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Mild cognitive impairment: associations with sleep disturbance, apolipoprotein e4, and sleep medications

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Abstract

Objective: Mild cognitive impairment (MCI) is associated with increased memory problems although the ability to complete daily life activities remains relatively intact. This study examined: (1) if sleep disturbance increased the hazard of MCI; (2) if APOE e4 carriers with sleep disturbance experience an increased risk of MCI; and, (3) if prescription sleep medications provide a protective effect against MCI. We hypothesized that sleep disturbance increases the hazard of MCI, this relationship is stronger among APOE e4 carriers reporting a sleep disturbance. Furthermore, we hypothesized that sleep medications decrease the hazard of MCI.

Methods: To determine whether sleep medication mediates the risk of developing MCI for individuals with sleep disturbance and/or APOE e4, we analyzed the National Alzheimer's

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016Zj.sleep.2018.09.001.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016Zj.sleep.2018.09.001.

Coordinating Center Uniform Data Set. We selected participants with normal cognition at baseline (n = 6798), and conduced survival analyses.

Results: Our main findings indicated that the hazard of MCI was significantly associated with sleep disturbance. The hazard remained among those who did not use sleep medication. Trazodone and zolpidem users did not have a significant hazard of MCI, but the significant hazard remained for those who did not use these medications. APOE e4 carriers had a significantly higher hazard of MCI. Among e4 carriers who used trazodone or zolpidem, there was not a statistically significant risk of MCI.

Conclusion: This study demonstrated the potential utilization of trazodone and zolpidem in the treatment of sleep disturbance while potentially mitigating the risk of MCI. While trazodone and zolpidem have been shown to positively impact sleep disturbance in individuals with normal cognition, further research should explore these findings given that these medications are potentially inappropriate for older adults.

Keywords

Sleep disturbance; Medication; Trazodone; Zolpidem; Mild cognitive impairment; Apolipoprotein e

1. Introduction

Mild cognitive impairment (MCI) is defined as a syndrome of impaired cognition and is typically categorized as two subtypes — amnestic (primarily characterized by memory loss) and non-amnestic (impairment in domains other than memory loss) [1]. MCI is typically diagnosed in a person who is experiencing age-related cognitive changes and characterized by cognitive declines that are more substantial than expected based on the chronological age of a person [2]. MCI is often characteristic of early dementia [3,4] or Alzheimer's disease (AD) [2,5], but the person with MCI usually remains functionally able to conduct daily living activities despite memory loss [6,7].

Sleep disturbance and related disorders in older adults are frequently indicative of comorbidities [8], including MCI. Sleep disturbance may be predictive of cognitive impairment and deficiency among older adults [9,10]. Over the past 10 years, studies have indicated that between 50 and 70 million Americans [11–13] experience sleep disturbances. Moreover, approximately one quarter to one half of individuals over the age of 65 in the U.S experience sleep disturbances [14,15].

Insomnia is the most common type of sleep disturbance and is estimated to impact 10–15% of the general U.S. population [16,17]. Symptoms of insomnia include difficulties with sleep onset and/or sleep maintenance accompanied with daytime fatigue, mood disturbance, or cognitive impairment [18]. Insomnia can be classified as either chronic or primary. Chronic insomnia is defined as continued sleep disturbance for at least three times a week for at least one month. Primary insomnia is defined as chronic insomnia without an identifiable underlying cause or disorder [19]. While the cause of insomnia is uncertain, the risk of primary insomnia increases with age and may be associated with psychological factors in aging [19,20].

Sleep is a critical factor for cognition and memory performance. Quality sleep can also affect the memory and limit the offline decline of episodic memory representations, resulting in superior memory retention [21]. Sleep disturbance and poor quality of sleep can have negative effects on memory [22–24]. Research links sleep spindles with overnight memory consolidation [23]. An individual may consolidate sleep-related memories with their own experiences during the time of memory loss [5]. Moreover, evidence exists to support an association between length of slow-wave sleep (SWS) and episodic memory loss [25]; as well as an association between time spent on non-rapid eye movement SWS and long-term episodic memory impairment across offline time periods [21]. Evidence shows that in general, length of sleep can affect episodic memory among older adults [25]. Therefore, disrupted sleep and atypical nighttime behaviors are considered hallmark symptoms of MCI [1,26,27].

Sleep disturbance can contribute to negative health outcomes, including depression [28]. Up to 90% of individuals diagnosed with depression indicate problems with the quality of their sleep, including insomnia as well as problems in initiating and maintaining sleep, or awakening [29]. It is notable that the distinction and bidirectional relationship [30] -sleep disturbance can be a predictor of depression and interrupted sleep can be a symptom of depression. Sleep disruption can negatively impact quality of life, lead to neurobehavioral impairment, and increase the likelihood of developing depressive symptoms [30]. Furthermore, current and historical studies have indicated that depressive symptoms can result from chronic insomnia [30–33]. Additionally, evidence suggests the disruption of serotonin production in the brain due to sleep disturbances is associated with depression and a change in sleep cycle [34,35]. Antidepressants, which increase the serotonergic tone of serotonin in the brain, may in turn inhibit REM sleep, as REM sleep depends on a decrease of this tone within the brainstem [36].

Seminal research in the field has demonstrated a genetic link between the apolipoprotein (APOE) e4 and subsequent AD development, and this risk is dose-dependent [37,38]. Moreover, the presence of APOE e4 in older adults with MCI could be associated with cognitive decline [39]. APOE e4 provides the brain with instructions to create proteins with the main purpose of facilitating lipid transport and the repair of neural injury within the brain [40]. The presence of the e4 isoform (an APOE allele) is the highest risk factor for the development from MCI to subsequent AD [37,41,42]. This risk factor is present in over 50% of individuals with MCI and AD, versus 15% of individuals without impaired cognition [42,43]. APOE e4 binds to multiple receptors on cell surfaces upon the delivery of both lipids as well as hydrophobic amyloid-β (Aβ) peptide, acting as a catalyst for subsequent neurodegeneration [40].

1.1. Medications

Modern management of the symptoms of sleep disturbance includes pharmacological intervention through commonly prescribed medications, including trazodone and zolpidem. These medications can improve sleep and consequently may enhance cognitive performance [44]. Trazodone is a derivative of triazolopyridine, and is classified as a serotonin antagonist and reuptake inhibitors (SARIs) [45]. While trazadone is an antidepressant, it is also

commonly used as an off-label medication for sleep disturbance; and one of the most popular prescription medications used for sleep [46]. Popularity of this medication is partly due to its low cost, limited restrictions in its duration of use, and its availability as a generic agent [47]. The utilization of trazodone at a small dosage can have a modulating effect on serotonin inhibitors (with 10 mg dosage impacting 50% of serotine receptors), thereby aiding sleep [48]. Limited evidence exists to support the effectiveness of trazodone among older adults with dementia [49]. However, the negative side effects of trazodone, such as drowsiness, dizziness, weight gain [50], and hypotension [45] can adversely impact the quality of life in older adults. Furthermore, there is reluctance to prescribe trazodone in older populations due to limited existing efficacy data within this age cohort [50,51].

Zolpidem is a widely prescribed non-benzodiazepine hypnotic used for the treatment of insomnia [52]. A short-term sleep disturbance treatment, zolpidem is effective for up to five continuous weeks, or 12 weeks of intermittent usage with adults and older patients [53]. Evidence exists to support the efficacy of the extended-release 12.5 mg zolpidem (used three to seven nights per week in a period of up to six months) in improving onset and maintenance of sleep [54]. Moreover, the modified-release formulation of this medication (6.25 mg and 12.5 mg) has demonstrated efficacy in improving sleep quality [55]. Studies have shown that zolpidem can improve next-day concentration and daytime cognitive functioning [54,56,57]. In a randomized, double-blind study of zolpidem with placebo-controlled parallel-groups, zolpidem improved next-day concentration among adults aged between 18 and 64 years [54]. In a comparison study on the effects of zolpidem and flunitrazepam on daytime cognitive functions, zolpidem (10 mg) preserved daytime cognitive functions, while flunitrazepam notably impaired attention among 12 male patients with sleep disturbance [56]. Although zolpidem has demonstrated high effectiveness in treatment and positive effects on cognition, it has shown adverse reactions in some patients [58]. In the past 10 years, studies have indicated that patients using zolpidem may experience moderate potential for dependence and abuse [59,60]. Zolpidem has also been associated with negative side effects including hallucinations, amnesia, and nocturnal behaviors, such as sleepwalking and eating [53,58]. Moreover, zolpidem usage has been associated with an increased risk of bone fracture and falls in older patients [61–63].

Based on findings from our previous research [64,65] indicating an increased hazard of probable AD development among individuals with sleep disturbance, we were interested in the following research questions: (1) does sleep disturbance increase the hazard of MCI development?; (2) are APOE $_{E4}$ carriers more likely to experience MCI?; and (3) do prescribed sleep medications (general or specific drugs) neutralize or even provide a protective effect against the hazard of MCI development?

Given our prior findings that antidepressants moderate the hazard of AD development among individuals with depression [66], and that anxiolytic drugs moderate the hazard of AD development among individuals with anxiety [67]; we sought to explore a similar pattern in the current study but instead focused on sleep disturbance and drugs designed to treat this problem. Recently we demonstrated that sleep disturbance was significantly associated with eventual AD development [68]. Using NACC data, we were able to determine that among individuals taking general sleep medications, no relationship between

sleep disturbance and eventual AD was observed. However, among individuals not taking sleep medications, the increased hazard between sleep and AD remained significant. Among APOE e4 carriers, the hazard of AD due to sleep disturbance was significant, except among those taking zolpidem. As a result, we hypothesized, in the current study, that sleep disturbance increases the hazard of MCI, and this relationship is stronger among APOE e4 carriers reporting a sleep disturbance. While our analyses of sleep medication use are exploratory, based on our previous work [67] we hypothesized that the sleep medications decrease the hazard of MCI development.

2. Methods

We utilized the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) to examine the association between sleep disturbance and MCI, and to study whether sleep medication mediates the risk of developing MCI among individuals with sleep disturbance and/or APOE E4 carriers. The NACC UDS is a longitudinal database started in 2005, and data is collected from participants at Alzheimer's Disease Centers (ADC) [69]. As of June 2018, the database contained observations from more than 38,000 participants. The current study utilized data collected between September 2005 and May 2018, and intentionally selected participants with normal cognition at baseline (n = 6798), as these individuals were deemed free from MCI and AD symptoms. The participants' first visit was considered as the baseline data. Participants voluntarily presented to one of the ADCs for approximately annual observations, including a full battery of memory and non-memory neuropsychological tests. Versions 2 and 3 of the neuropsychological battery were used by ADCs for assessment and diagnosis during the time period for which the current data was collected, and the full battery has been described extensively in the literature [69,70]. Participants could also elect to participate in additional study aims by providing blood, cerebrospinal fluid, and other specimens for genotyping and analysis. All participants were required to attend visits with an informant who knows him/her well. A diagnosis of MCI was administered at the ADC level, usually by a consensus diagnosis, although sometimes by a single clinician using 2011 National Institute on Aging/Alzheimer's Association guidelines [71,72]. The main outcome was the first diagnosis of MCI. MCI defined as a decline from previous functioning, an impairment in memory, executive functioning, visuospatial, language, or attention domains, and a relative preservation of functional abilities [71].

Sleep disturbance at the first visit was measured by the Neuropsychiatric Inventory Questionnaire [73]. An informant responded to the question "Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?" Of those who reported sleep disturbance, only seven participants also reported sleep apnea. Sleep apnea and other assessments of sleep behavior were introduced in UDS version 3 (implemented in March 2015), which was likely the reason for the large volume (97%) of missing data related to sleep apnea.

The use of sleep medication was recorded at baseline and follow-up visits, first with the question "Is the subject currently taking any medication?" If the respondent answered "yes," the clinician recorded all medications taken within the last two weeks of the study visit. The

specific sleep medications examined in the study included: (1) a general category of all sleep medications (includes doxepin, estazolam, temazepam, trazodone, triazolam, zaleplon, and zolpidem), (2) zolpidem, and (3) trazodone. Trazodone and zolpidem were examined independently because other sleep medications were only used by very few or none of the participants, providing a lack of statistical power to detect any meaningful relationship between sleep medications and MCI. Effects of these two sleep medications and sleep medications in general including use of either doxepin, estazolam, temazepam, trazodone, triazolam, zaleplon, or zolpidem were studied separately.

APOE genotype was determined independently by the ADC, using either a buccal swab or blood draw. All six possible genotypes were reported to NACC, although for the purposes of this study we included only whether the participant was an APOE e4 carrier (one or two e4 alleles) or not. Individuals with APOE e2/e4, e4/e4, and e4/e4 were considered e4 carriers and individuals with APOE e2/e2, e3/e3, and e2/e3, were not e4 carriers.

The main outcome was the onset of MCI. We conducted three sets of analyses, with different variables of interest: (1) the presence of sleep disturbance at baseline, (2) whether the participant is an APOE e4 carrier (one or two e4 alleles), and (3) the interaction between the presence of sleep disturbance at baseline and whether the participant is an APOE e4 carrier. For each set of analyses, we conducted analyses on (1) the overall sample, (2) the subsample of participants who used sleep medication (the general category, zolpidem, and trazodone), and (3) the subsample of participants who did not use sleep medication.

Descriptive analyses were used for individual characteristics including age, sex, race/ethnicity, and educational attainment level at baseline, by whether participants eventually developed MCI, or by whether participants used sleep medications (the general category, trazodone, and zolpidem). Chi-square test or two-sample test was used to compare the above individual characteristics across medication groups. Cox [74] proportional hazard models were used for the survival analysis. For the analyses, time length was measured in days. Moreover, the analytic sample was censored given that true survival time was unknown for those who did not develop MCI by the last visit.

The first and second sets of analyses examined the independent effect of sleep disturbance, or APOE e4 status on the hazard of developing MCI. By performing separate survival analyses for those who used sleep medication and those who did not, we studied the differential hazard of developing MCI due to sleep disturbance among the two groups. The third set of analyses examined the additive effect of sleep disturbance and APOE e4 status by including both variables and an interaction term of the two as the key variables of interest.

For each set of analyses with the whole analytic sample or a specific subsample, we also ran four models: (1) Unadjusted regression models with only the key variable of interest; (2) Adjusted regression models with age, sex, race/ethnicity categories (White non-Hispanic [reference group], Black non-Hispanic, Hispanic, and other non-Hispanic races), and education level (high school or lower [reference group], college graduates, and beyond college education level); (3) Adjusted regression models with above-mentioned covariates

and APOE e4 status (only for the set of analyses with the presence of sleep disturbance at baseline as the variable of interest); (4) Adjusted regression models with further inclusion of the use of AD medications.[1] Running four different models allowed us to examine the incremental effects of adding in demographic covariates, APOE e4 status, and lastly, the use of dementia medication. STATA/MP 14.1 (StataCorp, 2015) was utilized for the analyses, and a p value < 0.05 was considered statistically significant.

3. Results

3.1. Descriptive results

There were 884 older adults who were diagnosed with MCI by the end of the observation period who had at least an initial visit as well as a follow-up visit (total number of participants 8,043, analytical sample = 6798). The minimum amount of time under observation was from 250 days until the first occasion that the MCI diagnosis occurred, and the maximum was 4019 days (mean = 1353.08; median: 1104; standard deviation (SD): 945.79).

The mean age of participants with normal cognition at visit one was 71.62 (SD: 9.97; Median: 72). Out of the sample, 66.25% were female, 81.32% were White, 11.87% were African American, 4.53% percent were of Hispanic origin, and 2.28% were from other ethnic groups. Most participants (43.75%) were college graduates, some (39.34%) had education beyond college, and a few (16.92%) had high school or lower education. Fewer than one-third (30.54%) of participants were APOE e4 carriers. Percentages, means, and standard deviations (where applicable) are displayed in Table 1. The results showed that there were no significant differences between sleep medication users and non-medication users for individual characteristics, except for race. White participants represented the highest percentage of sleep medication users (see supplemental Tables 1 and 2).

3.2. Main effects for MCI development

Table 2 summarizes the independent effects of sleep disturbance on the hazards of developing MCI and how sleep medication mediates this effect. The hazard of MCI was statistically significant and higher for individuals with sleep disturbance (HR = 1.36; 95% Confidence Interval (CI) [1.11—1.67]). The significant association persists (HR = 1.39; 95% CI [1.13—1.72]) even when adjusting for demographics, APOE e4 carrier status, and AD medication. The use of sleep medication completely eliminated the significant association between sleep disturbance and MCI (HR = 1.14; 95% CI [0.69–1.90]). Among those who did not use sleep medication, the significant association remained when examining the specific effects of zolpidem and trazadone (HR = 1.42; 95% CI [1.14–1.78]). Among users of trazodone, there was no significant association between sleep disturbance and MCI development (HR = 1.31 ; 95% CI [0.54–3.19]). This was also true for users of zolpidem (HR = 1.14; 95% CI [0.60–2.17]). For those who did not use zolpidem or trazadone, the statistically significant association remained (trazodone: HR = 1.37; 95% CI [1.11–1.69]; zolpidem: HR = 1.40; 95% CI [1.13–1.74]). The main effects of sleep disturbance remain

[1]For the analyses of hazard of developing MCI with the variable of interest APOE Ɛ4 status, only models (1), (2) and (4) were used.

significant when adjusting for demographic correlates, APOE, and AD medication in other models.

Table 3 summarizes the independent effect of APOE E4 carrier status on the hazard of developing MCI and how sleep medication mediates this effect. The hazard of MCI was statistically significant and higher among E4 carriers (HR 1.30; 95% CI [1.14–1.50]). The association remained significant even when adjusted for all covariates (HR = 1.60; 95% CI: [1.39–1.84]). This significant association was eliminated for those who used sleep medication (HR = 1.21 ; 95% CI: [0.81–1.80]), a significant trend that persisted even when adjusting for covariates. Among the participants who used trazodone and zolpidem, there was no statistically significant association between APOE e4 and MCI development (trazodone: HR = 1.17; 95% CI [0.59–2.34]; zolpidem: HR = 1.13; 95% CI [0.68–1.88]). However, the association was statistically significant for those who did not take these medications (trazodone: HR = 1.31; 95% CI [1.14–1.51]; zolpidem: HR = 1.32; 95% CI [1.14–1.52]).

3.3. Additive effects for MCI development

Table 4 summarizes a stratified analysis demonstrating the additive effects of sleep disturbance and APOE e4 status on MCI development, as well as how the use of sleep medication mediated the additive effects. There was no statistically significant higher hazard of MCI development among e4 carriers with sleep disturbance (HR = 1.08; 95% CI: 0.71–1.65); this remained insignificant when adjusting for demographics and AD medication (HR = 1.24; 95% CI: [0.81–1.90]). We also observed a lack of significantly different hazards of MCI development among e4 carriers with sleep disturbance, whether or not they used general or specific sleep medication. The non-significant relationship is consistent with models adjusting for demographics and AD medication. However, the unadjusted coefficients for sleep disturbance (HR = 1.32; 95% CI: 1.02–1.72) and APOE e4 status (HR = 1.29; 95% CI: 1.12–1.50) are significant for the analyses with the whole analytic sample. The significant association between APOE e4 status and the hazard of developing MCI persists when we adjust for demographic characteristics and AD medication use (HR = 1.57; 95% Cl: 1.35–1.83). However, the association between APOE e4 status and the hazard of developing MCI becomes insignificant when we adjust those additional covariates. For the subsample analyses on the patients who did not use a general or a specific sleep medication, APOE e4 status and sleep disturbance is associated with hazard of developing MCI that persists in the unadjusted and adjusted models. The association becomes insignificant among sleep medication users, whether or not we adjust for demographic characteristics or AD medication use.

4. Discussion

For this investigation, we hypothesized that sleep disturbance would increase the hazard of MCI, while sleep medications would decrease this hazard. Our findings support the hypotheses. Specifically, the main findings indicate that the hazard of MCI was statistically significant and higher for individuals with sleep disturbance (HR = 1.36; [95% CI 1.11—1.67]), even when adjusting for demographics, APOE e4 carrier status, and AD medication.

These findings are consistent with the previous studies in the field [2,6,9,23,75,76] and affirm the association between sleep disturbance and some level of cognitive decline. The use of general sleep medication (which includes either doxepin, estazolam, temazepam, trazodone, triazolam, zaleplon, or zolpidem) did not produce a significant association between sleep disturbance and an increased hazard of MCI, and the association remained among those who did not use sleep medication. This is also true for specifics type of sleep medication, including trazodone and zolpidem.

The hazard of MCI was increased and statistically significant among e4 carriers (HR 1.30; 95% CI 1.14—1.50), even when adjusting for all covariates (HR = 1.60; 95% CI: 1.39—1.84]). Previous studies suggest that APOE e4 could be a risk factor for development and progression of MCI and AD [38,77—79]. However, the identified association between APOE e4 and MCI in this study was eliminated for those who used sleep medication. When adjusting for covariates the association existed, and the hazard returned to the original rate experienced by e4 carriers. This pattern suggests an unforeseen influence of sociodemographic factors whereby the hazard returned after accounting forage, race/ethnicity, and education. It is possible that some ethnicities/races and individuals with lower educational attainment may be less likely to take sleep medication [80,81]. Therefore, when accounting for race/ethnicity and education, the hazard returned. Supporting our hypotheses, among e4 carriers who used trazodone or zolpidem, there was not a statistically significant risk of MCI, though the hazard persisted for those who did not take these medications. Finally, there was a statistically significant hazard of MCI development among e4 carriers with sleep disturbance, which remained and increased when adjusting for demographics and AD medication. In the additive model, zolpidem use completely eliminated this hazard and trazodone use did not positively affect the statistical hazard of MCI development for e4 carriers with sleep disturbance.

Findings of this study suggest that the use of zolpidem may be effective in mitigating the risk of MCI development because of the relationship between sleep disturbance and MCI/AD. The finding that zolpidem completely eliminated the hazard of MCI is particularly relevant as prior literature indicated wide use of zolpidem in treating sleep disturbance [82–84], and high efficacy for this medication among older adults [85–87]. It is important to note that some adverse effects for zolpidem were reported in literature, specifically among senior populations. For instance, evidence exists that zolpidem may increase the risk of falls, fractures, and injuries among older adults [88–90]. However, insomnia and sleep disturbance independently can also increase the risk of fall and injuries [91]. Furthermore, research indicates that in some patients with comorbidities (eg, stroke, diabetes, and hypertension) an increased accumulative dosage of zolpidem may lead to a higher risk of developing dementia [92], yet evidence is limited to support such association. Additionally, zolpidem has been studied with other possibly inappropriate medications and found to negatively affect cognition in persons with MCI (Weston et al. [93]). This adverse effect could be managed by controlling the type and dosage of prescribed medications.

Similar to zolpidem, trazodone use resulted in a statistically insignificant association between sleep disturbance and hazard of MCI in this study. Results of analyses with subsamples consistently suggest the statistically significant association between sleep

disturbance and an increase hazard of MCI that becomes insignificant among users of general sleep medication, trazodone, and zolpidem. Although it has an antidepressant classification, traza-done has been commonly prescribed and determined efficacious for the treatment of sleep disturbance and insomnia as well as depression in general populations [47,94–96]. However, the medication has been found to be associated with disequilibrium, cardiac events, and an impairment in short-term memory [47,95,97,98]. While rare, these associations are especially notable when considered along with the gap in the literature related to the administration of this medication in populations with MCI [50,51].

4.1. Limitations

Secondary data analysis or analysis of existing data has several limitations such as limitations with respect to the variables that are available for inclusion. In the dataset utilized for this study, sleep disturbance was reported by a knowledgeable informant, creating a risk of bias as co-participants could have overstated or understated the symptoms. Future studies should consider the use of objective measures, such as actigraphy or polysomnography, to assess sleep disturbance to mitigate limitations of self-report and informant provided perspectives and recollections. Moreover, in the NACC dataset, sleep disturbance was a categorical variable which prevented us from characterizing the type of sleep issues. Sleep disturbance may consist of an inability to fall asleep, stay asleep, early morning waking, and frequent and excessive napping among other possibilities; however, limitations of our dataset precluded any analysis on these types of sleep issues. Furthermore, sleep disturbance in this study did not include sleep-disorder breathing or sleep apnea, which is highly prevalent in the adult population [99]. Future studies should employ data collection methods that enable researchers to distinguish between different types of sleep problems, and should consider sleep apnea as one of the important types of sleep issues.

Similar to sleep disturbance, details regarding sleep medication usage (eg, dosing schedule and primary reason for the prescription) were not available or recorded in the utilized dataset. We examined whether or not participants who reported taking sleep medications had a future diagnosis of MCI, though variations in effect may be found if dosing were taken into account. In addition, as reported by Weston and colleagues (2010), individuals taking sleep medications may display symptoms consistent with MCI. The secondary nature of this analysis did not allow the research team to disentangle whether the MCI was due to an ongoing pathophysiological neurodegenerative process, or secondary to sleep medication. However, MCI and AD diagnosis in the dataset was provided by either a consensus team or a neuropsychological expert following the administration of a full battery of instruments designed to detect these problems in aging populations. Moreover, the in-dividual(s) providing the MCI or AD diagnosis had access to the participant record and medication list, which is presumably taken into account and ruled-out.

Concern remains that zolpidem and trazodone may affect cognition or cause cognitive impairment that clinically manifests as MCI. Despite the limitations associated with secondary data analysis, where we were unable to discern whether cognitive impairment was due to ongoing neurodegenerative processes or medication usage, our findings suggest a lack of an association between zolpidem or trazodone use and MCI. This finding would also

exclude the possibility that the secondary symptoms of zolpi-dem and trazodone were masquerading as MCI. Among individuals taking zolpidem or trazodone, there was no appearance of MCI as far as our analyses were able to determine. Therefore, our findings suggest that sleep medication, specifically zolpidem and trazodone, may decrease cognitive decline among individuals experiencing sleep disturbance.

In addition, observations in this study are right-censored, meaning that some participants in our analytic sample may proceed to a diagnosis of MCI, but the event has not happened yet and we were unable to account for the possibility. Similarly, we were unable to retrospectively examine sleep disturbance symptomology of a historical nature, such as if the sleep disturbance occurred before the participant's first observation. As a result, it was difficult to determine the duration of the sleep disturbance. However, our analytic sample was required to have a diagnosis of normal cognition at their first observation, which allowed forward inference to be possible even though causal inference was not feasible.

5. Conclusions and implications

Our findings indicate an association between sleep disturbance and cognitive decline, and a higher MCI hazard among APOE e4 carriers, which has been suggested by previous studies in the field. More notably, our findings provide formative data to inform future studies examining the utilization of trazodone and zolpidem for treatment of sleep disturbance, which may be trialed as a method to mitigate the risk of MCI development even among APOE e4 carriers. Further research is necessary to understand the potential biological mechanisms and/or sociodemographic factors that may have contributed to use of sleep medication and our findings, although the potential effects of trazodone and zolpidem in moderating development of MCI is noteworthy due to the relationship between sleep disturbances and MCI development. Based on this finding, clinicians who prescribe trazadone and zolpidem should consider assessment for symptoms related to MCI. Furthermore, in the spirit of patient empowerment, there are potential opportunities for patients who are prescribed sleep medications to pay attention to MCI symptoms. Finally, given the increasing charge to mitigate MCI and AD development, our findings provide opportunities for researchers, clinicians, and patients to engage in discussions about the effectiveness of sleep medications. For instance, while trazodone and zolpidem can positively impact sleep disturbance in individuals with normal cognition [45,93,100], additional research is needed to support these findings in the context of MCI mitigation among individuals over the age of 65.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary statistics for analytic sample.

		At Visit One —	MCI		Any Sleep Medication		Trazodone		Zolpidem	
			Yes	No	Yes	No	Yes	No	Yes	No
Normal Cognition										
Female		66.25%	62.67%	66.79%	68.03%	66.04%	67.54%	66.20%	69.25%	66.05%
Age		71.62 [9.97]	77.28 [9.11]	70.77 [9.82]	71.63 [9.97]	71.62 [9.98]	71.19 [10.21]	71.64 [9.97]	71.91 [9.68]	71.60 [10.00]
Race	White	81.32%	82.24%	81.18%	90.44%	80.22%	90.67%	80.93%	90.66%	80.67%
	African-American	11.87%	10.97%	12.01%	4.78%	12.73%	6.34%	12.10%	3.87%	12.42%
	Hispanic	4.53%	4.52%	4.53%	3.01%	4.71%	2.24%	4.62%	3.19%	4.62%
	Other	2.28%	2.26%	2.28%	1.78%	2.34%	0.75%	2.34%	2.28%	2.28%
Education	High School	16.92%	19.68%	16.50%	17.90%	16.80%	22.39%	16.69%	16.17%	16.97%
	College	43.75%	48.08%	43.10%	40.57%	44.13%	40.67%	43.87%	39.86%	44.02%
	Beyond College	39.34%	32.24%	40.40%	41.53%	39.07%	36.94%	39.43%	43.96%	39.02%
E4 Carrier		30.54%	35.29%	29.83%	30.19%	30.58%	33.58%	30.41%	30.07%	30.57%
Number of observations		6798	884	5914	732	6066	268	6530	439	6359

Table 2

Cox proportional hazards—main effects for sleep disturbance. Outcome: MCI.

Predictor Variables	Analytic Sample Size	Sleep Disturbance	Sleep Disturbance	Sleep Disturbance	Sleep Disturbance
		Main Effects (Unadjusted)	Main Effects Adjusted[a] w/o E4 Carrier Status	Main Effects Adjusted w/E4 Carrier Status	Main Effects Adjusted w/E4 Carrier Status and AD Medication Use[b]
		Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Whole Analytic Sample	6798	1.36(1.11 — 1.67)***	1.40(1.14—1.73)***	1.43 (1.16—1.76)***	1.39(1.13—1.72)***
Use of sleep medication	732	1.14(0.69—1.90)	1.16(0.69—1.96)	1.17 (0.71—1.95)	1.10(0.65—1.88)
Did not use sleep medication	6066	1.42 (1.14—1.78)***	1.49 (1.19—1.88)***	1.52 (1.21—1.91)***	1.50(1.19—1.89)***
- Trazodone Use	268	1.31 (0.54—3.19)	1.39 (0.58—3.37)	1.28 (0.54—3.04)	1.32 (0.55—3.19)
- No Trazodone Use	6530	1.37 (1.11 — 1.69)***	1.40(1.13—1.74)***	1.44 (1.16—1.78)***	1.42 (1.14—1.76)***
- Zolpidem use	439	1.14(0.60—2.17)	1.13 (0.58—2.19)	1.15 (0.59—2.21)	1.06 (0.55—2.04)
- No Zolpidem use	6359	1.40(1.13—1.74)***	1.47 (1.18—1.83)***	1.49 (1.20—1.85)***	1.45 (1.16—1.81)***

*** $p < 0.01$,

** $p < 0.05$,

* $p < 0.1$.

[a] Adjusted for sex, age, education, race, and Hispanic origin.

[b] Adjusted for sex, age, education, race, Hispanic origin, and AD medication use.

Table 3

Cox proportional hazards—main effects for e4 carrier status. Outcome: MCI.

Predictor Variables	Analytic sample size	$_{E4}$ Carrier Main Effects (Unadjusted) Hazard Ratio (95% CI)	$_{E4}$ Carrier Main Effects Adjusted[a] Hazard Ratio (95% CI)	$_{E4}$ Carrier Main Effects Adjusted[b] w/AD Medication use Hazard Ratio (95% CI)
Whole Analytic Sample	6798	1.30(1.14-1.50) ***	1.62 (1.41–1.87) ***	1.60(1.39–1.84) ***
Use of sleep medication	732	1.21 (0.81–1.80)	1.52 (1.02–2.28) **	1.44 (0.95–2.16)
Did not use sleep medication	6066	1.32 (1.14-1.52) ***	1.64 (1.41–1.91) ***	1.63 (1.40–1.90) ***
- Trazodone Use	268	1.17 (0.59-2.34)	1.56 (0.77–3.15)	1.62 (0.76–3.48)
- No Trazodone Use	6530	1.31 (1.14-1.51) ***	1.63 (1.41–1.89) ***	1.62 (1.40–1.87 ***
- Zolpidem use	439	1.13 (0.68-1.88)	1.46 (0.86–2.50)	1.30 (0.76–2.22)
- No Zolpidem use	6359	1.32 (1.14-1.52) ***	1.63 (1.41–1.89) ***	1.62 (1.39–1.88) ***

*** p < 0.01,

** p < 0.05,

* p < 0.1.

[a] Adjusted for sex, age, education, race, and Hispanic origin.

[b] Adjusted for sex, age, education, race, Hispanic origin, and AD medication use.

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Table 4

Cox proportional hazards—additive effects for sleep disturbance x e4 carrier status. Outcome: MCI.

Predictor Variables	Analytic Sample Size		Main Effects (Unadjusted)	Main Effects Adjusted[a]	Main Effects Adjusted w/AD Medication use[b]
			Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Whole Analytic Sample	6,798	Sleep Disturbance × E4 Carrier	1.08 (0.71–1.65)	1.26 (0.83–1.93)	1.24 (0.81–1.90)
		Sleep Disturbance	1.32 **(1.02–1.72)	1.32 **(1.01–1.72)	1.29 *(0.99–1.69)
		E4 Carrier	1.29 ***(1.12–1.50)	1.59 ***(1.37–1.85)	1.57 ***(1.35–1.83)
Use of sleep medication	732	Sleep Disturbance × E4 Carrier	2.48 (0.89–6.94)	2.40 (0.87–6.63)	2.25 (0.79–6.47)
		Sleep Disturbance	0.82 (0.42–1.62)	0.84 (0.41–1.72)	0.81 (0.39–1.68)
		E4 Carrier	1.03 (0.66-1.60)	1.29 (0.82–2.04)	1.24 (0.79–1.96)
Did not use sleep medication	6,066	Sleep Disturbance × E4 Carrier	0.91 (0.57–1.44)	1.07 (0.67–1.71)	1.11 (0.69–1.78)
		Sleep Disturbance	1.47 ***(1.11–1.94)	1.48 ***(1.11–1.98)	1.45 **(1.08–1.94)
		E4 Carrier	1.33 ***(1.14-1.55)	1.64 ***(1.40–1.92)	1.62 ***(1.38–1.91)
Trazodone Use	268	Sleep Disturbance × E4 Carrier	6.84 (0.67–69.59)	5.57 (0.50–62.58)	5.66 (0.51–63.58)
		Sleep Disturbance	0.39 (0.05–2.96)	0.43 (0.05–3.61)	0.44 (0.05–3.73)
		E4 Carrier	0.83 (0.37–1.88)	1.13 (0.49–2.63)	1.17 (0.49–2.81)
No Trazodone Use	6,530	Sleep Disturbance × E4 Carrier	0.99 (0.64–1.54)	1.17 (0.75–1.83)	1.20 (0.77–1.86)
		Sleep Disturbance	1.38 **(1.06–1.79)	1.37 **(1.05–1.79)	1.34 **(1.02–1.76)
		E4 Carrier	1.32 ***(1.13–1.53)	1.62 ***(1.39–1.89)	1.60 ***(1.37–1.87)
Zolpidem use	439	Sleep Disturbance × E4 Carrier	1.45 (0.35–5.98)	1.52 (0.39–5.98)	1.47 (0.35–6.13)
		Sleep Disturbance	1.03 (0.48–2.22)	1.01 (0.44–2.30)	0.94 (0.40–2.19)
		E4 Carrier	1.07 (0.62–1.85)	1.37 (0.77–2.45)	1.22 (0.68–2.20)
No Zolpidem use	6,359	Sleep Disturbance × E4 Carrier	1.05 (0.68–1.63)	1.20 (0.77–1.87)	1.18 (0.75–1.86)
		Sleep Disturbance	1.37 **(1.04–1.81)	1.40 **(1.05–1.85)	1.37 **(1.03–1.82)
		E4 Carrier	1.31 ***(1.12–1.52)	1.61 ***(1.38–1.88)	1.59 ***(1.36–1.87)

*** p < 0.01,

** p < 0.05,

* $p < 0.1$.

[a] Adjusted for sex, age, education, race, and Hispanic origin.

[b] Adjusted for sex, age, education, race, Hispanic origin, and AD medication use.