SLEEPJ, 2021, 1–9

doi: 10.1093/sleep/zsaa150
Advance Access Publication Date: 24 September 2020
Original Article

ORIGINAL ARTICLE

Insomnia with objective short sleep duration is associated with cognitive impairment: a first look at cardiometabolic contributors to brain health

Julio Fernandez-Mendoza[1,*], Fan He[2], Kristina Puzino[1], Gregory Amatrudo[1], Susan Calhoun[1], Duanping Liao[2], Alexandros N. Vgontzas[1] and Edward Bixler[1]

[1]Sleep Research and Treatment Center, Department of Psychiatry & Behavioral Health, Penn State Health Milton S. Hershey Medical Center, Penn State University College of Medicine, Hershey, PA and [2]Department of Public Health Sciences, Penn State University College of Medicine, Hershey, PA

*Corresponding author. Julio Fernandez-Mendoza, Sleep Research & Treatment Center, Department of Psychiatry & Behavioral Health, Penn State Health Milton S. Hershey Medical Center, Penn State University College of Medicine, 500 University Dr. H073, Hershey, PA 17603. Email: jfmendoza@psu.edu.

Abstract

Study Objectives: Insomnia with objective short sleep duration has been previously associated with adverse cardiometabolic health outcomes as well as poorer cognitive performance in otherwise noncognitively impaired adults. However, studies demonstrating an increased prevalence of cognitive impairment (CI) in this insomnia phenotype are lacking.

Methods: We analyzed data from Penn State Adult Cohort (N = 1,524; 48.9 ± 13.4 years; 53.4% women). Self-reported sleep difficulty was defined as normal sleep (n = 899), poor sleep (n = 453), and chronic insomnia (n = 172). Objective short sleep duration was defined as less than 6-h of sleep, based on in-lab, 8-h polysomnography. CI (n = 155) and possible vascular cognitive impairment (pVCI, n = 122) were ascertained using a comprehensive neuropsychological battery. Analyses adjusted for age, sex, race, education, body mass index, apnea/hypopnea index, smoking, alcohol, psychoactive medication, and mental and physical health problems.

Results: Participants who reported poor sleep or chronic insomnia and slept objectively less than 6 hours were associated with a 2-fold increased odds of CI (OR = 2.06, 95% confidence limits [CL] = 1.15–3.66 and OR = 2.18, 95% CL = 1.07–4.47, respectively) and of pVCI (OR = 1.94, 95% CL = 1.01–3.75 and OR = 2.33, 95% CL = 1.07–5.06, respectively). Participants who reported poor sleep or chronic insomnia and slept objectively more than 6 hours were not associated with increased odds of either CI (OR = 0.72, 95% CL = 0.30–1.76 and OR = 0.75, 95% CL = 0.21–2.71, respectively) or pVCI (OR = 1.08, 95% CL = 0.42–2.74 and OR = 0.76, 95% CL = 0.16–3.57, respectively).

Conclusions: Insomnia with objective short sleep duration is associated with an increased prevalence of CI, particularly as it relates to cardiometabolic health (i.e. pVCI). These data further support that this insomnia phenotype may be a more biologically severe form of the disorder associated with cardiovascular, cerebrovascular, and neurocognitive morbidity.

Statement of Significance

This study shows that insomnia with objective short sleep duration is associated with prevalent cognitive impairment, particularly as it relates to vascular and metabolic contributors to brain health. Our findings provide further evidence that objective sleep measures in insomnia may be a useful marker of the biological severity, phenotyping, and adverse impact of this highly prevalent and chronic disorder. Future studies should examine which subclinical conditions and underlying mechanisms account for the increased risk of vascular cognitive impairment potentially associated with insomnia with objective short sleep duration.

Key words: insomnia; short sleep duration; cognitive impairment; brain health; cardiometabolic health

Submitted: 23 March, 2020; **Revised:** 27 June, 2020

Introduction

Insomnia is the most prevalent sleep disorder and is associated with impaired quality of life, occupational dissatisfaction, and other healthcare-related outcomes [1]. Approximately, 20%–30% of the general population experience insomnia symptoms (i.e. poor sleep), while 8%–15% experience chronic insomnia (i.e., insomnia syndrome) [2–4]. Multiple studies have established that poor sleep and chronic insomnia are highly comorbid with psychiatric disorders and are a risk factor for depression, anxiety, and suicide [5]. Comparatively, fewer studies have established the association between insomnia and other adverse health outcomes, such as cardiometabolic health or cognitive impairment (CI).

It is estimated that about 13% of the population has some form of CI [6, 7], that approximately 50 million people worldwide have dementia, and that the number of people living with dementia will double by 2030 and triple by 2050. Mild CI (MCI) is identified as a noticeable decline in cognitive abilities that does not interfere with daily activities and is considered a precursor of Alzheimer's disease (AD) in up to 30% of cases [8]. While there are no effective strategies for resolving dementia, yet, there is growing evidence to suggest that sleep disturbances make individuals particularly vulnerable to developing MCI and progress into AD and other types of major neurocognitive disorders [9]. However, most cross-sectional and longitudinal population-based studies have examined the association between self-reported sleep with CI, and we still lack large studies that include objective measures of sleep to better ascertain severity and control for important potential confounders, such as sleep apnea.

Increasing evidence also suggests that self-reported cognitive complaints may represent the earliest phases of cognitive decline; however, there continues to be an absence of sensitive biomarkers that can determine who of these individuals is at a particular risk for developing dementia [10]. Individuals who report insomnia typically complain of difficulties with cognitive performance, such as concentration, attention, or memory, in their daily activities at home, at work, or in their social life, and attribute these difficulties to their nighttime sleep disturbances [11]. However, the link between chronic insomnia and objective performance deficits in noncognitively impaired adults has been, at best, modest and has remained elusive [12–14]. Given the accumulating evidence that insomnia with objective short sleep duration may be a more biologically severe phenotype of the disorder [15, 16], including its association with performance deficits [17–19], it is likely that this insomnia phenotype may be at a higher risk for CI. Furthermore, given the evidence on the association between this insomnia phenotype with cardiometabolic conditions such as hypertension, diabetes, cardiovascular, and cerebrovascular disease [20–25], which are known vascular contributors to MCI and increased risk of AD [26], it is also likely that this insomnia phenotype may be at a particularly increased risk for vascular cognitive impairment (VCI) [27].

Based on these previous observations and significant gaps in the neurocognitive literature, we hypothesized that adults who report insomnia symptoms and sleep objectively short in the lab will show a greater likelihood of having CI. Based on the previous cardiometabolic observations, we also hypothesized that the increased prevalence of CI in adults with insomnia symptoms and objective short sleep duration is particularly high for VCI. Thus, the aim of the present study was to test the role of objective short sleep duration, as measured by in-lab polysomnography (PSG), in the association between insomnia and CI, as identified by objective neuropsychological testing, and with possible VCI (pVCI), as identified by the presence of concurrent cardiometabolic conditions.

Methods

Participants

The data presented here were collected as part of the Penn State Adult Cohort (PSAC), a randomly-selected, population-based sample of 1,741 adults, which used a two-phase protocol in order to recruit adult participants of various age groups to estimate the prevalence and risk factors for sleep-disordered breathing in adults [28, 29]. The second phase of the study randomly recruited 741 men and 1,000 women to be studied in the sleep laboratory (response rates of 67.8% and 65.8%, respectively) between 1990 and 1999. Detailed descriptions of the sampling procedure and the cohort composition have been extensively described in previous publications [18, 22, 24, 25, 28–33]. After giving a complete description of the study to the participants, written informed consent was obtained. The study protocol study complied with the Declaration of Helsinki and was approved by the Institutional Review Board at Penn State University College of Medicine.

Sleep laboratory

All participants were evaluated for one night in the sleep laboratory in sound-attenuated and light- and temperature-controlled rooms. During this evaluation, each participant was continuously monitored for 8 hours (fixed-time period) using 16-channel PSG, including electroencephalogram, electrooculogram, and electromyogram. Bedtimes were adjusted to conform to participants' usual bedtimes, and participants were recorded between 22:00 pm–23:00 pm and 06:00 am–07:00 am. The sleep recordings were subsequently scored independently, according to standardized criteria [34]. 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. The presence of obstructive sleep apnea (OSA) was defined as an apnea/hypopnea index (AHI) ≥ 5 events per hour of sleep based on standard criteria [11]. According to the median PSG-measured sleep duration, we categorized the entire study sample into two groups: ≥50th percentile (i.e. ≥6 hours) and <50th percentile (i.e. <6 hours). This cutoff has previously been shown to be associated with adverse health outcomes in adults who report poor sleep or chronic insomnia [20–25, 28–33].

Sleep difficulty

All participants completed a standardized questionnaire to assess the presence of sleep disorders, physical health conditions, mental health problems, and substance use during their in-lab study. Commensurate with our previous studies, the presence of sleep difficulty was established based on three levels of severity [2, 18, 22, 24, 25, 30–33]. First, "chronic insomnia" was defined by a complaint of insomnia ("Do you have insomnia?"), with all participants reporting a duration of at least 1 year. Second, "poor sleep" was defined as a moderate-to-severe complaint,

based on a 4-point Likert scale, of difficulty falling asleep ("Do you have difficulty falling asleep?"), difficulty staying asleep ("Do you have difficulty staying asleep?"), early morning awakening ("Do you wake up in the morning earlier than desired?"), and/or nonrestorative sleep ("Do you still feel groggy and unrefreshed after morning awakening?"). Finally, "normal sleep" was defined by the absence of either of these two categories. These three levels of severity were mutually exclusive; no participant in the poor sleep group reported chronic insomnia and no participant in the normal sleep group reported either chronic insomnia or poor sleep [2, 18, 22, 24, 25, 30–33].

Clinical history

Participants' history of mental health conditions, including depression, suicidal ideation or attempts, loneliness, marital problems, alcohol abuse, or drug abuse, was obtained. A composite binary variable was created based on a positive response to any of these mental health conditions [2, 35, 36]. Also, a history of physical health conditions, including allergies/asthma, anemia, birth defects, cancer/tumor, colitis, diabetes, encephalitis, epilepsy, heart disease, hypertension, kidney/bladder disorders, migraine, Parkinson's disease, rheumatism, stroke, thyroid, or ulcer, was obtained [2, 35, 36]. A composite binary variable was created based on a positive response to any physical health condition, except cardiometabolic conditions [2]. We identified cardiometabolic conditions by the presence of stage 2 hypertension, type 2 diabetes, heart disease, and/or stroke. Stage 2 hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive medication [24, 25, 35, 36]. Type 2 diabetes was defined as fasting glucose levels ≥ 126 mg/dL or a report of having been diagnosed with or received treatment for diabetes [24, 25, 35, 36]. As part of the clinical history, participants also reported on the medications used, which were classified into broad classes; psychoactive medication use was defined as a report of the use of hypnotics, anxiolytics, anti-depressants, anti-psychotics, or other central nervous system medication. Participants' daily consumption of caffeine (number of cups/day), tobacco (number of cigarettes/day), and alcohol (number of drinks/day) as well as demographic characteristics, including age, sex, race/ethnicity, and years of education, were also obtained [35, 36].

Cognitive impairment

As reported in our previous studies [18, 35, 36], each participant completed a battery of standardized neuropsychological tests consisting of measures commonly used in clinical practice to assess a wide range of cognitive domains on the evening before the sleep recording (19:00 pm and 20:00 pm). This battery included the Mini-Mental State Examination (MMSE) [37–39], the Symbol Digit Modalities Test (SDMT) [40, 41], the Trail Making Test (TMT) part-A (TMT-A) and part-B (TMT-B) scored for its derived outcomes (TMT B-A, TMT B/A) [42–46], the Benton Visual Retention Test (BVRT) scored for its type of errors [47], and the Thurstone Word Fluency Test (TWFT) in oral and written forms [48]. While the availability of the 16 outcomes that this test battery yields is an advantage over having one single test score, it also imposes statistical (i.e. experiment-wise error rate) and clinical (i.e. overlapping cognitive functions) limitations when testing our hypothesis. As previously reported [35], Z scores for each test outcome were computed based on the raw score, with their respective sample mean and standard deviation (SD) and principal component analysis (PCA) reduced the 16 outcomes into a smaller number of clinically meaningful and psychometrically reliable cognitive domains consistent with established models of cognition. In brief, PCA yielded a four-factor solution explaining 89% of the total variance and representing "processing speed," "executive attention," "short-term visual memory," and "verbal fluency"; a fifth unspecific factor, indexed by the MMSE score, was removed from the PCA as it loaded across all domains and represented "global cognitive status" [35]. To identify participants with CI, we used a 2-fold approach commensurate with our previous study [35]. First, individuals with impaired "global cognitive status" (i.e. MMSE score of <25), regardless of scores from other cognitive domains, were identified as cognitively impaired [38, 39]. Second, individuals with a Z_{sum} > 90th percentile of the study population in the four other cognitive domains were also identified as cognitively impaired, based on the estimated 13% prevalence of CI in the US population (we chose the 90th percentile rather than the 85th percentile to rely on a more conservative definition). The algorithm for calculating Z_{sum} consisted of the following equation [35]:

$$Z_{sum} = Z_{TMT-A} - Z_{SDMT} + Z_{TMT\ B-A} + Z_{TMT\ B/A} - Z_{BVRT\ correct} + Z_{BVRT\ error} - Z_{TWFT\ oral} - Z_{TWFT\ \ written}$$

A total of 217 participants did not have data in all neurocognitive tests and, thus, were excluded from the analyses, which yielded an effective sample size of 1,524. Out of these 1,524 participants, 155 were categorized as cognitively impaired [35]. In addition, a group with "pVCI" was defined by the coexistence of cardiometabolic conditions (i.e. stage 2 hypertension, type 2 diabetes, heart disease, and/or stroke) and CI (n = 122). This group was labeled as "possible" (vs. "probable") VCI [35] given the absence of biomarker or brain imaging data that could establish a definitive vascular etiology [49] and should be carefully interpreted as a proxy for pVCI.

Statistical analyses

The demographic and clinical characteristics of the study population were evaluated and presented as mean (SD) and proportions for continuous and categorical variables, respectively. To compare these characteristics according to CI and the three-level sleep difficulty, analysis of variance or chi-square tests were used, as appropriate.

To evaluate the cross-sectional association between the three-level self-reported sleep difficulty and the two-level objective sleep duration variables with CI and pVCI, multivariable-adjusted binary logistic regression models were used. In these models, age, sex, race, education, BMI, smoking, alcohol use, psychoactive medication, AHI, mental health problems, and physical health problems were considered major co-variables and were controlled for. In the model examining the association with CI, the binary variable physical health problems included hypertension, diabetes, heart disease, and stroke. In the model examining the association with pVCI, the binary variable physical health problems included all other conditions except hypertension, diabetes, heart disease, and stroke. Odds ratios (ORs) with the corresponding 95% confidence limits (95% CL) for

self-reported sleep difficulty and objective short sleep duration with respect to their independent relationship with CI and pVCI were estimated.

Based on the presence of self-reported sleep difficulty and objective short sleep duration, six mutually exclusive groups were established: participants who reported normal sleep and slept objectively more than 6 hours (i.e. reference group), participants who reported poor sleep and slept objectively more than 6 hours, participants who reported chronic insomnia and slept objectively more than 6 hours, participants who reported normal sleep and slept objectively less than 6 hours, participants who reported poor sleep and slept objectively less than 6 hours, and participants who reported chronic insomnia and slept objectively less than 6 hours. The association of these six mutually exclusive groups with CI and pVCI was further assessed in two multivariable-adjusted binary logistic regression models while adjusting for the same major co-variables mentioned above. To graphically illustrate the role of objective short sleep duration in the association between self-reported sleep difficulty with CI and pVCI, we projected the multivariable-adjusted rates across the six subgroups while accounting for equal demographic and clinical characteristics (i.e. aged 48.9 years, 46.6% men, 91.5% white, 13.6 years of education, 27.6 kg/m^2 BMI, 22% smoker, 1.1 alcoholic drinks/day, 11.8% psychoactive medication use, 2.4 event/hour AHI, 21.5% with a history of mental health problems, and 53.6% with a history of physical health problems). The log odds of CI and pVCI rates were estimated by applying these values, along with objective sleep duration stratum and sleep difficulty status, to the fitted logistic regression model. The inverse logit function was then applied to transform log odds to CI and pVCI probabilities. Statistical significance was set at a two-sided $p < 0.05$. All analyses were performed using SAS version 9.4 [50].

Results

Table 1 presents the demographic, sleep, and clinical characteristics of the sample as well as stratified by the presence of CI and sleep difficulty. The presence of CI was significantly associated with all demographic and clinical characteristics, except mental health problems or psychoactive medication use, while the presence of self-reported sleep difficulty was significantly associated with several demographic and clinical characteristics, except years of education, diabetes, heart disease, smoking, alcohol use, AHI, or OSA (Table 1).

The results of multivariable models that examined the association of the three-level self-reported sleep difficulty and the two-level objective sleep duration with CI and pVCI after adjusting for each other and potential confounders are presented in Table 2. While poor sleep and chronic insomnia were not significantly associated with either CI or pVCI, objective short sleep duration was significantly associated with CI (OR = 1.90, 95% CL = 1.22–2.95) and marginally associated with pVCI (OR = 1.53, 95% CL = 0.93–2.52). Based on the association of objective short sleep duration with CI, we split the three-level self-reported sleep difficulty into objective sleep duration subgroups and examined their association with CI and pVCI after adjusting for potential confounders. As shown in Table 3, when compared to the reference group, participants who reported poor sleep or chronic insomnia and slept objectively less than 6 hours were significantly associated with increased odds of CI (OR = 2.06, 95% CL = 1.15–3.66 and OR = 2.18, 95% CL = 1.107–4.47, respectively) as well as increased odds of pVCI (OR = 1.94, 95% CL = 1.01–3.75 and OR = 2.33, 95% CL = 1.07–5.06, respectively).

In contrast, participants who reported poor sleep or chronic insomnia and slept objectively more than 6 hours were not significantly associated with increased odds of

Table 1. Demographic and clinical characteristics of the overall sample as well as stratified by the presence of CI and self-reported sleep difficulty

		CI			Sleep difficulty			
	Overall (*N* = 1,524)	No (*n* = 1,369)	Yes (*n* = 155)	P†	Normal sleep (*n* = 899)	Poor sleep (*n* = 453)	Chronic insomnia (*n* = 172)	P‡
Age, years	48.9 (13.4)	48.1 (13.3)	59.3 (11.5)	<0.01	49.8 (14.6)	46.1 (11.7)	49.4 (9.6)	<0.01
Male, %	46.6	45.6	58.8	<0.01	52.2	37.0	23.9	<0.01
Non-Hispanic White, %	91.5	92.3	82.4	<0.01	91.5	93.7	85.8	0.03
Education, years	13.6 (2.8)	13.8 (2.8)	11.2 (2.2)	<0.01	13.6 (3.2)	13.5 (2.3)	13.5 (2.0)	0.77
BMI, kg/m^2	27.6 (5.6)	27.5 (5.6)	28.5 (5.4)	0.08	27.1(5.4)	28.8 (5.5)	28.9 (6.2)	<0.01
Hypertension, %	34.9	33.9	48.6	<0.01	33.2	34.8	51.7	<0.01
Diabetes, %	13.7	12.5	29.3	<0.01	13.3	13.6	18.6	0.29
Heart disease, %	10.0	9.3	19.5	<0.01	9.0	12.5	12.1	0.13
Stroke, %	1.6	1.3	4.9	<0.01	1.1	2.9	1.8	0.06
Physical health problems, %	53.6	54.3	48.8	0.05	47.8	65.1	71.4	<0.01
Mental health problems, %	21.5	21.2	24.7	0.39	13.5	37.7	45.3	<0.01
Psychoactive medications, %	11.8	11.3	15.5	0.13	8.0	14.6	23.8	<0.01
Smoker, %	22.0	20.6	39.2	<0.01	21.5	23.8	20.9	0.64
Alcohol use, drinks/day	1.1 (5.5)	1.1 (5.8)	0.5 (1.2)	<0.01	1.3 (7.0)	0.7 (2.0)	0.5 (1.1)	0.12
AHI, events/hour	2.4 (7.5)	2.1 (7.0)	5.3 (10.7)	<0.01	2.4 (8.2)	2.4 (6.6)	2.2 (5.6)	0.97
OSA, %	10.8	10.1	19.7	<0.01	11.1	10.4	9.7	0.86
Objective sleep duration, hours	5.9 (1.2)	6.0 (1.2)	5.0 (1.2)	<0.01	5.9 (1.3)	6.0 (1.1)	5.6 (1.0)	0.03
<6 hours, %	44.8	42.1	78.2	<0.01	43.7	44.3	55.7	0.05

AHI, apnea–hypopnea index; BMI, body mass index. OSA = AHI ≥ 5 events per hour of sleep.

†*p* value for CI.

‡*p* value for sleep difficulty.

Table 2. Association between self-reported sleep difficulty and objective short sleep duration with CI and pVCI

	No. (%) with CI	OR (95%CL)†	No. (%) with pVCI	OR (95%CL)‡
Sleep difficulty				
Normal sleep	88 (9.8)	1.00	65 (7.2)	1.00
Poor sleep	46 (10.2)	1.17 (0.76–1.81)	39 (8.6)	1.42 (0.89–2.29)
Chronic insomnia	21 (12.2)	1.25 (0.69–2.26)	18 (10.5)	1.57 (0.84–2.96)
Objective sleep duration				
≥6 hours	39 (5.3)	1.00	29 (3.9)	1.00
<6 hours	116 (14.7)	1.90 (1.22–2.95)*	93 (11.8)	1.53 (0.93–2.52)

†OR and 95% CL adjusted for age, race, sex, education, BMI, smoking, alcohol use, psychoactive medication, AHI, mental health problems, and physical health problems, including hypertension, diabetes, heart disease, and stroke.
‡OR and 95% CL adjusted for age, race, sex, education, BMI, smoking, alcohol use, psychoactive medication, AHI, mental health problems, and physical health problems, except hypertension, diabetes, heart disease, and stroke that were used to define the outcome.
*p value < 0.05.

Table 3. Association between self-reported sleep difficulty subgroups based on objective sleep duration with CI and pVCI

		N	No. (%) with CI	OR (95%CL)†	No. (%) with pVCI	OR (95%CL)‡
Normal sleep	≥6 hours	452	28 (6.2)	1.00	19 (4.2)	1.00
Poor sleep	≥6 hours	211	8 (3.8)	0.72 (0.30–1.76)	8 (3.8)	1.08 (0.42–2.74)
Chronic insomnia	≥6 hours	74	3 (4.1)	0.75 (0.21–2.71)	2 (2.7)	0.76 (0.16–3.57)
Normal sleep	<6 hours	447	60 (13.4)	1.48 (0.86–2.55)	46 (10.3)	1.23 (0.66–2.32)
Poor sleep	<6 hours	242	38 (15.7)	2.06 (1.15–3.66)*	31 (12.8)	1.94 (1.01–3.75)*
Chronic insomnia	<6 hours	98	18 (18.4)	2.18 (1.07–4.47)*	16 (16.3)	2.33 (1.07–5.06)*

†OR and 95% CL adjusted for age, race, sex, education, BMI, smoking, alcohol use, psychoactive medication, AHI, mental health problems, and physical health problems, including hypertension, diabetes, heart disease, and stroke.
‡OR and 95% CL adjusted for age, race, sex, education, BMI, smoking, alcohol use, psychoactive medication, AHI, mental health problems, and physical health problems, except hypertension, diabetes, heart disease, and stroke that were used to define the outcome.
*p value < 0.05.

either CI (OR = 0.72, 95% CL = 0.30–1.76 and OR = 0.75, 95% CL = 0.21–2.71, respectively) or increased odds of pVCI (OR = 1.08, 95% CL = 0.42–2.74 and OR = 0.76, 95% CL = 0.16–3.57). Furthermore, participants who reported normal sleep and slept objectively less than 6 hours were also not associated with significantly increased odds of CI (OR = 1.48, 95% CL = 0.86–2.55) or pVCI (OR = 1.23, 95% CL = 0.66–2.32) when compared with the reference group of participants who reported normal sleep and slept objectively more than 6 hours (Table 3).

As shown in Figure 1, the projected rates of CI for participants who reported normal sleep, poor sleep, or chronic insomnia and slept objectively more than 6 hours were 3.1%, 2.3%, and 2.6%, respectively. Among participants who reported sleep difficulty, those who slept objectively less than 6 hours showed a significantly stronger association (Figure 1, plot A). The projected CI rate for participants who reported normal sleep and slept objectively less than 6 hours was 4.5%, whereas the projected rates for participants who reported poor sleep or chronic insomnia and slept objectively less than 6 hours were 6.3% and 6.9%, respectively. The substantial differences with respect to the association of these subgroups with identical demographic and clinical characteristics with the CI rates shown in Figure 1, plot A, were commensurate with the rates for pVCI shown in Figure 1, plot B. It should be noted that the ratio of these projected rates can provide a closer estimate of associated risk than the ORs reported above. For example, we could estimate that the risk of CI and pVCI is 2.7 times (6.9% vs. 2.6%) and 3.0 times (3.7% vs. 1.2%) higher, respectively, in participants who reported chronic insomnia and slept objectively less than 6 hours than those sleeping more than 6 hours.

Discussion

This is the first study to demonstrate that insomnia with objective short sleep duration is significantly associated with prevalent CI as it relates to cardiometabolic contributors to brain health, i.e. pVCI. This association was independent of factors frequently associated with insomnia or CI, such as age, sex, race, education, smoking, obesity, sleep apnea, or other mental and physical health problems. Our findings provide further evidence that objective sleep measures in insomnia may be a useful marker of the biological severity, phenotyping, and adverse impact of this highly prevalent and chronic disorder.

Sleep serves many functions, ranging from tissue restoration to brain metabolite clearance of potential neurotoxic waste products that accumulate during wakefulness [51]. While normal, adequate sleep may actively promote restoration, consolidation, and integration of cognitive information, it is likely that inadequate sleep serves as a catalyst to impair performance on attention and executive control tasks [52]. In the present study, adults with insomnia and objective short sleep duration were associated with a 2-fold increased odds of prevalent CI or pVCI. Previous studies indicate that noncognitively impaired adults with chronic insomnia may have faster processing speed on simple reaction time tasks but struggle greatly when the complexity of the task is slightly increased [53]. We have shown that noncognitively impaired adults with chronic insomnia and objective short sleep duration demonstrated lower performance on tasks tapping higher-order cognitive functions (i.e. executive/set-switching attention), while adults with insomnia and normal sleep duration did not show decreased cognitive performance in any cognitive task [18]. This finding was consistent

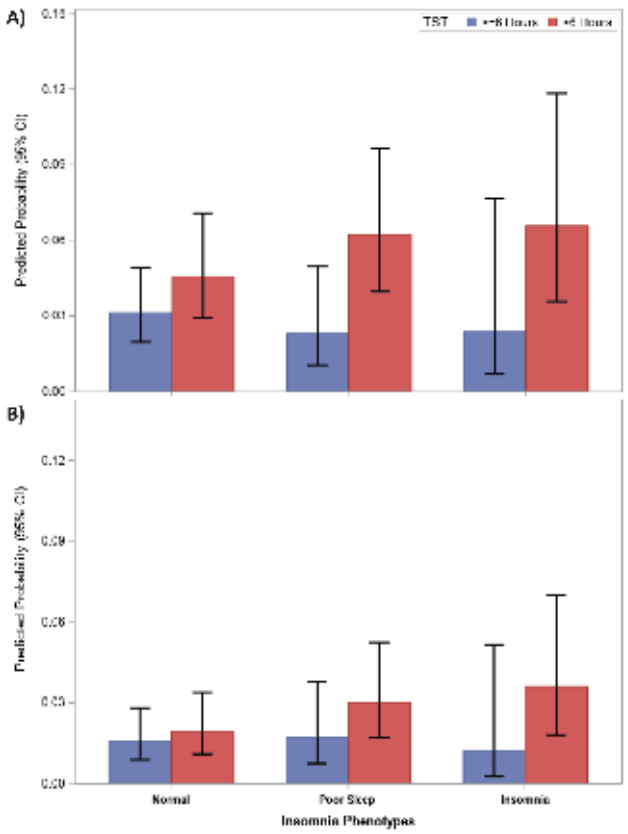

Figure 1. Multivariable-adjusted probabilities of CI and pVCI across insomnia phenotypes. Data are expected probability rates of (A) CI and (B) pVCI across insomnia phenotypes based on objective sleep duration with identical demographic (e.g. age, sex, race, and years of education) and clinical (e.g. prevalence of smoking, alcohol use, psychoactive medication, obesity, obstructive sleep apnea, mental health problems, and physical health problems) characteristics.

with previous [54, 55] and subsequent studies using objective sleep measures [56, 57] and more directly replicated in two independent studies [17, 19] of also noncognitively impaired adults with chronic insomnia and objective short sleep duration. The novel finding of the current large, population-based study of a wide age-range is that this insomnia phenotype appears to be more likely to present with prevalent CI, a finding similar to that observed in older adults [58]. Future clinical studies of large samples with well-diagnosed minor or major neurocognitive disorders (e.g. MCI, VCI, and AD) should examine the differential neurocognitive profiles and potential underlying mechanisms of those with a history of chronic insomnia who demonstrate short sleep duration vs. normal sleep duration.

Another novel, but preliminary, finding of this study is that the association of insomnia with objective short sleep duration with CI is particularly strong for pVCI, as identified by the coexistence of cardiometabolic conditions and CI in this study. Several studies have supported that insomnia with objective short sleep duration is associated with physiologic hyperarousal, including hyperactivity of the hypothalamic–pituitary–adrenal and sympatho–adrenal–medullary axes [59–61] and impaired cardiac autonomic modulation [23, 54, 62], as well as an increased risk of adverse cardiometabolic health outcomes [20–22, 24, 25, 60, 63–66]. Moreover, two recent studies have found that shorter PSG-measured sleep duration is associated with lower GABA levels in the anterior cingulate cortex [67] and that lower PSG-measured sleep efficiency is associated with greater waking connectivity between the retrosplenial cortex/hippocampus and various nodes of the default mode network in adults with insomnia [68]. In addition, two studies have shown that insomnia with objective short sleep duration is associated with altered brain-based biomarkers, such as decreased glutamate metabolites [57], and brain-derived neurotrophic factor [17]. Taken together, these data can lead us to surmise that the etiology of CI in middle-aged adults with insomnia with objective short sleep duration may be more likely related to dysfunction of the neurovascular unit and microvascular brain damage, such as asymptomatic deep brain infarction, white matter hyperintensities, and accelerated brain atrophy [27]. If followed up as older adults, these individuals' CI will eventually result from a mixture of cerebral amyloid angiopathy and microinfarction, microhemorrhage, and macrohemorrhage of the brain, which typically underlie VCI [27]. Additional research into the association between insomnia and objective short sleep duration with CI is vital, especially to further understand the specific underlying central mechanisms of neurocognitive dysfunction and its progression to major neurocognitive disorders. There is a clear need for longitudinal studies making use of objective sleep and cognitive measures that can address these hypotheses.

In contrast, adults with insomnia with objective normal sleep duration were not associated with increased odds of either CI or pVCI. This finding is consistent with our and others' previous studies showing a lack of performance deficits in noncognitively impaired adults who report chronic insomnia and sleep objectively longer [17–19, 55, 57] or lack physiologic hyperarousal [56]. Furthermore, these data are also consistent with the absence of an increased risk of adverse cardiometabolic health outcomes in this insomnia phenotype with normal sleep duration [21–25]. It is important to note that this insomnia phenotype has been shown to be associated with sleep misperception, anxious-ruminative traits, dysfunctional sleep beliefs, or poor coping resources [31, 55, 69], which appear to partially account for its increased risk of psychiatric morbidity [33]. Thus, insomnia with objective normal sleep duration should not be regarded simply as a "symptom of the worried-well" but rather as a disorder in which specific cognitive-emotional (e.g. dysfunctional beliefs, cognitive arousal, and performance anxiety) and behavioral (e.g. sleep-incompatible and sleep-inhibitory behaviors) factors play a primary perpetuating role [15, 16, 69]. Our novel data further support that objective sleep duration can be a useful marker not only for predicting the biological severity of insomnia but also for a meaningful phenotyping of the disorder.

It is worth mentioning that in univariate analyses, adults who reported normal sleep and slept objectively short in the lab showed a significantly higher prevalence of CI (13.4%) when compared to those who also reported normal sleep but slept objectively longer (6.2%). Multivariable-adjusted analyses, thereafter, showed that these participants were associated with a nonsignificant 1.5-fold increased odds of CI. These data indicate that the co-variables adjusted for may have accounted for some of the risk of CI observed in these short sleepers without insomnia symptoms. Our previous study in noncognitively impaired adults [18] showed that this group of non-complaining short sleepers had poorer processing speed but no signs of performance deficits in higher-order cognitive functions (i.e. executive attention, short-term memory, or verbal fluency). Future studies should examine which clinical

conditions account for the potential increased risk of CI of short sleepers without insomnia complaints.

Some limitations should be considered when interpreting our results. First, the cross-sectional design of this study precludes any conclusion regarding the direction of the associations found. It is equally plausible that adults who complain of insomnia and sleep objectively short in the lab have an increased risk of CI, as it is that adults with CI who complain of insomnia are more likely to sleep objectively shorter in the lab. Second, the definition of sleep difficulty differentiated those with "poor sleep" (i.e. moderate-to-severe insomnia symptoms) and those with "chronic insomnia" (i.e. a complaint of insomnia lasting at least a year) but did not include frequency or daytime impairment criteria. Our previous studies have supported the face, construct, and predictive validity of the "poor sleep" and "chronic insomnia" definitions used in this population-based cohort [2, 18, 22, 24, 25, 30–33]. These definitions are similar to those of "insomnia symptoms" and "insomnia syndrome" in other cohorts that have used improved, more sophisticated measures including frequency and daytime impairment criteria [3]. Third, the objective sleep duration in this study was based on one-night, 8-hour PSG, which may not be representative of the participants' habitual sleep duration. Fourth, we did not have the ability to confirm the type of diagnoses or medications via medical record data, either for sleep/insomnia, CI, heart disease, stroke, or other physical or mental health conditions, as reported by the participants during the clinical history and physical examination. Fifth, the lack of biomarker or brain imagining data precluded the diagnosis of VCI and, thus, the use of the term "possible" should be cautiously interpreted as a proxy of VCI. Finally, the PSAC is a predominantly non-Hispanic white cohort with an average of 13.5 years of education. Thus, future population-based studies should incorporate longitudinal designs with multiple time points and multiple night recordings and test our hypotheses in more racially/ethnically diverse cohorts, thereby extending the generalizability of our findings and informing the causal direction of the associations found.

Funding

This study was in part funded by the American Heart Association under award number 14SDG19830018 (Fernandez-Mendoza) and by the National Heart Lung and Blood Institute of the National Institutes of Health under award numbers R01HL51931 and R01HL40916 (Bixler).

Acknowledgments

The work was performed at the Sleep Research and Treatment Center of Penn State Health Milton S. Hershey Medical Center, and the staff members are especially commended for their efforts.

Conflict of interest statement. The authors declare no other financial interests. Nonfinancial disclosure: none.

References

1. Léger D, *et al*. Societal costs of insomnia. *Sleep Med Rev*. 2010;**14**(6):379–389.
2. Bixler EO, *et al*. Insomnia in central Pennsylvania. *J Psychosom Res*. 2002;**53**(1):589–592.
3. Morin CM, *et al*. Prevalence of insomnia and its treatment in Canada. *Can J Psychiatry*. 2011;**56**(9):540–548.
4. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002;**6**(2):97–111.
5. Baglioni C, *et al*. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord*. 2011;**135**(1-3):10–19.
6. Gillis C, *et al*. The incidence of mild cognitive impairment: a systematic review and data synthesis. *Alzheimers Dement (Amst)*. 2019;**11**:248–256.
7. Hu C, *et al*. The prevalence and progression of mild cognitive impairment among clinic and community populations: a systematic review and meta-analysis. *Int Psychogeriatr*. 2017;**29**(10):1595–1608.
8. Albert MS, *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;**7**(3):270–279.
9. Benedict C, *et al*. Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. *Alzheimers Dement*. 2015;**11**(9):1090–1097.
10. Rabin LA, *et al*. Subjective cognitive decline in preclinical Alzheimer's disease. *Annu Rev Clin Psychol*. 2017;**13**:369–396.
11. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
12. Ballesio A, *et al*. Executive functions in insomnia disorder: A systematic review and exploratory meta-analysis. *Front Psychol*. 2019;**10**:101.
13. Fortier-Brochu E, *et al*. Insomnia and daytime cognitive performance: a meta-analysis. *Sleep Med Rev*. 2012;**16**(1):83–94.
14. Shekleton JA, *et al*. Searching for the daytime impairments of primary insomnia. *Sleep Med Rev*. 2010;**14**(1):47–60.
15. Fernandez-Mendoza J. The insomnia with short sleep duration phenotype: an update on it's importance for health and prevention. *Curr Opin Psychiatry*. 2017;**30**(1):56–63.
16. Vgontzas AN, *et al*. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev*. 2013;**17**(4):241–254.
17. Fan TT, *et al*. Objective sleep duration is associated with cognitive deficits in primary insomnia: BDNF may play a role. *Sleep*. 2019; **42**(1): doi:10.1093/sleep/zsy192
18. Fernandez-Mendoza J, *et al*. Insomnia with objective short sleep duration is associated with deficits in neuropsychological performance: a general population study. *Sleep*. 2010;**33**(4):459–465.
19. Khassawneh BY, *et al*. Neurocognitive performance in insomnia disorder: the impact of hyperarousal and short sleep duration. *J Sleep Res*. 2018;**27**(6):e12747.
20. Bathgate CJ, *et al*. Objective but not subjective short sleep duration associated with increased risk for hypertension in individuals with insomnia. *Sleep*. 2016;**39**(5):1037–1045.
21. Bertisch SM, *et al*. Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. *Sleep*. 2018; **41**(6): doi:10.1093/sleep/zsy047
22. Fernandez-Mendoza J, *et al*. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension*. 2012;**60**(4):929–935.
23. Jarrin DC, *et al*. Cardiovascular autonomic dysfunction in insomnia patients with objective short sleep duration. *J Sleep Res*. 2018;**27**(3):e12663.

24. Vgontzas AN, *et al*. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep*. 2009; **32**(4): 491–497.
25. Vgontzas AN, *et al*. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diabetes Care*. 2009;**32**(11):1980–1985.
26. Iadecola C, *et al*.; American Heart Association Council on Hypertension; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. *Hypertension*. 2016;**68**(6):e67–e94.
27. Gorelick PB, *et al*.; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;**42**(9):2672–2713.
28. Bixler EO, *et al*. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med*. 1998;**157**(1):144–148.
29. Bixler EO, *et al*. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med*. 2001;**163**(3 Pt 1):608–613.
30. Vgontzas AN, *et al*. Persistent insomnia: the role of objective short sleep duration and mental health. *Sleep*. 2012;**35**(1):61–68.
31. Fernandez-Mendoza J, *et al*. Sleep misperception and chronic insomnia in the general population: the role of objective sleep duration and psychological profiles. *Psychosom Med*. 2011;**73**(1):88–97.
32. Fernandez-Mendoza J, *et al*. Clinical and polysomnographic predictors of the natural history of poor sleep in the general population. *Sleep*. 2012;**35**(5):689–697.
33. Fernandez-Mendoza J, *et al*. Insomnia and incident depression: role of objective sleep duration and natural history. *J Sleep Res*. 2015;**24**(4):390–398.
34. Rechtschaffen A, *et al*. *A Manual of Standardized Terminology, Technique and Scoring System for Sleep Stages of Human Sleep*. Los Angeles, CA: Brain Information Service; 1968.
35. Fernandez-Mendoza J, *et al*. Objective short sleep duration increases the risk of all-cause mortality associated with possible vascular cognitive impairment. *Sleep Health*. 2020;**6**(1):71–78.
36. Fernandez-Mendoza J, *et al*. Interplay of objective sleep duration and cardiovascular and cerebrovascular diseases on cause-specific mortality. *J Am Heart Assoc*. 2019;**8**(20):e013043.
37. Folstein MF, *et al*.. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;**12**(3):189–198.
38. Crum RM, *et al*. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA*. 1993;**269**(18):2386–2391.
39. Kukull WA, *et al*. The Mini-Mental State Examination score and the clinical diagnosis of dementia. *J Clin Epidemiol*. 1994;**47**(9):1061–1067.
40. Sheridan LK, *et al*. Normative Symbol Digit Modalities Test performance in a community-based sample. *Arch Clin Neuropsychol*. 2006;**21**(1):23–28.
41. Smith A. *Symbol Digits Modalities Test*. Los Angeles, CA: Western Psychological Services; 1982.
42. Reitan RM. The relation of the trail making test to organic brain damage. *J Consult Psychol*. 1955;**19**(5):393–394.
43. Crowe SF. The differential contribution of mental tracking, cognitive flexibility, visual search, and motor speed to performance on parts A and B of the Trail Making Test. *J Clin Psychol*. 1998;**54**(5):585–591.
44. Sánchez-Cubillo I, *et al*. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc*. 2009;**15**(3):438–450.
45. Gaudino EA, *et al*. Construct validity in the Trail Making Test: what makes part B harder? *J Clin Exp Neuropsychol*. 1995;**17**(4):529–535.
46. Kortte KB, *et al*. The trail making test, part B: cognitive flexibility or ability to maintain set? *Appl Neuropsychol*. 2002;**9**(2):106–109.
47. Sivan AB. *Benton Visual Retention Test*. 5th ed. San Antonio, TX: Psychological Corporation; 1992.
48. Thurstone LL, *et al*.. *Primary Mental Abilities*. Chicago, IL: University of Chicago Press; 1938.
49. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
50. SAS [computer program]. Version 9.4. Cary, NC: SAS Inst.; 2003.
51. Xie L, *et al*. Sleep drives metabolite clearance from the adult brain. *Science* 2013;**342**(6156):373–377.
52. Banks S, *et al*.. Sleep deprivation. In: Kryger M, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Philadelphia, PA: Elsevier; 2017: 49–55.
53. Altena E, *et al*. Prefrontal hypoactivation and recovery in insomnia. *Sleep*. 2008;**31**(9):1271–1276.
54. Bonnet MH, *et al*.. 24-Hour metabolic rate in insomniacs and matched normal sleepers. *Sleep*. 1995;**18**(7):581–588.
55. Bonnet MH, *et al*. Physiological activation in patients with Sleep State Misperception. *Psychosom Med*. 1997;**59**(5):533–540.
56. Edinger JD, *et al*. Does physiological hyperarousal enhance error rates among insomnia sufferers? *Sleep*. 2013;**36**(8):1179–1186.
57. Miller CB, *et al*. Clusters of insomnia disorder: an exploratory cluster analysis of objective sleep parameters reveals differences in neurocognitive functioning, quantitative EEG, and heart rate variability. *Sleep*. 2016;**39**(11):1993–2004.
58. Biddle DJ, *et al*. Associations of objective and subjective sleep disturbance with cognitive function in older men with comorbid depression and insomnia. *Sleep Health*. 2017;**3**(3):178–183.
59. Vgontzas AN, *et al*. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab*. 2001;**86**(8):3787–3794.
60. D'Aurea C, *et al*. Objective short sleep duration is associated with the activity of the hypothalamic-pituitary-adrenal axis in insomnia. *Arq Neuropsiquiatr*. 2015;**73**(6):516–519.
61. Castro-Diehl C, *et al*. Association of sleep duration and quality with alterations in the hypothalamic-pituitary adrenocortical axis: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Clin Endocrinol Metab*. 2015;**100**(8):3149–3158.

62. Spiegelhalder K, *et al*. Heart rate and heart rate variability in subjectively reported insomnia. *J Sleep Res*. 2011;**20**(1 Pt 2):137–145.
63. Nakazaki C, *et al*. Association of insomnia and short sleep duration with atherosclerosis risk in the elderly. *Am J Hypertens*. 2012;**25**(11):1149–1155.
64. Vasisht KP, *et al*. Differences in insulin secretion and sensitivity in short-sleep insomnia. *Sleep*. 2013;**36**(6):955–957.
65. Hein M, *et al*. Prevalence and risk factors of type 2 diabetes in insomnia sufferers: a study on 1311 individuals referred for sleep examinations. *Sleep Med*. 2018;**46**:37–45.
66. Hein M, *et al*. Objective sleep alterations and long-term use of short or intermediate half-life benzodiazepine receptor agonists are risk factors for high blood pressure in individuals with insomnia: a study in 1272 individuals referred for sleep examinations. *Sleep Med*. 2019;**53**:115–123.
67. Spiegelhalder K, *et al*. Magnetic resonance spectroscopy in patients with insomnia: a repeated measurement study. *PLoS One*. 2016;**11**(6):e0156771.
68. Regen W, *et al*. Objective sleep disturbances are associated with greater waking resting-state connectivity between the retrosplenial cortex/ hippocampus and various nodes of the default mode network. *J Psychiatry Neurosci*. 2016;**41**(5):295–303.
69. Edinger JD, *et al*. Insomnia and the eye of the beholder: are there clinical markers of objective sleep disturbances among adults with and without insomnia complaints? *J Consult Clin Psychol*. 2000;**68**(4):586–593.