Published in final edited form as:

J Aging Health. 2019 February ; 31(2): 322–342. doi:10.1177/0898264318795567.

Treatment of Sleep Disturbance May Reduce the Risk of Future Probable Alzheimer's Disease

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Abstract

Objective: This study explored two research questions: (a) Does sleep medication neutralize or provide a protective effect against the hazard of Alzheimer's disease (AD)? (b) Do apolipoprotein (APOE) e4 carriers reporting a sleep disturbance experience an increased risk of AD?

Method: This study is a secondary analysis of the National Alzheimer's Coordinating Center's Uniform Data Set (n = 6,782) using Cox proportional hazards regression.

Results: Sleep disturbance was significantly associated with eventual AD development. Among the subset of participants taking general sleep medications, no relationship between sleep disturbance and eventual AD was observed. Among individuals not taking sleep medications, the increased hazard between the two variables remained. Among APOE e4 carriers, sleep disturbance and AD were significant, except among those taking zolpidem.

Discussion: Our findings support the emerging link between sleep disturbance and AD. Our findings also suggest a continued need to elucidate the mechanisms that offer protective factors against AD development.

Keywords

sleep disturbance; insomnia; trazodone; zolpidem; Alzheimer's disease; apolipoprotein E

Alzheimer's disease dementia (AD) is characterized by irreversible memory loss and declined cognitive functioning (Bekris, Yu, Bird, & Tsuang, 2010). An estimated 5.7 million Americans are currently diagnosed with AD, and this number is expected to double by 2050 (Alzheimer's Association, 2018). Sleep disturbances, which may encompass difficulties with

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

sleep initiation, sleep maintenance, frequent and excessive napping, and unrefreshing sleep, tend to be one of the earliest symptoms identified in the development of neurodegenerative disorders (Abbott & Videnovic, 2016) such as AD. In fact, studies have indicated that up to 50% of individuals with AD experience some type of sleep disturbance (Cipriani, Lucetti, Danti, & Nuti, 2015; Moran et al., 2005; Pistacchi, Gioulis, Contin, Sanson, & Marsala, 2014; Urrestarazu & Iriarte, 2016). While prevalence estimates in the general population vary, approximately 10% to 20% of adults have insomnia disorder (Morin, LeBlanc, Daley, Gregoire, & Mérette, 2006; Morin et al., 2011; Ohayon, 2002; Roth, McCall, & Liguori, 2011) and 10% have a general sleep disturbance (Ferrie, Kumari, Salo, Singh-Manoux, & Kivimäki, 2011). Reports of sleep disturbance increase with age (Centers for Disease Control and Prevention, 2015) and the prevalence of prescription sleep medication use has shown a relative increase with age as well. Sleep medication usage has been reported in 6% of 50- to 60-year-olds, and 7% of adults older than the age of 80 (Chong, Fryar, & Gu, 2013).

AD has been associated with the dysfunction of neurotransmitter systems responsible for sleep (da Silva, 2015) including the cholingeric system, which includes memory and the sleep–wake cycle (Sarter & Bruno, 1997). Neurodegenerative impairment of cholingeric pathways can also affect the ascending reticular activating system, thereby contributing to daytime sleepiness and sleep disturbance (da Silva, 2015). Sleep disturbance and chronic insomnia may contribute to increased amyloid-beta production and aggregation (J. E. Kang et al., 2009), while excessive sleep during nontraditional hours has been associated with AD progression (Benito-León, Bermejo-Pareja, Vega, & Louis, 2009).

Apolipoprotein (APOE) e4 has been associated with higher levels of rapid eye movement (REM) sleep disruption and sleep disturbance (Mander, 2013), particularly in those with known cognitive decline (Gozal, Capdevila, Kheirandish-Gozal, & Crabtree, 2007; Mander, 2008). The APOE e4 allele is considered a major risk factor for AD (Mander, 2008). Individuals with APOE e4 (e4 carriers) have abnormal metabolic patterns within regions of the brain that are susceptible to AD prior to the experience of memory loss. Memory loss in these individuals may begin as early as late middle age (Mander, 2008). Reportedly, 20% of individuals in North America and Europe are e4 carriers (Mander, 2008).

Sleep disturbances can lead to declines in cognitive performance (Alhola & Polo-Kantola, 2007), immune function (Besedovsky, Lange, & Born, 2012), diabetes (Anothaisintawee, Reutrakul, Van Cauter, & Thakkinstian, 2016), cardiovascular disease (Sofi et al., 2014), and depression (Faulkner & Bee, 2016; Furihata et al., 2017; Hungin & Close, 2010). Approximately, 75% of individuals with depression experience sleep disturbance as a primary depressive symptom (Nutt, Wilson, & Paterson, 2008). Likewise, sleep disturbances can be a predictor or a symptom of depression (Al-Abri, 2015). Subsequent treatment of depressive symptoms can inadvertently exacerbate sleep disturbance; antidepressant medications act to increase serotonin in the brain while REM sleep, which is dependent upon decreased serotonin production, is disrupted (Adrien, 2002). As a result, it is now well-known that the relationship between sleep disturbance and depression is bidirectional. Similarly, the relationship between sleep disturbance, depression, and AD may operate in a bidirectional manner. Sleep disturbance and depression have also been found to be both

prodromal and comorbid AD symptoms (Burke, Maramaldi, Cadet, & Kukull, 2016a). Furthermore, there is evidence in the literature supporting the association between the presence of APOE e4, sleep disturbance, subsequent memory loss, and AD progression (Burke et al., 2016a; Burke, Maramaldi, Cadet, & Kukull, 2016b; Drogos et al., 2016). Evidence indicates that e4 carriers who also experience ongoing sleep disturbance are 4 times more likely to develop AD as non-e4 carriers; however, e4 carriers without sleep disturbance were only twice as likely to develop AD (Holtzman, 2013).

Contemporary treatment of the symptoms of sleep disturbance includes behavioral change strategies and pharmacological interventions. *Trazodone*, a sedating antidepressant, is classified as a serotonin antagonist and reuptake inhibitor (SARI; Fagiolini, Comandini, Dell'Osso, & Kasper, 2012). While historically used as an antidepressant, studies have shown that the off-label utilization of trazodone at lower doses has a modulating effect on serotonin inhibitors (with 10 mg dosage affecting ~50% of serotonin receptors), thereby aiding in sleep (Lie, Tu, Shen, & Wong, 2015). Side effects of trazodone include drowsiness, dizziness, weight gain (Deschenes & McCurry, 2009), and hypotension (Fagiolini et al., 2012). Furthermore, there has been trepidation in the literature related to the use of trazodone in older adults due to limited literature on efficacy in this population (Deschenes & McCurry, 2009; McCall, 2004).

Zolpidem is a nonbenzodiazepine hypnotic (Lie et al., 2015), which is often prescribed for sleep disturbance. Zolpidem has validated reduced residual hypnotic effects (D. J. Kang et al., 2012), and efficacy within older adult patients with diabetes and hypertension (Cotroneo, Gareri, Lacava, & Cabodi, 2004). Zolpidem has also been designated a potentially inappropriate medication (PIM) for use in older adult populations and has been associated with an almost double risk for fractures in older adults. While not altering retrograde memory, zolpidem has been associated with side effects, including nightmares, agitation, and dizziness (Lie et al., 2015).

Based on our previous research (Burke et al., 2016a, 2016b), indicating an increased hazard of probable AD development among individuals with sleep disturbance, we asked the following research questions:

> **Research Question 1:** Does sleep medication neutralize or provide a protective effect against the hazard of AD?
>
> **Research Question 2:** Do APOE e4 carriers reporting a sleep disturbance experience an increased risk of AD compared with e4 carriers without a sleep disturbance?

We hypothesized that sleep disturbance increases the hazard of AD, and the strength of this relationship is increased among APOE e4 carriers with sleep disturbance. While our analyses of sleep medication use are exploratory, we hypothesized that sleep medications affect the hazard of AD development.

Method

To study whether sleep medication effects the risk of developing probable AD for individuals with sleep disturbance and/or APOE e4 carriers, data from the National

Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) were analyzed. The NACC UDS has been previously described in the literature (Beekly et al., 2004). Briefly, the NACC is a repository for data collection at 35 Alzheimer's Disease Centers (ADCs) across the United States. Participants voluntarily present to one of the ADCs for annual observations, including a full battery of memory and nonmemory neuropsychological tests and, in most cases, neuroimaging. Participants can also elect to participate in additional study aims by providing blood, cerebrospinal fluid, and other specimens for genotyping and analysis. All participants are required to attend visits with an informant who knows him or her well. Participants with normal cognition at baseline (n = 6,782) were included in the current study. The main outcome was the first diagnosis of probable AD. Probable AD is defined as dementia where there has been an insidious onset of symptoms, definitively reported or observed cognitive decline, and either amnestic or nonamnestic cognitive deficit manifestation (McKhann et al., 2011).

The presence of sleep disturbance at baseline (the first visit) was measured by the Neuropsychiatric Inventory Questionnaire (Cummings et al., 1994). 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?" An additional question in the data collection instrument asks if the participant has sleep apnea. We attempted to disentangle sleep apnea from insomnia, sleep interruption, shortened sleep duration, and excessive daytime napping, but a large amount of missingness (97%) renders the sleep apnea data unreliable. Of those who reported sleep disturbance, only seven participants also reported 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 records all medications taken within the last 2 weeks of the baseline (or follow-up) visit. The specific sleep medications examined in the study include (a) a general category of all sleep medications (includes doxepin, estazolam, temazepam, trazodone, triazolam, zaleplon, and zolpidem), (b) zolpidem, and (c) trazodone. Trazodone and zolpidem are 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 AD.

APOE genotype is determined independently by the ADC, using either a buccal swab or blood draw. All six possible genotypes are reported to NACC, though for the purposes of this study we have only included whether the participant was an APOE e4 carrier (one or two e4 alleles).

Descriptive analyses were examined for individual characteristics at baseline (first visit) for the total sample, by eventual probable AD, and/or use of sleep medications (Table 1). Survival analysis was used to test the two hypotheses: that using sleep medication effects the hazard of developing probable AD for those with sleep disturbance and/or APOE e4. The enter time was defined as participant's first visit to NACC and time length was measured in years. The analytic sample is censored as the true survival time is unknown for those who did not develop probable AD by the last visit. All binary variables had binary (yes/no) response options. Covariates included age, sex, race/ethnicity, and education. The data

contain observations from 2005 through 2016, though the number of observations varies by participant.

The Cox proportional hazard model (Cox, 1972) was used for the survival analysis. To examine the independent effect of sleep disturbance and APOE e4, stepwise regression was utilized to isolate the variable of interest and determine its effect in the model. To examine the additive effect of these two factors, an interaction term consisting of (a) sleep disturbance at baseline and (b) APOE e4 carrier status was included in the regression as the key variables of interest. Four models were used to examine the research question: (a) unadjusted regression models with only the key variable of interest: either sleep disturbance, APOE e4, or the interaction between sleep disturbance and APOE e4; (b) adjusted regression models with age, sex, race/ethnicity groups, and education level; (c) adjusted regression models with abovementioned covariates, and APOE e4 status; and (d) adjusted regression models with all previous covariates plus the inclusion of the use of antidementia medications. These regression models were repeated for the overall sample, the sample who used sleep medication (the general category, zolpidem, and trazodone), and the sample who did not use sleep medication. Subgroup analyses were conducted to more thoroughly investigate the effect of sleep disturbance and e4 carrier status on AD development for participants taking sleep medications or those who did not. We examined these as two subgroups taking sleep medications separately. Without stratifying the analyses, we would receive a hazard ratio (HR) that indicates the relationship between sleep disturbance and/or e4 carrier and AD, but we wanted to see the independent effect of both taking the medication and not taking, which is why the analysis is stratified. Given the specific interest in the subgroup analysis, and based on previous literature, subgroup hypotheses and the direction of the subgroup effect was specified a priori. The subgroup analyses were completed prior to an interaction test to further examine subgroup findings (Kasenda et al., 2014; Sun, Briel, Walter, & Guyatt, 2010). As supplemental analyses, moderation effects of sleep medication on the association between sleep disturbance and probable AD were examined by including the interaction between sleep medication and sleep disturbance as the key variable of interest in the survival analyses. We also performed moderation analyses for each individual sleep medication by including the interaction between sleep disturbance and trazodone, and zolpidem, respectively, in the analyses. The stepwise regressions were also performed for the supplemental analyses (see Table 5). STATA/MP 14.1 (StataCorp., 2015) was utilized for the analyses, and a p value < .05 was considered statistically significant.

Results

The minimum amount of time under observation was 326 days until the first occasion that the AD diagnosis occurred, with a maximum of 3,389 days (M = 1,577.41, Mdn = 1,500.50, SD = 754.77). There were 208 participants diagnosed with probable AD by the end of the observation period among those who had an initial visit and at least one follow-up visit (n = 6,782). The descriptive summary statistics for participants are summarized in Table 1. The mean age of participants with normal cognition at Visit 1 was 71.60 (SD = 9.97, Mdn = 72). At Visit 1, 66.30% of the sample were female, 81.33% of the sample identified as White, 11.86% were Black/African American, 2.29% were from other ethnic groups, and 4.53% identified as Hispanic. About 44% of the sample were college graduates, some (39.40%) had

education beyond college, and a few (16.83%) had high school or lower education. APOE e4 carriers comprised 30.56% of the sample.

The Kaplan–Meier plot of survival curves for those with and without sleep disturbance probable AD were visually inspected (not shown). Of participants with normal cognition at the first visit, there were 653 individuals who indicated they were taking the general category of sleep medications, 238 taking trazodone, and 387 others taking zolpidem. There were 691 participants who reported a sleep disturbance at their first visit (see full sample breakdown in supplemental Table 1). The estimated coefficients and 95% confidence intervals (CIs) for the independent main effect of sleep disturbance on the hazard of developing probable AD were summarized in Table 2. The hazard of developing probable AD was statistically greater (HR = 1.76, 95% CI = [1.19, 2.61], $p < .01$) for participants with sleep disturbance, and it remained significant even when sequentially adjusted for demographic covariates, APOE e4 genotype, and AD medication. This relationship was completely eliminated when sleep medications were taken; there was no longer a statistically significant relationship between sleep medication and probable AD (row 2). When sleep medication is not taken, the increased hazard remains (row 3). Among users of trazodone, unadjusted models show a non-significant relationship between sleep disturbance and probable AD. When adjusted for APOE e4 and AD medication, there is a reduced hazard of probable AD among those with sleep disturbance, suggesting a protective effect (HR = 0.25, 95% CI = [0.07, 0.92)], $p < .001$). For participants not taking trazodone, the significant hazard between sleep disturbance and AD remained (HR = 1.98, 95% CI = [1.29, 3.03], $p < .01$). Interestingly, among those taking zolpidem, an increased hazard of probable AD was found (HR = 3.56, 95% C = [1.02, 12.46]), though the statistically significant effect dissipated completely when adjusted for demographics, e4 carrier status, and AD medications (HR = 3.56, 95% CI = [0.71, 17.8).

Table 3 summarizes the main effect of APOE e4 carrier status and the hazard of developing probable AD. APOE e4 carriers experienced a statistically significant higher hazard of probable AD (HR = 1.92, 95% CI = [1.46, 2.53], $p < .0001$) and this effect is further increased when adjusted (HR = 2.73, 95% CI = [2.06, 3.63], $p < .0001$). Among trazodone users, e4 carriers substantially increased their hazard of probable AD (HR = 9.08, 95% CI = [2.64, 31.30]) over non-e4 carriers, even when AD medications were also prescribed. This effect was reduced among nontrazodone users (HR = 2.51, 95% CI = [1.86, 3.38]). The e4 carriers using zolpidem did not have a statistically significant higher hazard of probable AD (HR = 2.39, 95% CI = [0.69, 8.21]) than non-e4 carriers using zolpidem, whereas e4 carriers not using the medication demonstrated a significantly higher hazard of AD (HR = 1.90, 95% CI = [1.44, 2.52], $p < .001$), suggesting a mechanism influenced by zolpidem that favorably interacts with e4 to decrease the hazard of AD.

Table 4 summarizes the additive interaction effects between sleep disturbance and APOE e4 status on AD development and how the use of sleep medication mediates the interaction effect. We found that the significant interaction effect was eliminated in the general medication group (HR = 2.40, 95% CI = [0.49, 11.7]) when the models accounted for the use of demographics and AD medication. The users of trazodone did not have a significant interaction effect, though the interaction was significant for those who did not use trazodone

(HR = 3.10, 95% CI = [1.75, 5.50], $p < .001$), reinforcing the favorable effects demonstrated in earlier analyses (Tables 2 and 3). Users of zolpidem experienced an escalating interaction effect in the adjusted models, culminating with a higher hazard of probable AD (HR = 12.00, 95% CI = [2.28, 63.40], $p < .001$), though the CI suggests this effect should be tested in a larger sample.

The results of supplemental multiplicative interaction analyses were summarized in Table 5. The hazard ratios for the coefficient of the interaction between sleep disturbance and trazodone were significantly reduced when demographics and e4 carrier status were adjusted (HR = 0.29, 95% CI = [0.09, 0.93], $p < .05$) and when demographics, e4 carrier status, and AD medication use were adjusted (HR = 0.22, 95% CI = [0.06, 0.086], $p < .05$). This indicated that, among those who used trazodone, having sleep disturbance is associated with much lower hazard of developing probable AD. Statistically significant interactions were not found between sleep disturbance and the general medication category nor with the use of Zolpidem.

Discussion

This study sought to explore whether sleep disturbance increases the hazard of AD development and whether this relationship is stronger among APOE e4 carriers reporting a sleep disturbance. Once the relationship between sleep disturbance and AD was established, we also explored whether sleep medications decreased the hazard of AD and whether sleep medication will decrease the hazard of AD among APOE e4 carriers with sleep disturbance.

Our first hypothesis, that sleep disturbance increases the hazard of AD, was fully supported, given the statistically significant hazard posed by sleep disturbance in all adjusted and unadjusted models. We expected this relationship due to our previous work in this area, which demonstrated a significant hazard when examining sleep disturbance as a risk factor for subsequent AD (HR = 2.72, 95% CI = [2.11, 3.50], $p < .01$; blinded, 2016). Furthermore, this finding suggests that because of the increasing numbers of individuals diagnosed with AD, assessing and diagnosing sleep disturbance is even more critical.

We expected that the relationship between sleep disturbance and AD would be stronger among APOE e4 carriers. Instead, the hazard of AD among e4 carriers with sleep disturbance was roughly the same as the hazard when e4 carrier status was not taken into account. Among APOE e4 carriers, a statistically significant hazard of probable AD only increased when adjusted. This finding is consistent with existing literature that has indicated that the APOE e4 allele is present in 65% to 80% of all AD cases (Huang, 2011). Currently, the prevalence of sleep disturbance among APOE e4 carriers is unknown and these results indicate a need for further research.

Our main study findings indicate that there is a statistically significant relationship between the presence of sleep disturbance and probable AD, and this remains exactly the same when adjusted for APOE e4 carrier status, demographic covariates, and AD medication. Among the subset of participants who took sleep medication (general category), no statistically significant relationship between sleep disturbance and eventual AD was observed. Among

the subset of participants who did not take sleep medication (general category), results indicated that sleep disturbance is associated with a statistically significant greater hazard of probable AD.

Although this study is unable to establish a causal relationship between lack of sleep and AD risk, or sleep medication use and a decrease in AD risk, theoretical frameworks have begun to emerge that situate these findings in a possible explanatory framework. Researchers have long thought that a deficit in clearance systems in the brain may be partially contributing to the continued deposition of amyloid-beta peptides (Aβ) without removal or clearance from the brain. While Aβ can be cleared across the blood–brain barrier and blood–cerebrospinal fluid barrier (Iliff et al., 2012), the efficiency of this system declines with age (Pascale et al., 2011). The glymphatic system, the mechanism by which extracellular proteins are circulated throughout and subsequently cleared from the brain, is important because the interstitial space is increased during sleep (Xie et al., 2013). Both sleep (without medication) and anesthesia were found to increase interstitial space in the brain by 60% in rats (Xie et al., 2013). During the sleep cycle, there is a convective flow or exchange between interstitial fluid, which contains extracellular proteins such as Aβ, and the cerebrospinal fluid (Xie et al., 2013). The current study can use previous work concerning the glymphatic system to hypothesize as to why the association between sleep disturbance and AD risk is eliminated when sleep medication is introduced. Given existing frameworks, this risk may decrease due to the activation and subsequent clearance of Aβ that occurs in the brain while sleeping. If a medication induces sleep, and treats the hazard posed by sleep deficits, then perhaps the mechanism through which this occurs is the clearance of Aβ provided by the glymphatic system. Further studies are needed to explore the hypothesis that if sleep disturbance is effectively treated, the risk of AD may decrease among individuals with sleep disorders.

Using the glymphatic system to connect sleep disturbance and AD risk and development leads to an assumption that the treatment of sleep disturbance diminishes AD risk. Although logical at the surface, many clinicians call into question the efficacy of sleep medications. Though it is possible that drugs, such as trazodone and zolpidem, exert a physiological effect even if the intended symptomology is not adequately addressed, the current literature base has consistently found that zolpidem is effective in increasing sleep duration and decreasing waking from sleep (Roehrs & Roth, 2015). A recent study examining low-dose zolpidem use in cognitive intact men and women older than the age of 80, found adverse symptoms in only 6% of users. The most common adverse effects involved balance and/or falls (1.8%) and morning drowsiness (1.3%; Kajiwara et al., 2016). Given that zolpidem is a nonbenzodiazepine receptor modulator, it is considered safer than benzodiazepine administration in older adults and has a considerably shorter half-life (2 hr).

Similarly, a recent meta-analysis of randomized placebo-controlled trials of trazodone indicated that trazodone was associated with a decrease in sleep fragmentation, improved sleep quality, and was tolerable for short-term use (Yi et al., 2018). In our study, trazodone was found to eliminate the significant association between sleep disturbance and AD even among e4 carriers (additive effects model). Although the original data collection tool did not ask the participants whether or not the sleep medication actually treated their sleep problem, further studies should examine the mechanism by which trazodone, an antidepressant that is

very effective in treating insomnia, may also decrease neurodegenerative risk or influence the associated pathophysiological process.

While this study uses a population deemed to be free of cognitive impairment at baseline and examines the effect of sleep medication on AD, other studies have examined the use of trazodone, zolpidem, and temazepam in populations already diagnosed with mild cognitive impairment and AD (Weston, Weinstein, Barton, & Yaffe, 2010). Clinicians and prescribers have expressed concern that these medications will negatively affect cognition among patients already showing signs of cognitive impairment or cause cognitive impairment that clinically manifests as a dementia spectrum disorder. It is difficult to separate, at times, whether these effects are due to age-related cognitive impairment or the medication use specifically. Existing evidence in the literature has indicated that antidepressant medications (SARIs) can exacerbate sleep disruption through an increased production of serotonin during REM sleep cycles (Adrien, 2002). In this study, among e4 carrying users of trazadone (a common SARI), the usage of trazadone increased probable AD compared with e4 carriers not taking trazadone. Furthermore, the introduction of AD medication reduced the hazard of AD in e4 carriers using traza-done, suggesting a protective factor. The hazard remained for e4 carriers with sleep disturbance who did not use trazodone in the additive model.

Users of zolpidem in the current study experienced an escalating hazard of probable AD, culminating with a high hazard of probable AD in the adjusted model. This is consistent with prior research, where zolpidem has been shown to affect central nervous system functioning, confusion, and lead to cognitive impairment (D. J. Kang et al., 2012; Kolla, Lovely, Mansukhani, & Morgenthaler, 2013; Shih et al., 2015; Wang, Bohn, Glynn, Mogun, & Avorn, 2001). Despite the increased hazard of probable AD found among those taking zolpidem, the introduction of AD medication dissipated the statistical significance of AD hazard. This provides evidence for the efficacy of the AD medications described and their ability to counteract the reversible dementia-related effect of the zolpidem in older adults, which has been described in previous literature (Shih et al., 2015). APOE e4 carriers using zolpidem did not have a statistically significant hazard of probable AD, compared with those who used the medication, suggesting that there is some mechanism in zolpidem that favorably interacts with APOE e4. This requires further investigation, however, as this relationship was no longer true when demographic and AD medication covariates were accounted for in the statistical models.

Limitations and Strengths

Given that this study was a secondary data analysis, limitations exist with respect to the variables that were available for inclusion. For instance, sleep disturbance, as measured in this study, is a subjective self-reported categorical variable that does not allow researchers to specify the type of sleep issue but does exclude REM sleep disorder, given that this is accounted for in the NACC UDS. While we attempted to disentangle sleep apnea from insomnia, sleep interruption, shortened sleep duration, and excessive daytime napping, a large amount of missingness (97%) renders the sleep apnea data unreliable. Of those who reported sleep disturbance, only seven individuals also reported sleep apnea. Although a limitation, our analysis would not change if we eliminated the seven individuals with sleep

apnea as this small subsample would not have a discernable effect. Future studies should employ more objective data collection methods that enable researchers to specify types of sleep issues with measures such as polysomnographs or actigraphy (Peterson et al., 2012; Marino et al., 2013). A second limitation is that medications were reported to researchers as a list. Additional details, such as dosing and primary reason for the prescription, were not recorded. We examined whether or not participants who reported taking these medications had a future diagnosis of AD, though variations in effect of the medications may be found if dosing and cumulative use were able to be taken into account. A third limitation is that the Cox regression analyses for medication groups were underpowered due to the small percentage of AD cases in the medication group, which may have especially affected the interaction analyses displayed in Table 5. Observations in this study are right censored. Thus, individuals included in our analytic sample may have eventually proceeded to a diagnosis of AD but because the event occurred after data capture, we are unable to account for this possibility in our analyses. Similarly, we are unable to retrospectively examine symptomology of a historical nature prior to the participant's first observation. Thus, it is difficult to ascertain the extent of reported sleep disturbances and medication usage. To attempt to disentangle cognitive impairment risk and development, our analytic sample had a diagnosis of normal cognition at their first observation. While causal inference is not possible, given the limitations of the data set, the research team modified the analytic strategy to attempt forward inference. Finally, the NACC UDS data are not intended to be a nationally representative sample and are comprised of a primarily White and highly educated population. Given that UDS recruitment methods vary by ADC and over time, UDS participants are best described as a clinical case series of patients from each ADC. As such, this is a limitation in the data and the results should be interpreted in light of these considerations.

Conclusion

This study demonstrated a significant relationship between sleep disturbance and probable AD. As hypothesized, in most cases, the relationship between sleep disturbance and AD was no longer significant among individuals who reported to take sleep medications. In the absence of sleep medication use, the increased hazard of AD remained. Among APOE e4 carriers, this was only true for those taking zolpidem in unadjusted models, a finding that spurs additional questions and a need for further research. Additive models affirmed the substantially increased hazard of AD when e4 carriers with sleep disturbance take zolpidem. Future studies should procure a larger sample of individuals prescribed zolpidem and controls to further address this line of inquiry. In addition, in cases where sleep medication was associated with a decreased hazard of AD development, researchers should explore the exact physiological mechanism by which this may occur. For instance, given that zolpidem is a nonbenzodiazepine receptor modulator, researchers should explore the effect of $GABA_A$ receptor subunit selectivity and the pharmacokinetic profile on differing endpoints, beyond insomnia, to explore the ways in which this drug influences the neurodegenerative process. Previous literature has suggested that changes in the molecular composition of the $GABA_A$ receptor may be associated with the process of aging (Rissman & Mobley, 2011). In addition, significant consideration should be given to the interaction between medications.

Areas of the brain vulnerable to neurodegeneration (e.g., hippocampus, cortex, thalamus, amygdala) have shown to be vulnerable to receptor modification and affinity during the coadministration of zolpidem and other medications (Poisnel, Dhilly, Le Boisselier, Barre, & Debruyne, 2009). Given that zolpidem was associated with a significant hazard of AD among users and nonusers, except users who also took AD medication, further exploration with neurodegenerative endpoints is essential.

This study contributes to the literature examining the relationship between sleep medication and AD. Sleep disturbance is a common condition for which patients often seek treatment through medications and counseling. These treatments, while not specifically designed to treat AD, may have the indirect effect of both increasing and decreasing risk of the observable effects of neurodegeneration. Understanding modifiable risk factors for AD continues to be critical area of research. Future studies should aim to further clarify and explore the link between sleep issues and AD, with a specific focus on understanding the mechanistic role medications may play in decreasing the risk of AD while treating sleep disturbance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Table 1.

Descriptive Summary Statistics.

			Dermentia		Any sleep medication (general category)		Trazodone		Zolpidem	
		At Visit 1	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Normal cognition										
Female		66.30%	68.75%	66.22%	68.04%	66.09%	67.42%	66.25%	69.41%	66.08%
Age		71.60 [9.97]	79.88 [7.28]	71.34 [9.93]	71.59 [9.97]	71.61 [9.97]	71.13 [10.19]	71.62 [9.96]	71.89 [9.68]	71.58 [9.99]
Race	White	81.33%	88.46%	81.10%	90.40%	80.23%	90.64%	80.95%	90.64%	80.68%
	African American	11.86%	6.73%	12.02%	4.80%	12.71%	6.37%	12.08%	3.88%	12.41%
	Hispanic	4.53%	4.33%	4.53%	3.02%	4.71%	2.25%	4.62%	3.20%	4.62%
	Other	2.29%	0.48%	2.34%	1.78%	2.35%	0.75%	2.35%	2.28%	2.29%
Education	High school	16.83%	28.85%	16.45%	17.70%	16.72%	22.10%	16.61%	15.98%	16.89%
	College	43.78%	43.75%	43.78%	40.60%	44.16%	40.82%	43.90%	39.95%	44.04%
	Beyond college	39.40%	27.40%	39.77%	41.70%	39.12%	37.08%	39.49%	44.06%	39.07%
e4 carrier		30.56%	44.71%	30.11%	30.32%	30.59%	33.71%	30.43%	30.14%	30.59%
Number of observations		6,782	208	6,572	729	6,051	267	6,513	438	6,342

Table 2.

Cox Proportional Hazards—Main Effects for Sleep Disturbance: Outcome: Probable AD.

	Sleep disturbance	Sleep disturbance	Sleep disturbance	Sleep disturbance
	Main effects (unadjusted)	Main effects adjusted[a] for demographics	Main effects adjusted with demographics and e4 carrier status	Main effects adjusted with demographics, e4 carrier status, and AD medication use[b]
Predictor variables	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**
Sleep disturbance	1.76 [1.19,2.61] ***	1.80 [1.21, 2.69] ***	1.90 [1.28,2.81] ***	1.76 [1.17, 2.65] ***
Use of sleep Medication (general)	1.32 [0.54, 3.22]	1.38 [0.54,3.53]	1.33 [0.55,3.24]	0.87 [0.29, 2.63]
Did not use sleep medication	1.85 [1.19,2.87] ***	1.91 [1.21,3.01] ***	2.02 [1.29, 3.16] ***	1.93 [1.21, 3.06] ***
Trazodone use	0.71 [0.17, 2.96]	0.80 [0.22, 2.89]	0.32 [0.13,0.81] **	0.25 [0.07, 0.92] **
No trazodone use	1.88 [1.25,2.83] ***	1.91 [1.26,2.91] ***	2.05 [1.35,3.11] ***	1.98 [1.29, 3.03] ***
Zolpidem use	3.56 [1.02, 12.5] **	3.43 [0.88, 13.4]	3.81 [0.99, 14.7]	3.56 [0.71, 17.8]
No zolpidem use	1.69 [I.I 1,2.58] **	1.76 [1.15,2.71] ***	1.84 [1.21, 2.79] ***	1.70 [1.10,2.64] **

Note. AD = Alzheimer's disease; CI = confidence interval.

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

[b]Adjusted for sex, age, education, race, Hispanic origin, and AD medication use. *$p < .1$.

**$p < .05$.

***$p < .01$.

Table 3.

Cox Proportional Hazards—Main Effects for e4 Carrier Status: Outcome: Probable AD.

	e4 carrier	e4 carrier	e4 carrier
	Main effects (unadjusted)	Main effects adjusted[a] with demographics	Main effects adjusted[b] with demographics and AD medication use
Predictor variables	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**
e4 Carrier	1.92 [1.46,2.53]***	2.77 [2.09, 3.68]***	2.73 [2.06, 3.63]***
Use of sleep Medication (general)	2.66 [1.33,5.31]***	4.28 [1.99,9.18]***	3.74 [1.69,8.25]***
Did not use sleep medication	1.81 [1.34,2.44]***	2.59 [1.91, 3.51]***	2.57 [1.89, 3.50]***
Trazodone use	3.34 [1.39,8.02]***	10.2 [3.27, 31.6]***	9.08 [2.64, 31.3]***
No trazodone use	1.79 [1.34,2.39]***	2.53 [1.88,3.40]***	2.51 [1.86,3.38]***
Zolpidem use	2.39 [0.69,8.21]	2.92 [0.84, 10.1]	3.06 [0.95, 9.87]
No zolpidem use	1.90 [1.44, 2.52]***	2.73 [2.05, 3.65]***	2.71 [2.02,3.63]***

Note. AD = Alzheimer's disease; CI = confidence interval.

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

[b]Adjusted for sex, age, education, race, Hispanic origin, and AD medication use. *$p < .1$. **$p < .05$.

***$p < .01$.

Table 4.

Cox Proportional Hazards—Additive Effects for Sleep Disturbance × e4 Carrier Status: Outcome: Probable AD.

	Sleep disturbance × e4 carrier(unadjusted)	Sleep disturbance × e4 carrier adjusted[a] with demographics	Sleep disturbance × e4 carrier adjusted[b] with demographics and AD medication use
	Hazard ratio (95% Cl)	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**
Sleep disturbance × e4 carrier	3.02 [1.77,5.13]***	4.83 [2.90, 8.03]***	4.38 [2.54, 7.55]***
Use of sleep medication (general)	3.57 [1.26, 10.1]**	4.61 [1.76, 12.1]***	2.40 [0.49, 11.7]
Did not use sleep medication	2.80 [1.51, 5.20]***	4.80 [2.58, 8.92]***	4.70 [2.50, 8.85]***
Trazodone use	1.64 [0.41, 6.65]	1.64 [0.60,4.46]	0.79 [0.15,4.11]
No trazodone use	3.10 [1.75, 5.50]***	5.11 [2.88,9.05]***	5.03 [2.81,9.03]***
Zolpidem use	6.43 [1.39,29.7]**	7.82 [1.56, 39.1]**	12.0 [2.28,63.4]***
No zolpidem use	2.81 [1.59,4.95]***	4.54 [2.64, 7.78]***	4.16 [2.34,7.39]***

Note. AD = Alzheimer's disease; CI = confidence interval.

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

[b]Adjusted for sex, age, education, race, Hispanic origin, and AD medication use. *$p < .1$.

**$p < .05$.

***$p < .01$.

Table 5.

Cox Proportional Hazards—Interaction Effects for Sleep Disturbance × Sleep Medication Outcome: Probable AD.

	Sleep disturbance	Sleep disturbance	Sleep disturbance	Sleep disturbance
	Main effects (unadjusted)	Main effects Adjusted[a] for demographics	Main effects adjusted with demographics and e4 carrier status	Main effects adjusted with demographics, e4 carrier status, and AD medication use[b]
Predictor variables	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**	**Hazard ratio (95% Cl)**
Sleep disturbance × Sleep medication (general)	0.72 [0.26, .95]	0.67 [0.24, 1.90]	0.63 [0.24, 1.69]	0.58 [0.21, 1.59]
Use of sleep Medication (general)	1.35 [0.89,2.04]	1.37 [0.90, 2.09]	1.38 [0.91, 2.09]	1.38 [0.91,2.09]
Sleep disturbance	1.84 [1.19,2.86] ***	1.90 [1.21, 2.99] ***	2.04 [1.30, 3.19] ***	1.93 [1.21,3.08] ***
Sleep disturbance × Trazodone	0.38 [0.09, 1.68]	0.42 [0.1 1, 1.64]	0.29 [0.09, 0.93] **	0.22 [0.06, 0.86] **
Use of trazodone	2.76 [1.71, 4.46] ***	2.70 [1.66,4.38] ***	2.72 [1.71, 4.33] ***	2.67 [1.70,4.21] ***
Sleep disturbance	1.88 [1.25,2.83] ***	1.92 [1.26,2.92] ***	2.08 [1.37, 3.15] ***	1.98 [1.29,3.05] ***
Sleep disturbance × Zolpidem	2.19 [0.56,8.53]	1.98 [0.48,8.26]	2.11 [0.51,8.67]	2.24 [0.55, 9.20]
Use of zolpidem	0.47 [0.21, 1.05]	0.46 [0.20, 1.05]	0.47 [0.21, 1.07]	0.48 [0.21, 1.09]
Sleep disturbance	1.69 [I.I 1,2.57] **	1.75 [1.14,2.69] ***	1.83 [1.21, 2.77] ***	1.68 [1.08,2.61] **

Note. AD = Alzheimer's disease; CI = confidence interval.

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

[b]Adjusted for sex, age, education, race, Hispanic origin, and AD medication use. *$p < .1$.

**$p < .05$.

***$p < .01$.