had a 21% increased risk of diabetes (HR 1.21; 95% CI 1.00, 1.47) and those sleeping 6 hours had a 5% increased risk (1.05; 95% CI 0.99, 1.11).

In unadjusted Cox proportional hazards models, individuals with Berlin scores suggestive of sleep-disordered breathing were 43% more likely to develop diabetes than those with low-risk Berlin scores (HR 1.43; 95% CI 1.38,1.49; $p < 0.01$; Table 2). The association was attenuated after adjustment but still statistically significant (HR 1.31; 95% CI 1.26,1.37; $p < 0.01$). When we examined Berlin score as a continuous rather than categorical variable, every one-point increase in Berlin score was associated with a 40% increase in risk of diabetes in unadjusted analysis (HR 1.4; 95% CI 1.37,1.43) and a 32% increase in risk in adjusted analysis (HR 1.32; 95% CI 1.29,1.35, $p < 0.01$; Figure 1).

No significant association was observed between insomnia (WHIIRS score) and diabetes risk in unadjusted or adjusted analyses (p = 0.47; Table 2), nor was there a significant association when the WHIIRS score was examined as a continuous variable (Figure 1).

There was no significant effect modification of the association between WHIIRS score as a continuous variable and diabetes risk by BMI category or race/ethnicity. However, we did find effect modification by race and ethnicity on the association between Berlin score (suggestive of possible sleep-disordered breathing) as a continuous variable and diabetes risk (p = 0.02): participants who self-identified as White had a 38% increase in risk of developing diabetes with each one-unit increase on the Berlin score (HR 1.38; 95% CI 1.34, 1.42); while those who self-identified as Black had an 18% increase in risk per unit of the Berlin score (HR 1.18; 95% CI 1.09, 1.27); and those identified as Asian had a 28% increase per unit (HR 1.28; 95% CI 1.10, 1.47; Figure 1). Among participants who self-identified as Hispanic, there was 26% increased risk of diabetes per unit increase in Berlin score (HR 0.26; 95% CI 1.13, 1.40).

Compared to those who remained in the same sleep duration category, individuals whose sleep duration declined at 3 years post-baseline had a 16% increased risk of diabetes in the unadjusted analysis and 9% increased risk in the adjusted analysis (HR 1.16; 95% CI 1.09, 1.23 and HR 1.09; 95% CI 1.02, 1.16, p = 0.01, respectively; Table 3). No association was found between change in insomnia category and diabetes incidence in adjusted analyses.

In additional sensitivity analyses, findings did not change when we included individuals in intervention arm of the Diet Modification Trial, and there was no effect modification between arm of this trial and any of the sleep variables. Risk estimates did not change substantially when only individuals in the observational cohort were examined, or when individuals who were diagnosed with diabetes within two years after baseline were excluded.

Discussion

We found a non-linear association between sleep duration and risk of diabetes in postmenopausal participants, with sleep durations under 7 hours associated with increased risk of treated diabetes. High likelihood of sleep-disordered breathing was also a significant risk factor for diabetes in this population, but self-reported insomnia was not.

The non-linear association between sleep duration and diabetes risk, which has been previously reported (24, 28–30), may be due to unmeasured confounders such as poor sleep quality, as well as comorbidities associated with increased risk of diabetes, such as depression (31). Non-linear associations with sleep have also been seen for other cardiovascular risk factors such as blood pressure and alcohol use (32, 33).

While past reports have found that “catch-up” sleep or return to normal sleep improved insulin resistance and hyperglycemia, we did not observe that increased sleep duration from baseline to 3 years resulted in decreased risk of diabetes. This may be due to the short time windows (4 weeks) over which we assessed sleep duration at each timepoint.

This study also confirms an association between sleep-disordered breathing and development of diabetes, increasing the body of evidence on this topic to include postmenopausal people. Our study, which used a short questionnaire to measure sleep-disordered breathing, also shows that this screening is sufficient ot identify diabetes risk, without a formal sleep apnea diagnosis.

We had hypothesized that subjectively reported insomnia would be associated with increased diabetes risk (34, 35), but we did not confirm this finding. To evaluate insomnia over a longer time frame, we compared those with insomnia at both baseline and at 3 years' follow-up to those without insomnia at either timepoint. However, there was still no association between insomnia and diabetes risk in the adjusted analysis.

To our knowledge, this is the first prospective study to examine the association between sleep factors and diabetes risk in postmenopausal people. Menopause itself is associated with sleep disruption, particularly among those with symptoms such as night sweats and mood swings. Our findings in this population are consistent with prior studies conducted in men and women of differing ages that show associations between sleep factors and diabetes risk (4, 28) and with experimental studies in the general population showing that inducing inadequate sleep in healthy volunteers resulted in insulin resistance (36–40). The consistency of the association between sleep duration and sleep disordered breathing and diabetes risk across different populations and experimental methods demonstrates the robustness of the findings.

We found effect modification by race and ethnicity on the association between between sleep disordered breathing and diabetes risk. Compared to White participants, the risk was somewhat attenuated among Black and Asian participants; risk was also slightly lower in Hispanic compared to NonHispanic participants. However, the WHI cohort did not have sufficient diversity to fully examine the impact of race and ethnicity. Previous work in more diverse samples (which included postmenopausal people) found stronger associations between sleep duration and diabetes risks among those identified as Filipino, Japanese American, or Native Hawaiian compared to other racial//ethnic groups (24, 41). No study do date has examined all racial groups or fully examined the role of social determinants of health in these associations (42, 43). A large, diverse cohort with data on social determinants of health is needed to understand how race and ethnicity may moderate impacts of sleep on diabetes risk.

Short sleep duration and sleep-disordered breathing could negatively affect glucose metabolism via effects on diet and exercise. Insufficient sleep can increase appetite and lead to unhealthy food choices (44, 45), as well as decreased physical activity (46). Metabolic mechanisms could mediate the associations between sleep and hyperglycemia**.** Experimental sleep deprivation is associated with increases in inflammatory markers (47) and sympathetic nervous system activation (37), which may contribute to the development of insulin resistance and diabetes (48, 49). Other posited biological mechanisms include altered levels of peptides mediating energy homeostasis and appetite (48, 49); alterations in the hypothalamic-pituitary axis (24, 37, 39) affecting glucose regulation and central fat

distribution; and deficits in pancreatic β-cell function and insulin signaling in adipocytes (40).

Among U.S. adults, the estimated prevalence of diabetes ranges from 5.8% to 12.9% (50). Therefore, the increased risk associated with short sleep duration could have a significant clinical impact. Indeed, the absolute risk increase for individuals with short sleep (<=5 hours) was 5.6 diagnostic events per 1000 person-years.

Our study had several strengths. We prospectively followed participants for diabetes treatment. We had a sufficient sample size to detect clinically significant associations, and we used multiple imputation to avoid potential bias due to missing data.

The study also had several limitations. Data on sleep duration and insomnia were only collected at one timepoint for primary analyses, and only reflected sleep in the previous four weeks. Sleep duration and quality can fluctuate due to work schedule, commitments, and stressors. Even sensitivity analysis only reflected data from two 4-week periods. Also, self reported sleep duration can overestimate or underestimate sleep duration (51–53).

Because of the WHI study-design, we used self-reported treated diabetes rather than diabetes diagnosis. However, self-reports of treated diabetes in WHI have previously been shown to be sufficiently accurate to allow use in epidemiologic studies (16). We used the date an individual reported initiating diabetes treatment instead of the date of diagnosis, and did not examine diabetes treated only with lifestyle change. We did not adjust for multiple comparisons. We also did not evaluate other factors that could be associated with diabetes risk, including polycystic ovarian syndrome and infertility, nor did we not collect data on what contributed to short and long sleep duration (some lifestyle, environmental, psychosocial, and medical factors may not be modifiable). Finally, the WHI dataset did not capture data on the reason for medication use; therefore, we were unable to adjust analyses for use of sleep medications.

Conclusions

In postmenopausal people, who are at increased risk of metabolic dysfunction, short sleep duration and sleep disordered breathing were associated with increased diabetes risk. For individuals whose sleep problems are modifiable, addressing sleep factors may be an easier way to reduce diabetes risk than changing diet and activity levels or starting a medication. Further, initiating conversations about sleep during the menopause transition could identify sleep-disordered breathing, vasomotor symptoms, and depression, which could then be addressed as part of a diabetes prevention strategy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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LP declares that there is no duality of interest associated with this manuscript. With regard to potential conflicts of interest, LP has served on Scientific Advisory Boards for Janssen, and has or had research support from Merck, Pfizer, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, Abbvie, Vascular Pharmaceuticals, Janssen, Glaxo SmithKline, and the Cystic Fibrosis Foundation. LP is also a cofounder and Officer and Board member and stockholder for a company, Diasyst, Inc., which markets software aimed to help improve diabetes management.

LH is a Board member of the National Sleep Foundation and received an honorarium from the NSF when she served as the Editor-in-Chief of their journal Sleep Health. She is also a member of the Idorsia Alliance for Sleep.

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Clinical Significance:

- Sleep duration and sleep-disordered breathing were prospectively associated with risk of diabetes in postmenopausal people
- Given the high prevalence of diabetes in the US population (estimated to be 6 to 13%), the increased risk associated with short sleep duration could have a significant clinical impact
- These findings have important public health implications for postmenopausal women given that menopause is associated with both increased risk of diabetes and with sleep changes

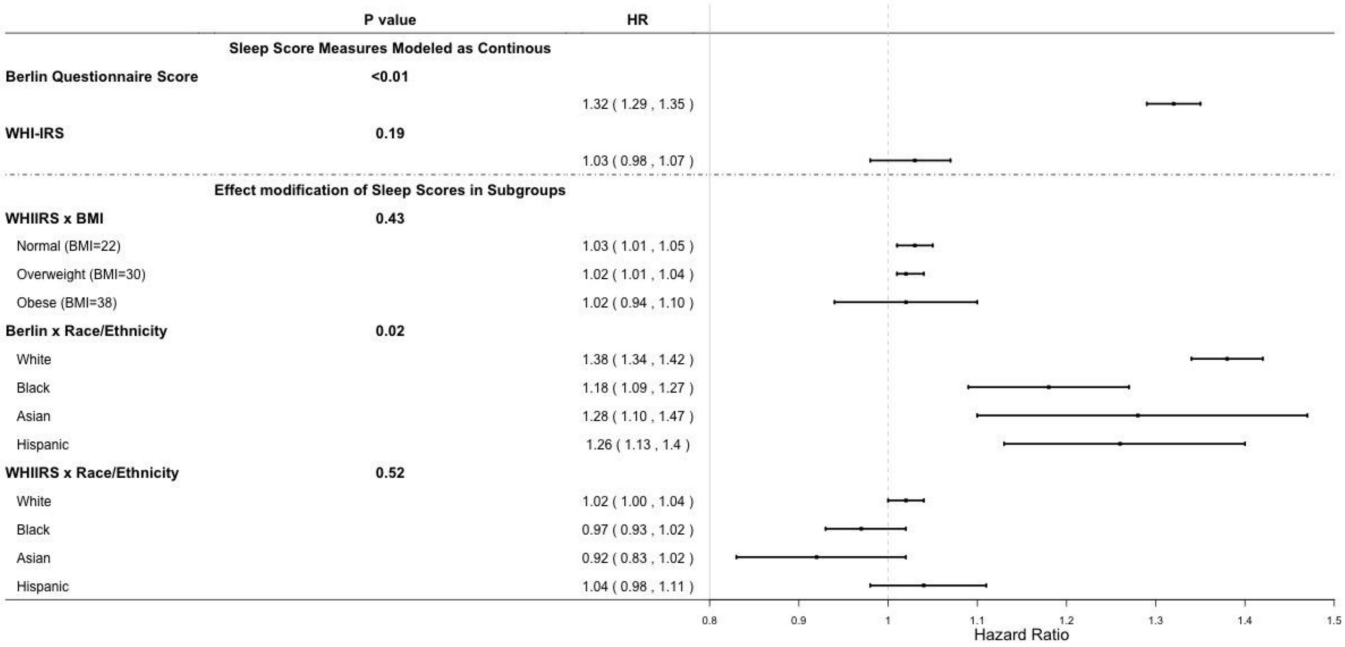

Figure 1: Associations Between Continuous Sleep Scores and Diabetes Risk

Note: The estimates above the dotted line show the overall association while the estimates below the line show the estimated associations within subgroups. BMI was treated as continuous in our model. We selected BMIs of 22, 30, and 38 to represent the normal, overweight, and obese subgroups.

Table 1:

Description of Sleep Questionnaires

Questionnaire	Measure	Questions	Responses (Scoring)	Scoring
Sleep duration	Duration of sleep over the past 4 weeks	About how many hours of sleep did you get on a typical night during the past 4 weeks?	<=5 hours 6 hours 7 hours 8 hours >=9 hours	Reference: 7 hours Short duration: <=6 hours Long duration: >=8 hours
Berlin (modified)	Sleep disordered Breathing over the past 4 weeks	Over the past 4 weeks, did you snore? Over the past 4 weeks, did you fall asleep during quiet activities?	No, not in the past 4 weeks (0) Yes, less than once a week (0) Yes, 1 or 2 times a week (0) Yes, 3 or 4 times a week (1) Yes, 5 or more times a week (1) Do not know (0) Hypertension (self-reported or measured at study visit) and/or BMI >30 kg/m^2 (1)	Summed scores of the 3 items with range of total score from 0 to 3 High risk: Total score >=2 Low risk: Total score <2
WHIRS	Insomnia over the past 4 weeks	Did you have trouble falling asleep? Did you wake up several times at night? Did you wake up earlier than you planned to? Did you have trouble getting back to sleep after you woke up too early? Overall, was your typical night's sleep during the past 4 weeks: very sound or restful, sound or restful, average quality, restless, or very restless?	No, not in the past 4 weeks (0) Yes, less than once a week (1) Yes, 1 or 2 times a week (2) Yes, 3 or 4 times a week (3) Yes, 5 or more times a week (4)	Summed score of the 5 items with range of total score from 0 to 20 Insomnia: Total score of >=9

Table 2:

Baseline Characteristics by Insomnia

			Insomnia*			
	Level	**Overall**	**No**	**Yes**	**Missing**	**ASD†**
N		135,964	92,018	41,095	2,851	
Hours of Sleep (%)	<=5 hours	11112 (8.2%)	3291 (3.6%)	7555 (18.4%)	266 (9.3%)	0.78
	6 hours	37016 (27.2%)	20902 (22.7%)	15433 (37.6%)	681 (23.9%)	
	7 hours	50812 (37.4%)	37761 (41.0%)	12238 (29.8%)	813 (28.5%)	
	8 hours	30381 (22.3%)	25085 (27.3%)	4880 (11.9%)	416 (14.6%)	
	>=9 hours	5949 (4.4%)	4914 (5.3%)	949 (2.3%)	86 (3.0%)	
	Missing	694 (0.5%)	65 (0.1%)	40 (0.1%)	589 (20.7%)	
Berlin Score (%)	<2	100870 (75.7%)	70272 (77.5%)	29047 (71.7%)	1551 (74.9%)	0.58
	>=2	32344 (24.3%)	20346 (22.5%)	11478 (28.3%)	520 (25.1%)	
	Missing	2750 (2.0%)	1400 (1.5%)	570 (1.4%)	780 (27.4%)	
Age (Mean (±SD))		63.32 (7.28)	63.16 (7.24)	63.60 (7.34)	64.59 (7.50)	0.13
Asian or Pacific Islander (%)	No	132134 (97.2%)	89145 (96.9%)	40198 (97.8%)	2791 (97.9%)	0.04
	Yes	3830 (2.8%)	2873 (3.1%)	897 (2.2%)	60 (2.1%)	
White (%)	No	17703 (13.0%)	12144 (13.2%)	4846 (11.8%)	713 (25.0%)	0.23
	Yes	118261 (87.0%)	79874 (86.8%)	36249 (88.2%)	2138 (75.0%)	
Black (%)	No	124874 (91.8%)	84425 (91.7%)	38063 (92.6%)	2386 (83.7%)	0.19
	Yes	11090 (8.2%)	7593 (8.3%)	3032 (7.4%)	465 (16.3%)	
Ethnicity (%)	Not Hispanic/Latino	128851 (94.8%)	87454 (95.0%)	38912 (94.7%)	2485 (87.2%)	0.19
	Hispanic/Latino	5999 (4.4%)	3805 (4.1%)	1870 (4.6%)	324 (11.4%)	
	Missing	1114 (0.8%)	759 (0.8%)	313 (0.8%)	42 (1.5%)	
BMI (%)	Normal or Underweight	50479 (37.1%)	34953 (38.0%)	14585 (35.5%)	941 (33.0%)	0.09
	Overweight	46985 (34.6%)	31873 (34.6%)	14131 (34.4%)	981 (34.4%)	
	Obesity	37207 (27.4%)	24320 (26.4%)	11988 (29.2%)	899 (31.5%)	
	Missing	1293 (1.0%)	872 (0.9%)	391 (1.0%)	30 (1.1%)	
Total energy expended from recreational physical activity (Mean (±SD))		12.92 (±14.01)	13.37 (±14.23)	11.94 (±13.42)	12.38 (±14.39)	0.07
Alcohol use (%)	<=1 drink/week	86885 (63.9%)	58505 (63.6%)	26397 (64.2%)	1983 (69.6%)	0.10
	1–3 drinks/week	16089 (11.8%)	11028 (12.0%)	4752 (11.6%)	309 (10.8%)	
	>3 drinks/week	32729 (24.1%)	22316 (24.3%)	9867 (24.0%)	546 (19.2%)	
	Missing	261 (0.2%)	169 (0.2%)	79 (0.2%)	13 (0.5%)	
Smoking (%)	Past Smoker	68301 (50.2%)	46665 (50.7%)	20223 (49.2%)	1413 (49.6%)	0.24
	Current Smoker	56455 (41.5%)	37877 (41.2%)	17558 (42.7%)	1020 (35.8%)	
	Never Smoked	9427 (6.9%)	6399 (7.0%)	2842 (6.9%)	186 (6.5%)	
	Missing	1781 (1.3%)	1077 (1.2%)	472 (1.1%)	232 (8.1%)	
Education (%)	Less than High School	7012 (5.2%)	4027 (4.4%)	2647 (6.4%)	338 (11.9%)	0.22

			Insomnia*			
	Level	**Overall**	**No**	**Yes**	**Missing**	**ASD†**
	High School	22889 (16.8%)	14441 (15.7%)	7970 (19.4%)	478 (16.8%)	
	College or more	105016 (77.2%)	72873 (79.2%)	30156 (73.4%)	1987 (69.7%)	
	Missing	1047 (0.8%)	677 (0.7%)	322 (0.8%)	48 (1.7%)	
Income	<$35, 000	51253 (37.7%)	32733 (35.6%)	17231 (41.9%)	1289 (44.0%)	0.21
	>=$35,000	75429 (55.5%)	53151 (57.8%)	21043 (51.2%)	1235 (42.1%)	
	Missing	9282 (6.8%)	6134 (6.7%)	2821 (6.9%)	327 (11.2%)	
Marital Status	Married/living as married	84494 (62.1%)	57615 (62.6%)	25363 (61.7%)	1516 (51.7%)	0.14
	Not married/iving as married	50829 (37.4%)	34012 (37.0%)	15518 (37.8%)	1379 (47.0%)	
	Missing	641 (0.5%)	391 (0.4%)	214 (0.5%)	36 (1.2%)	
History of hypertension (%)	Never hypertensive	87769 (64.6%)	60853 (66.1%)	25290 (61.5%)	1626 (57.0%)	0.19
	Untreated hypertensive	10402 (7.7%)	6666 (7.2%)	3520 (8.6%)	216 (7.6%)	
	Treated hypertensive	31599 (23.2%)	20393 (22.2%)	10474 (25.5%)	732 (25.7%)	
	Missing	6194 (4.6%)	4106 (4.5%)	1811 (4.4%)	277 (9.7%)	
Postmenopausal Hormone Therapy Use (%)	Ever	95125 (71.4%)	63820 (70.8%)	29501 (73.1%)	1804 (64.9%)	0.12
	Never	38110 (28.6%)	26277 (29.2%)	10858 (26.9%)	975 (35.1%)	
Age at menopause (%)	<45	28727 (21.1%)	18534 (20.1%)	9592 (23.3%)	601 (21.1%)	0.19
	45–55	89412 (65.8%)	61318 (66.6%)	26417 (64.3%)	1677 (58.8%)	
	>55	10271 (7.6%)	7043 (7.7%)	2993 (7.3%)	235 (8.2%)	
	Missing	7554 (5.6%)	5123 (5.6%)	2093 (5.1%)	338 (11.9%)	
Randomization to CaD arm (%)	No	123152 (90.6%)	83190 (90.4%)	37367 (90.9%)	2595 (91.0%)	0.01
	Yes	12812 (9.4%)	8828 (9.6%)	3728 (9.1%)	256 (9.0%)	
CT Participant (%)	No	89774 (66.0%)	60738 (66.0%)	27142 (66.0%)	1894 (66.4%)	0.01
	Yes	46190 (34.0%)	31280 (34.0%)	13953 (34.0%)	957 (33.6%)	
OS Participant (%)	No	46190 (34.0%)	31280 (34.0%)	13953 (34.0%)	957 (33.6%)	0.01
	Yes	89774 (66.0%)	60738 (66.0%)	27142 (66.0%)	1894 (66.4%)	
Hot Flash (%)	No	102495 (75.4%)	72333 (78.6%)	28453 (69.2%)	1709 (59.9%)	0.53
	Yes	32478 (23.9%)	19409 (21.1%)	12493 (30.4%)	576 (20.2%)	
	Missing	991 (0.7%)	276 (0.3%)	149 (0.4%)	566 (19.9%)	
Night Sweat (%)	No	100753 (74.1%)	72220 (78.5%)	26832 (65.3%)	1701 (59.7%)	0.56
	Yes	33963 (25.0%)	19359 (21.0%)	14020 (34.1%)	584 (20.5%)	
	Missing	1248 (0.9%)	439 (0.5%)	243 (0.6%)	566 (19.9%)	
Depression (%)	No	117956 (89.2%)	84356 (93.6%)	31790 (79.3%)	1810 (87.0%)	0.66
	Yes	14327 (10.8%)	5764 (6.4%)	8292 (20.7%)	271 (13.0%)	
Family history of diabetes (%)	No	87318 (64.2%)	60123 (65.3%)	25588 (62.3%)	1607 (56.4%)	0.21
	Yes	41717 (30.7%)	27625 (30.0%)	13214 (32.2%)	878 (30.8%)	

			Insomnia*			
	Level	**Overall**	**No**	**Yes**	**Missing**	**ASD†**
	Missing	6929 (5.1%)	4270 (4.6%)	2293 (5.6%)	366 (12.8%)	

ASD: absolute standardized difference; BMI: body mass index; CaD: calcium and vitamin D; CT: clinical trial; OS: observational study; SD: standard deviation

*According to Women's Health Initiative Insomnia Rating Scale (WHIIRS) Category (Total score >=9 considered insomnia)

†A larger ASD corresponds to a larger difference between the groups (< 0.2 = trivial difference; 0.2 = small difference; 0.5 = medium difference; 0.8 = large difference).

Table 3:

Associations Between High vs Low Risk Sleep Categories and Diabetes Risk

Variables	Levels	N (%) at baseline	Unadjusted HR (95% CI)	Unadjusted p-value	Adjusted HR (95% CI)	Adjusted p-value
Sleep Duration	<=5 Hrs	11112 (8.2%)	1.50 (1.38, 1.62)	<0.01	1.21 (1.00, 1.47)	<0.01
	6 Hrs	37016 (27.4%)	1.20 (1.14, 1.26)		1.05 (0.99, 1.11)	
	7 Hrs	50812 (37.6%)	Reference		Reference	
	8 Hrs	30381 (22.5%)	1.03 (0.97, 1.08)		1.02 (0.96, 1.10)	
	>=9 Hrs	5949 (4.4%)	1.16 (0.94, 1.43)		1.06 (0.97, 1.16)	
Sleep Disordered Breathing Risk (Berlin Score)	<2	100870 (75.7%)	Reference	<0.01	Reference	<0.01
	≥2	32344 (24.3%)	1.43 (1.38, 1.49)		1.31 (1.26, 1.37)	
Insomnia (WHIIRS)	<9	92018 (69.1%)	Reference	0.13	Reference	0.47
	≥9	41095 (30.9%)	1.1 (0.96, 1.27)		1.09 (0.82, 1.45)	

WHIIRS: Women's Health Initiative Insomnia Rating Scale; HRs: hours; HR: Hazard Ratio; CI: Confidence Interval

*Model is adjusted for age, race, ethnicity, BMI (except for Berlin Score models), physical activity level, alcohol use, tobacco exposure, education, income, marital status, age at menopause, randomization to CaD arm, OS or CT enrollment, presence of hot flashes and night sweats at baseline, family history of diabetes

Table 4:

Associations Between Three-Year Change in Sleep Risk Categories and Diabetes Risk

Sleep Variable	Levels	Unadjusted HR (95% CI)	Unadjusted p-value	Adjusted HR* (95% CI)	Adjusted p-value
Typical Sleep Duration					
	Shorter Duration vs Same	1.16 (1.09, 1.23)	<0.01	1.09 (1.02, 1.16)	0.01
	Longer Duration vs Same	1.08 (1.01, 1.15)	0.02	1.01 (0.95, 1.08)	0.66

HR: Hazard Ratio; CI: Confidence Interval

* Model is adjusted for age, race, ethnicity, BMI (except for Berlin Score models), physical activity level, alcohol use, tobacco exposure, education, income, marital status, age at menopause, randomization to CaD arm, OS or CT enrollment, presence of hot flashes and night sweats at baseline, family history of diabetes