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Self-Reported Sleep Apnea and Dementia Risk: Findings from the Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADViSE) Alzheimer's Disease Prevention Trial

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Abstract

Background—Sleep apnea is a common condition and has a direct impact on cognitive function. The impact of sleep apnea, and its interplay with other established risk factors on the risk of incident dementia, warrants exploration.

Objectives—To investigate the association between baseline sleep apnea and risk of incident dementia in the Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADViSE) study and explore whether the association depends on *APOE* ε4 allele status.

Design—Secondary analysis based on data collected during PREADViSE.

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Author contributions: X. Ding contributed to the design of the current study, performed the analyses, and drafted and revised the manuscript. R. Kryscio contributed to the design of PREADViSE and revised the manuscript. J. Turner contributed to the design of the study, collected data, and revised the manuscript. G. Jicha evaluated participants for dementia and revised the manuscript. G. Cooper evaluated participants for dementia and revised the manuscript. A. Caban-Holt contributed to the design of PREADViSE and revised the manuscript. F. Schmitt contributed to the design of PREADViSE, evaluated participants for dementia, and revised the manuscript. E. Abner contributed to the design of the study, supervised the analyses, and drafted and revised the manuscript.

Sponsor's role: NCI was involved in the design of SELECT. Otherwise, the sponsors had no role in the design and conduct of the current study; in the collection, analysis, and interpretation of data; in the preparation of the manuscript; or in the review or approval of the manuscript.

Setting—Participants were assessed at 128 local clinical study sites during the clinical trial phase and later were followed by telephone from a centralized location.

Participants—7,547 male subjects were enrolled in PREADViSE.

Measurements—Participants were interviewed at baseline for sleep apnea. The Memory Impairment Screen (MIS) was administered to each participant annually. Subjects who failed to this initial screen were tested with secondary screening tests. Additional measures collected include medical history, medication use, and the AD8 dementia screening instrument.

Results—The effect of self-reported sleep apnea on dementia risk depended on *APOE* ε4 status. When the allele was absent, baseline self-reported sleep apnea was associated with a 66% higher risk of developing dementia (95% CI 2%–170%), while self-reported sleep apnea conferred no additional risk for participants with an ε4 allele.

Conclusion—Sleep apnea may increase risk of dementia in the absence of *APOE* ε4. This may help inform prevention strategies for dementia or AD in older men with sleep apnea.

Registration—PREADViSE is registered at ClinicalTrials.gov: NCT00040378.

Keywords

self-reported sleep apnea; dementia; *APOE*

INTRODUCTION

Dementia is a syndrome that affects memory, thinking, behavior and ability to perform everyday activities. In 2010, Wimo and colleagues estimated global dementia prevalence at 35.6 million people, and this number is expected to double by 2030 and more than triple by 2050. Moreover, estimated annual costs of dementia reached $604 billion (U.S. dollars) in 2010[1, 2]. With rising prevalence, these costs are expected to increase by 85% by 2030, which would make dementia the most expensive chronic disease associated with aging.

Sleep apnea is a common age-associated type of sleep disordered breathing (SDB), with clinical symptoms including loud snoring, breathing pauses such as choking or gasping during sleep, morning headaches, insomnia, and daytime sleepiness [3–5]. Sleep apnea and risks associated with it, such as obesity, are becoming an increasingly important public health issues for adults [3, 4, 6–9]. The prevalence of sleep apnea varies by age and sex and is more common in older adults and men [4, 10, 11]. It is estimated to be present in 20 to 50% of older adults [4]. For people aged 50–70 years old, 17% of men and 9% of women are estimated to have moderate-to-severe SDB [12].

Sleep apnea is associated with cognitive impairment and dementia in older populations [13, 14]; however, the relationship between pre-existing sleep apnea and incident cognitive impairment and dementia remains poorly characterized. Many existing studies are limited by cross-sectional study designs, small sample size, or short follow-up time [15, 16]. Three cross-sectional studies in populations aged over 65 years found no association between the apnea-hypopnea index and cognitive function [17–19]. By contrast, in a prospective study of 298 women, Yaffe et al. [20] found that SDB was associated with a 71% increased risk of

developing mild cognitive impairment (MCI) or dementia over 5 years after adjusting for age, race, body mass index, education level, smoking status, presence of diabetes, and hypertension. A retrospective population-based study also showed increased risk of developing dementia for a Taiwanese population aged over 40 years who participated in a national health insurance program [21]. Sleep apnea patients had a 170% increase in dementia risk compared with patients without sleep apnea after adjustment for age, sex, hypertension, diabetes, stroke, and hyperlipidemia during the 5-year follow-up period [21]. Finally, an eight-year study of older adults found only small effects of SDB on decline in attention, but not memory, once other medical comorbidities were included in their statistical models[14].

However, these cohort studies were unable to consider the effect of the genetic risk factor, *APOE* [22], on risk of dementia. Since *APOE* is a major unmodifiable risk factor for dementia due to Alzheimer's disease (AD), the most common form of dementia, it is important to understand whether sleep apnea or SDB might differentially influence the risk of dementia based on the status of *APOE* genotype. To our knowledge, only three studies have explored this association. O'Hara et al. conducted a small cross-sectional study (n=36) and found that SDB was only associated with impairment of verbal memory in *APOE* ε4 allele carriers [23], while Osorio and colleagues (n=95) found only a trend toward lower CSF Aβ-42 levels in *APOE* ε4 positive normal older adults with SDB [6]. A second study by Osorio and colleagues based on the Alzheimer's disease Neuroimaging Initiative database (n=2,285) found that SDB was associated with younger age at onset of MCI, and this was not affected by *APOE* ε4 carrier status [24]. Additional studies are needed to investigate this topic.

Using Prevention of Alzheimer's Disease (AD) by Vitamin E and Selenium (PREADViSE) trial data, which comprises 7,547 male subjects who were free from dementia at baseline, we sought to investigate two research hypotheses: (1) older men with self-reported sleep apnea prior to cognitive impairment have an increased risk of dementia, and (2) older men with self-reported sleep apnea have different risks for dementia based on *APOE* allele status.

METHODS

Study population and data sources

We conducted a secondary analysis of sleep apnea and incident dementia among 7,547 subjects enrolled in the PREADViSE trial [25]. The PREADViSE trial is an ancillary study to the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (a large prostate cancer prevention randomized controlled trial (RCT)) [26] and was designed to evaluate the effectiveness of antioxidant supplements vitamin E and selenium in preventing incident AD and other forms of dementia. PREADViSE investigators were blind to SELECT treatment assignment as of this writing, and so the effects of the antioxidant supplements will not be considered further here. During the recruiting period from 2002 to 2009, PREADViSE enrolled 7,547 non-demented male participants age 62 years and older (age 60 if African American) from 128 participating SELECT clinical sites in the US, Canada, and Puerto Rico. The eligibility criteria for participating in PREADViSE included active SELECT enrollment at a participating site and absence of dementia and other active neurologic

conditions that affect cognition such as major psychiatric disorder, including depression. All 7,547 participants are included in the current study; no further inclusion and/or exclusion criteria were applied for this secondary analysis.

The study supplements in SELECT were discontinued by its Data Safety Monitoring Committee in 2008 following a futility analysis [27]; PREADViSE and SELECT then continued as observational exposure cohort studies. The details of this evolution for PREADViSE can be found in Kryscio et al. [28]. All participants were asked to continue in the exposure study, and 4,271 of 7,547 original PREADViSE volunteers consented to participation (Figure 1). PREADViSE was approved by the University of Kentucky Institutional Review Board (IRB) as well as the IRBs at each SELECT study site. Each participant provided written informed consent. During the RCT phase, SELECT sites used a web-based data collection system to submit data directly to the Cancer Research and Biostatistics Group, who managed the data for SELECT. SELECT provided monthly snapshots of PREADViSE data elements to PREADViSE via a secure file transfer protocol (ftp) site. During the observational phase, data were collected at a single site, the University of Kentucky.

Case Ascertainment

The Memory Impairment Screen (MIS) [29] was used as the primary screening instrument for dementia in both the RCT and observational portions of PREADViSE. The MIS was given annually. If participants failed the MIS (that is, the participant scored 5 or less out of 8 on either the immediate or delayed recall portion of the MIS), a second tier screen was administered. An expanded Consortium to Establish a Registry in AD battery (CERAD-e) [30] was used during the RCT period and the modified Telephone Interview for Cognitive Status (TICS-m) [31], was used during the observational study. Both the CERAD-e and the TICS-m assessed participants' global cognitive function. Failure on the secondary screen (T score ≤ 35 on CERAD-e battery or total score ≤ 35 on TICS-m) would lead to a recommendation for a clinic visit with their local physician. Records from the clinic visit were reviewed by 3–5 expert clinicians, including two neurologists and at least one neuropsychologist, for a consensus diagnosis. In cases where the neurologists disagreed in their diagnoses, the study PI made the final determination. Annual screenings were completed in May 2014, and a small number of participants were followed for medical records through August 2015.

The incident dementia cases were identified through two methods. First, as described above, a medical records-based consensus diagnosis was used. Date of diagnosis was assigned as the date of the failed screen. Second, because many participants were reluctant to obtain medical workups for their memory, additional longitudinal measures including the AD8 Dementia Screening Interview [32], self-reported medical history, self-reported diagnosis of dementia, use of memory enhancing prescription drug, and cognitive scores including the MIS, CERAD-e T Score, NYU Paragraph Delayed Recall, and TICS-m were used to identify cases. The diagnostic criteria for the second method were AD8 total of ≥ 1 (at any time during follow-up) to indicate functional impairment [32] plus one of the following: a self-reported diagnosis of dementia, use of a memory enhancing prescription drug

(donepezil, rivastigmine, galantamine, or memantine), or cognitive score below cutoffs for intact cognition on any test (for example: 1.5 SDs below expected performance based on age and education normative data[3]. The date of diagnosis was assigned to the earliest event.

Sleep Apnea

All participants were asked during the baseline PREADViSE interview whether they had ever been treated for sleep apnea. Responses were recorded as “yes” or “no.”

APOE genotype

APOE ε4 positivity is a major risk factor for AD-type dementia [4]. *APOE* genotype was obtained for 7,180 participants (ε2/2: 51 (0.71%); ε2/3: 879 (12.24%); ε2/4: 190 (2.65%); ε3/3: 4,320 (60.17%); ε3/4: 1,599(22.17%); ε4/4: 141(1.96%)). The genotypes were converted to a dummy indicator for at least one ε4 allele, where the presence of at least one ε4 allele was considered a carrier. SAS 9.4® procedure PROC MI was used to impute missing values for the indicator variable (367/7547 (5%)) based on family history of dementia. Four imputed data sets were generated; participants with two or more positive imputations for *APOE* ε4 were coded as *APOE* ε4 positive.

Other Covariates

Other data collected included age at baseline, race, body mass index (BMI), years of education, as well as self-reported indicators of cardiovascular disease (i.e., diabetes, hypertension, and smoking). These are recognized risk factors for dementia [5]. History of significant cognitive or motor impairment due to stroke was a PREADViSE exclusion criterion so baseline prevalence of stroke in the cohort is extremely low (0.6%), thus stroke was not considered further.

Statistical analysis

Chi-square and *t* test statistics were used to examine differences in categorical and continuous variables between sleep apnea groups. The log-rank test was used to assess differences in crude cumulative risk of dementia between sleep apnea groups. A series of Cox proportional hazards regression models with self-reported sleep apnea as the independent variable, survival time to diagnosis of dementia as the dependent variable, and the covariates listed above were applied to simple and multivariable survival analyses, where follow-up time was defined as the period in years between date of PREADViSE study entry and date of dementia diagnosis or, in the absence of dementia, date of last assessment. The multivariable model included main effects for baseline age, years of education, body mass index (BMI), race (black vs. non-black), *APOE* (presence of *APOE* ε4 or absence of *APOE* ε4), smoking (yes vs. no), self-reported baseline status of diabetes and hypertension (coded present or absent). Covariates were fixed at baseline. The proportional hazards assumption was tested by checking the interaction between time and each covariate. Interaction terms between history of sleep apnea and each covariate in the model were also tested. None of the interactions were significant. Given the sufficient sample size in each *APOE* group (n = 2029 and 5518 in *APOE* ε4 positive group and negative group, respectively), we also evaluated the effect of sleep apnea on risk of dementia stratified by *APOE* ε4 to evaluate for

effect modification between sleep apnea and *APOE*. All data were analyzed by using SAS 9.4® (SAS Institute, Inc., Cary, NC), and 0.05 was set as the significance level.

RESULTS

Demographic attributes of participants from PREADViSE are shown in Table 1. Briefly, 7.3% (552/7547) of the men reported history of sleep apnea at baseline. The absolute difference in baseline age between men with and without sleep apnea was significant but not large (Table 1). Men with history of sleep apnea at baseline were significantly more likely to be of black race ($p = 0.02$), smokers ($p<0.001$), have higher BMI ($p < 0.001$), and were more likely to report hypertension ($p<0.001$) and diabetes ($p<0.001$). No significant differences were observed in educational attainment or proportion of *APOE* ε4 carriers.

A total of 310 (4.1%) men were diagnosed with dementia (4.0% for men without sleep apnea, 5.1% for men with history of sleep apnea, respectively; $p = 0.24$). The cumulative incidence accounting for censoring during follow-up was estimated to be 9.3% in the non-sleep apnea group and 24.4% in sleep apnea group (Figure 2). However, this difference was not significant due to the relatively small number of dementia cases in the sleep apnea group ($p = 0.14$ by the log-rank test).

Table 2 displays hazard ratios for dementia diagnosis from adjusted Cox models. History of sleep apnea was borderline significant in the adjusted model (HR = 1.44; 95% CI 0.96 – 2.17, $p = 0.08$). In this adjusted analysis, men with sleep apnea were more likely to develop dementia compared to men without sleep apnea. Black race, *APOE* ε4 carrier status, and baseline age were significantly associated with dementia risk. Interaction terms between sleep apnea and each covariate in the model were tested, but none were significant.

Stratified analyses by status of *APOE* ε4 were conducted, and results are shown in Table 2. For men without an *APOE* ε4 allele, history of sleep apnea conferred a 66% (95% CI 2%–170%) higher risk of developing dementia (Figure 3a). Sleep apnea had no effect when the *APOE* ε4 allele was present (Figure 3b).

DISCUSSION

In this study, self-reported baseline history of sleep apnea was borderline significantly associated with risk of dementia after adjustment for confounding ($p = 0.08$). Stratified analysis by *APOE* ε4 carrier status showed that baseline history of sleep apnea was associated with significantly increased risk of dementia in non-carriers. For the latter, self-reported sleep apnea was estimated to confer a 66% higher risk to develop dementia ($p = 0.0423$). Age, race, and *APOE* were significantly associated with the risk of dementia in the multivariable Cox model. We did not find any significant associations for years of education, smoking, BMI, presence of diabetes, or hypertension in either the primary or the stratified analyses with the exception of smoking, which significantly increased risk for *APOE* ε4 carriers. None of the two-way interactions between self-reported sleep apnea and other covariates were significant, including *APOE* ε4, which was likely due to a lack of sufficient statistical power to detect the interaction despite the difference in the stratified analysis.

There are very few prospective studies that have investigated the association between sleep apnea and risk of dementia in an older adult male population. We did not find clear evidence that history of sleep apnea, prior to cognitive impairment, was associated with dementia in men overall, which is similar to the findings reported in Osorio's recent study [24] and several other cross-sectional studies [17–19]. However, our results did show that sleep apnea is significantly associated with dementia risk for men who were *APOE* ε4 allele non-carriers. This is contradictory to the finding of one small cross-sectional study [23], which found that the association existed only for *APOE* ε4 allele carriers, but similar to Osorio et al.'s study [6], in which CSF amyloid beta 42 and tau were not associated with sleep apnea in *APOE* ε4 allele carriers but were associated in noncarriers [6]. Such discrepancies are likely the result of differences in exposure and outcome assessment, residual confounding, covariates adjusted for, sample size, study population, or study design.

Similar to other studies [6, 23], our results indicated an interaction effect of sleep apnea and *APOE* ε4 on the risk developing dementia. This is particularly important considering both the high prevalence of sleep apnea in older populations [4] and the high percentage of *APOE* ε4 non-carriers in the population (~75%) [33]. So far, several prevention trials [14, 33] have been completed with null or inconclusive results. Since the *APOE* ε4 allele is a well-known and non-modifiable risk factor for AD, the findings of this study may help inform prevention strategies for dementia or AD in older men with sleep apnea. Osorio and colleagues [32] suggest that treatment with continuous positive airway pressure (CPAP) may delay onset of MCI. It is of course important that all patients with sleep apnea are diagnosed and treated, but diagnosis and treatment of sleep apnea may be especially helpful in preventing or delaying incident cognitive impairment in the aging male population with SDB who are *APOE* ε4 non-carriers.

Possible mechanisms that could explain the association of sleep apnea with risk of incident cognitive decline and dementia include direct effects on cerebral oxygenation and the selective vulnerability of hippocampal neurons to hypoxia, or perhaps augmentation of vascular contributions that have been strongly linked to the development of MCI, AD, and other forms of dementia [20, 35]. Chronic hypoxia has been linked to hippocampal injury that may lower the threshold for the development and or spread of tau-associated neurodegeneration [36]. The development of sleep apnea has also been shown to exacerbate cardiovascular risk factors such as hypertension, and to be strongly associated with obesity, insulin resistance, hyperlipidemia, and the development of the metabolic syndrome [29, 37]. Thus, there may be many ways that sleep apnea contributes to derangements in metabolic pathways that have been strongly associated with increased risk of incident MCI or dementia in the aging population. Indeed, the present data demonstrate increased prevalence of hypertension and diabetes in those with sleep apnea, although the association with *APOE* status appeared independent of such conditions in the adjusted analysis, suggesting that other mechanistic factors may be important to consider.

Another possible mechanism for the association of sleep apnea and risk of dementia is that sleep may help regulate brain amyloid-β levels [38, 39]. A recent study in transgenic mice demonstrated that levels of brain amyloid-β increased when both normal and AD mouse models were awake and then decreased during sleep [40]. This diurnal variation in amyloid

production could be dramatically altered in persons with sleep apnea or other sleep disturbances [41]. A small study [42] of community-based older adults was able to demonstrate that shorter sleep duration was significantly associated with increased amyloid-β levels. There is also some evidence that *APOE* might play a role in degradation of amyloid-β [3]. *APOE* ε4 carriers show lower concentration of amyloid-β in the cerebrospinal fluid, indicating increased amyloid-β deposition in the brain [6]. In the presence of *APOE* ε4, any increase in brain amyloid-β associated with sleep apnea may be overwhelmed by that due to *APOE* ε4 alone. However, it remains unclear why amyloid-β is affected by the sleep cycle or how it depends on the *APOE* genotype. [44]

This study has some limitations. Not all participants who failed the memory screenings were willing to visit their doctors for a memory work-up, so case ascertainment may be less accurate due to lack of medical records. However, application of the secondary dementia criteria (positive AD8 screen, self-reported diagnosis, use of memory enhancing drug, and poor cognitive scores) demonstrated good agreement in the cases where the diagnosis was known (data not shown). Because only a subset of subjects participated in both the RCT as well as the exposure phases of PREADViSE, some cases may have been missed among the subjects who did not participate in the exposure study. Our data show there were 46.2% participants who had sleep apnea at baseline and did not continue to participate in the study, while 50.1% subjects without sleep apnea in the baseline cohort did not continue. Therefore, the loss of cases would be estimated to be the same for the subjects with and without sleep apnea. We measured sleep apnea with self-report, similar to Osorio et al. [24]. Due to the phrasing of the questionnaire, undiagnosed and or untreated sleep apnea subjects may have been missed [45]. However, because ascertainment of sleep apnea occurred at baseline, it is independent of dementia ascertainment. Therefore, if there is misclassification of sleep apnea exposure, it is non-differential misclassification, and will bias the association toward the null [44], that is, to lessen the degree of association. Thus, our analysis likely underestimates the effect of sleep apnea on dementia risk. Since the study population is all older men, the findings from this study cannot be generalized to older women. However, the current findings align quite well with those reported by Yaffe and colleagues who showed an increased risk for dementia with SDB in older women [20]. Strengths for the study include the large sample and long follow-up. We were also able to consider most well established risk factors for dementia including demographic, genetic, and medical characteristics, including cardiovascular risk factors.

CONCLUSION

Our study provides evidence that in the absence of *APOE* ε4, sleep apnea may increase the risk of dementia in older men. This may occur through the disruption of brain amyloid-β regulation that occurs during the sleep cycle, or through cerebrovascular damage, although the exact mechanism remains unclear [43]. Considering the limited number of publications in this area and the inconsistent findings, replication studies with objective measures of sleep apnea, long follow-up, and rigorous methods to diagnose dementia are needed to support this finding conclusively.

From the standpoint of clinical practice, many primary care physicians are unaware of their patients' genetic status and *APOE* genotype in particular. However, with adequate screening of SDB symptoms along with other risk factors (e.g., age, ethnicity) our findings along with those of O'Hara et al. [23] and Yaffe et al. [20] we would advise the clinician to work with all their patients to address sleep apnea problems as soon as possible given the association with future cognitive dysfunction.

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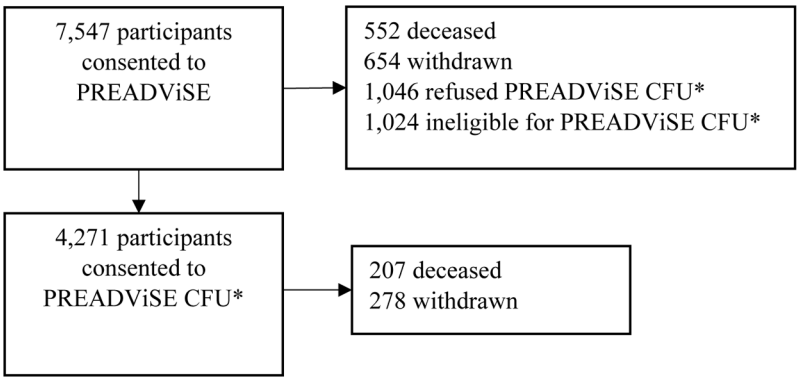


Figure 1.

Participant flow diagram for PREADViSE

*PREADViSE was an ancillary study to SELECT; enrollment was from May 2002 through November 2009 (N=7,547). PREADViSE participants were invited to participate in centralized follow-up (PREADViSE CFU) following the closure of SELECT due to a futility analysis. Some SELECT sites decided not to offer their participants the opportunity to participate in CFU; these participants are listed above as being ineligible. PREADViSE CFU continued to follow participants from August 2010 – August 2015.

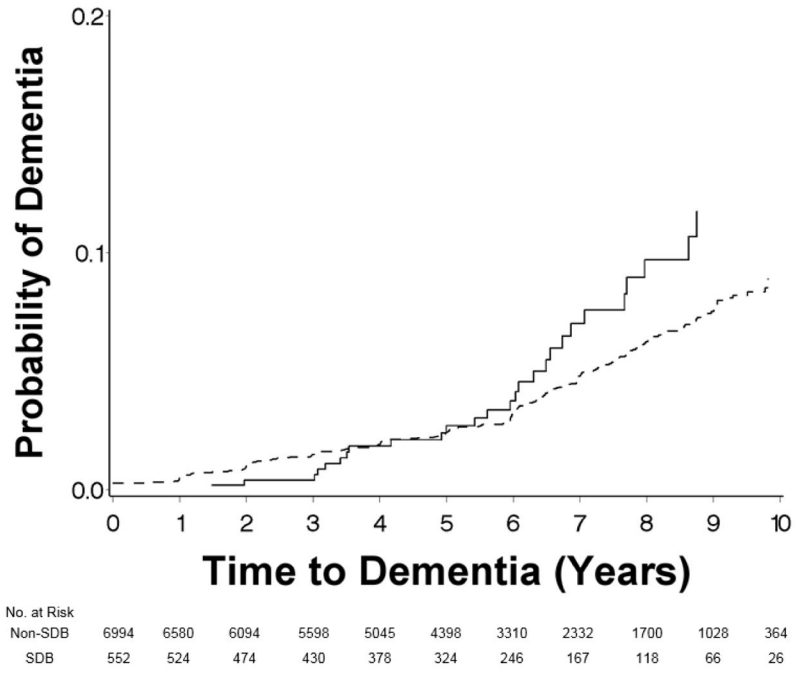
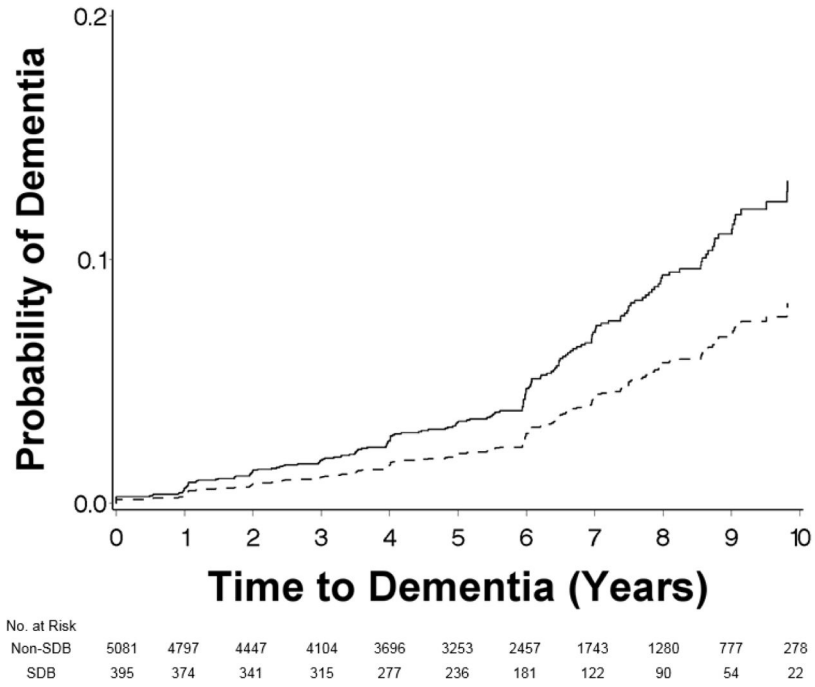
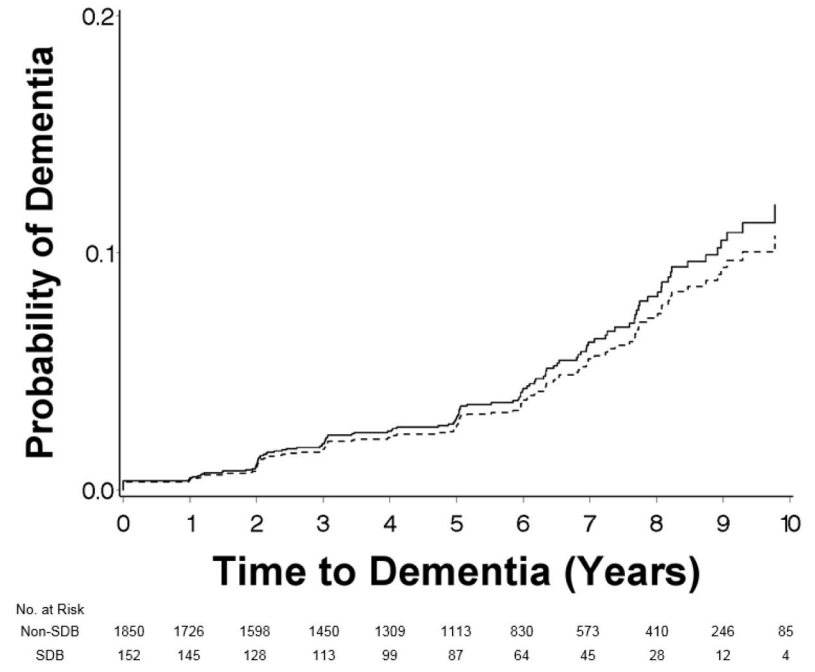


Figure 2.

Probability of dementia by history of sleep apnea (SDB) at baseline. Solid line indicates sleep apnea, dashed line indicates no sleep apnea. Time axis ends at 10 years for consistency among figures.



(a)



(b)

Figure 3.

Figure 3a & 3b. Probability of dementia at baseline by history of sleep apnea (SDB) status after adjusting other covariates in *APOE* ε4 non-carriers (a) and carriers (b). These hypothetical participants are white, age 68 at baseline, smoke, have 15 years of education and baseline BMI 28.5 kg/m^2, and comorbidities including presence of hypertension and diabetes. Solid line indicates sleep apnea, dashed line indicates no sleep apnea. Time axis ends at 10 years for consistency among figures.

Table 1

General Characteristics of the Study Population in PREADViSE

Characteristic	All Subjects (N=7,547)	No Sleep Apnea (n=6,995)	Sleep Apnea (n=552)	P value
Baseline age[a], y, mean±SD	67.5±5.3	67.6±5.3	66.6±4.5	< 0.001
Education[c], y, mean±SD	15.0±2.7	14.9±2.7	15.1±2.6	NS[b]
Black race	756 (10.0)	685 (9.8)	71 (12.9)	0.02
Baseline smoking[d]	4260 (56.6)	3916 (56.1)	344 (62.4)	0.004
APOE-ε4 (≥1 ε4)	2,029 (26.9)	1876 (26.8)	153 (27.7)	NS[b]
Baseline hypertension	2,998 (39.7)	2703 (38.6)	295 (53.4)	<0.001
Baseline diabetes	858 (11.4)	762 (10.9)	96 (17.4)	<0.001
Baseline BMI[ef], kg/m^2, mean±SD	28.5±4.4	28.2±4.2	31.6±5.3	<0.001
Follow-up time, y, mean±SD	5.7±2.8	5.7±2.8	5.5±2.8	NS[b]

[a] N = 7546 for age;

[b] NS: Not significant;

[c] N = 7,512 for education;

[d] N = 7528 for smoking;

[e] BMI: Body Mass Index;

[f] N = 7515 for BMI.

Note: Results presented are mean±SD or N (%). All PREADViSE participants are male.

Table 2

Association between History of Sleep Apnea and Risk of Dementia based on Adjusted Cox Model and Stratified Analysis by APOE ε4 Status

		Stratified Analysis Adjusted HR[b] (95% CI)	
	Adjusted HR[b] (95% CI)	**APOE ε4 carriers (N = 2,029)**	**APOE ε4 non-carriers**
Sleep apnea	1.44 (0.96–2.17)	1.13 (0.54–2.37)	**1.66 (1.02–2.70)**
Baseline age, 1 year	**1.11 (1.09–1.13)**	**1.14 (1.10–1.17)**	**1.09 (1.07–1.12)**
Education, 1 year	0.98(0.94–1.02)	1.01 (0.94–1.08)	0.95 (0.91–1.01)
Black race	**1.73 (1.19–2.52)**	1.71 (0.97–3.03)	**1.72 (1.05–2.82)**
Baseline smoking	1.20 (0.95–1.51)	**1.55 (1.06–2.26)**	1.03 (0.77–1.38)
APOE ε4 carrier	**1.99 (1.58–2.50)**	--	--
Baseline HTN[c]	0.92 (0.73–1.17)	0.83 (0.56–1.21)	0.98 (0.72–1.33)
Baseline diabetes	1.10 (0.78–1.57)	0.83 (0.43–1.58)	1.29 (0.85–1.97)
BMI[d], 1 kg/m^2	0.99 (0.97–1.02)	1.00 (0.95–1.04)	0.99 (0.96–1.03)

[a] All variables listed in the table were included in the adjusted models.

[b] HR: Hazard Ratio;

[c] HTN = hypertension;

[d] BMI = body mass index.