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Sleep Modifies the Relation of *APOE* to the Risk of Alzheimer Disease and Neurofibrillary Tangle Pathology

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Abstract

IMPORTANCE—The Apolipoprotein E (*APOE*) ε4 allele is a common and well-established genetic risk factor for Alzheimer Disease (AD). Sleep consolidation is also associated with AD

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Authors' Contributions:

Dr. Lim has responsibility for the integrity of the work as a whole. He conceived of the study hypotheses and design, analyzed and interpreted the data, carried out statistical analysis, drafted the manuscript, and approved the final manuscript. He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Yu contributed to the analysis of the data, performed statistical analysis, revised the article critically for important intellectual content, and approved the final manuscript. Dr. Kowgier contributed to the analysis of the data, performed statistical analysis, revised the article critically for important intellectual content, and approved the final manuscript. Dr. Schneider obtained funding, contributed to the study design, oversaw acquisition, analysis, and interpretation of the neuropathological data, revised the article critically for important intellectual content, provided administrative, technical, or material support, provided supervision, and approved the final manuscript. Dr. Buchman obtained funding, contributed to the study conception and design, oversaw data acquisition, contributed to data interpretation, revised the article critically for important intellectual content, provided administrative, technical, or material support, provided supervision, and approved the final manuscript. Dr. Bennett has responsibility for the integrity of the work as a whole. He obtained funding, contributed to the study conception and design, oversaw data acquisition, contributed to data interpretation, provided administrative, technical, or material support, provided supervision, revised the article critically for important intellectual content, and approved the final manuscript.

Conflicts of Interest and Disclosures:

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risk and previous work suggests that *APOE* genotype and sleep may interact to influence cognitive function.

OBJECTIVE—To determine whether better sleep consolidation attenuates the relation of the *APOE* genotype to the risk of incident AD and the burden of AD pathology.

DESIGN—Prospective longitudinal cohort study with up to 6 years of follow-up.

SETTING—Community-based.

PARTICIPANTS—We studied a volunteer sample of 698 community dwelling older adults without dementia (average age 81.7 years; 77% female) in the Rush Memory and Aging Project followed for up to 6 years.

EXPOSURES—We used up to 10 days of actigraphic recording to quantify the degree of sleep consolidation, and ascertained *APOE* genotype.

MAIN OUTCOME MEASURES—Subjects underwent annual evaluation for AD over a follow-up period of up to 6 years. Autopsies were performed on 201 deceased participants, and Aβ and neurofibrillary tangle (NFT) pathology were identified by immunohistochemistry and quantified.

RESULTS—Over a follow-up period, 98 individuals developed AD. In a series of Cox proportional hazards models, better sleep consolidation attenuated the effect of the ε4 allele on the risk of incident AD (HR 0.67 95%CI 0.46–0.97 p=0.036 per allele per 1SD increase in sleep consolidation). In a series of linear mixed effect models, better sleep consolidation also attenuated the effect of the ε4 allele on the annual rate of cognitive decline (interaction estimate +0.048 SE=0.012 p<0.001). In deceased individuals, better sleep consolidation attenuated the effect of the ε4 allele on NFT density (interaction estimate −0.42 SE=0.17 p=0.016), which accounted for the effect of sleep consolidation on the association between *APOE* genotype and cognition proximate to death.

CONCLUSIONS AND RELEVANCE—Better sleep consolidation attenuates the effect of *APOE* genotype on incident AD and NFT pathology. Assessment of sleep consolidation may identify *APOE* positive individuals at high risk for incident AD, and interventions to enhance sleep consolidation should be studied as potentially useful means to reduce the risk of AD and NFT pathology in *APOE* $\varepsilon4^+$ individuals.

INTRODUCTION

A confluence of genetic, behavioral and environmental factors contributes to the risk of Alzheimer disease (AD) in old age. The Apolipoprotein E (*APOE*) ε4 allele is the most well established genetic risk factor for AD[1–6]. Meanwhile, in older adults, sleep disturbance is common[7], poorer sleep consolidation is associated with worse cognition[8,9], and sleep apnea, which can impair sleep consolidation, is associated with a higher risk of incident mild cognitive impairment (MCI) and dementia[10]. While *APOE* genotype is immutable, many social, environmental, and medical contributors to poor sleep are modifiable.

Previous work has suggested a potentially complex relationship between *APOE* genotype, sleep disruption, and cognitive impairment. Some studies suggest that the ε4 allele may predispose to sleep disruption[11–13]. Others suggest that sleep disruption and *APOE* genotype may amplify each other's negative cognitive effects[14–17].

In prior work with data from participants in the Rush Memory and Aging Project (MAP), we reported that *APOE* genotype is associated with cognitive decline in old age and that AD pathology mediates this association[18–20]. We also reported an association between sleep consolidation – the extent to which sleep is uninterrupted by repeated awakenings – and incident AD risk[21]. The present study extends this work and examines whether better sleep

consolidation reduces the effect of *APOE* on the risk of incident AD and the burden of AD pathology.

METHODS

A full description of the methods is contained in the Supplementary Material.

Participants

We studied 698 participants with baseline actigraphy, *APOE* genotype, and serial cognitive assessments from the MAP cohort[22] – a community-based cohort study of aging and dementia, whose participants agree to organ donation upon death. A full description of inclusion/exclusion criteria is contained in the Supplementary Material.

The institutional review board of Rush University Medical Center approved this study. All participants signed written informed consent and an anatomical gift act for organ donation.

Quantifying Sleep Consolidation

Sleep consolidation is the extent to which sleep is uninterrupted by repeated awakenings. We obtained up to 10 days of actigraphy in participants' usual environments and quantified the sleep consolidation using the metric k_{RA}, as described and validated in prior publications[21,23,24]. Briefly, k_{RA} represents the probability per 15-second interval of having an arousal, indicated by movement, after a sustained (≥ ~5 minutes) period of inactivity (i.e., sleep). A lower k_{RA} indicates better sleep consolidation (and a higher k_{RA} indicates greater sleep fragmentation, as in our previous work[21,23,24]). We previously showed that k_{RA} correlates well with polysomnographic measures of sleep consolidation including sleep efficiency and wake time after sleep onset[21].

Determination of APOE Genotype

DNA was extracted from peripheral blood lymphocytes and *APOE* genotype determined as described previously[25] and in the Supplementary Material. Participants with ≥1 copies of the ε4 allele (i.e., ε3/ε4, ε2/ε4, and ε4/ε4) were considered $\varepsilon4^+$. All others were considered $\varepsilon4^-$.

Assessment of Cognition and Dementia

As described previously[26] and in the Supplementary Material, a composite measure of global cognitive function was computed based on 19 cognitive tests administered annually. Individuals were classified as having AD by NINDS-ADRDA criteria[27].

Neuropathological Assessment

At the time of these analyses, 201 participants with actigraphy, *APOE* genotype, and longitudinal cognitive data had died and undergone autopsies. As described previously[28–31] and in the Supplementary Material, we quantified and computed summary measures of the percent area occupied by Aβ, the density of neurofibrillary tangles (NFT), and the density of neuritic plaques (NP) in a series of defined cortical regions. We also noted the presence/absence of Lewy bodies (LB) and gross infarcts.

Assessment of Covariates

Age, sex, education, congestive heart failure (CHF), peripheral vascular disease (PVD), diabetes, smoking, hypertension, stroke, Parkinson disease (PD), medications, depression, and total daily activity were ascertained as described in the Supplementary Material.

Statistical Analyses

As described in the Supplementary Material, we used Cox proportional hazards models to assess the relationship between *APOE* genotype, baseline sleep consolidation, and AD risk. Next, we used linear mixed effect models, which account for differences in baseline cognition, to examine the relationship between baseline sleep consolidation, *APOE* genotype, and the annual rate of cognitive decline. Finally, we used linear and logistic regression models to assess the relationship between *APOE* genotype, sleep consolidation, postmortem pathology, and cognition proximate to death.

All analyses were carried out using R[32]. All models were validated graphically and analytically.

RESULTS

Characteristics of the Study Population

Baseline characteristics of the 698 study participants are shown in Table 1.

APOE Genotype, Sleep Consolidation, and Incident AD

In a linear model adjusted for age, sex, and education, baseline sleep consolidation did not differ by *APOE* genotype (p=0.29 for ε4+ vs. ε4−).

Over a mean (SD) follow-up of 3.5 (1.8) years, 98 participants developed AD. In Cox proportional hazards models adjusted for age, sex, and education, the ε4 allele was associated with higher incident AD risk while better sleep consolidation was associated with lower risk (Table 2 Models A–B). Combining both in the same model (Model C) resulted in negligible change in the effect estimates compared to Models A and B, suggesting that sleep consolidation is not in the causal pathway linking *APOE* genotype to AD risk.

We next examined whether the relationship between *APOE* genotype and AD risk varies depending on the degree of sleep consolidation by adding a sleep x *APOE* interaction term (Model D). This was significant. Each 1SD increase in sleep consolidation attenuated the impact of *APOE* genotype on AD risk by nearly 50%.

To illustrate this, we compared model predictions for hypothetical average (82 year old women with 15 years of education) *APOE* $\varepsilon4^-$ and $\varepsilon4^+$ individuals with poor (10^{th} percentile), median, and good (90^{th} percentile) sleep consolidation (k_{RA} = 0.037, 0.027 and 0.021; Figure 1A–C). *APOE* ε4 was associated with a higher risk of AD irrespective of the degree of sleep consolidation. However, the effect size varied. With poor sleep consolidation, *APOE* $\varepsilon4^+$ was associated with a predicted HR of 4.1 for incident AD compared to *APOE* $\varepsilon4^-$. With median sleep consolidation, this was attenuated to 2.5, and with good sleep consolidation this was further attenuated to 1.8.

In separate sensitivity analyses, the sleep-*APOE* interaction remained significant after excluding individuals with the lowest 5% of baseline global cognition, with baseline MCI, who developed AD within the first year, or ε2/ε4 heterozygotes (eTable 1 Models A–D).

Effect of Clinical and Demographic Covariates

Sleep consolidation may be marker of general health. Thus we conducted an additional analysis to examine potential confounding by depression, vascular diseases (CHF, stroke, PVD), and vascular risk factors (diabetes, smoking, hypertension), on the sleep-*APOE* interaction. The strength of the interaction was materially unchanged (eTable 1 Model E).

Stroke and PD can affect sleep and cognition. However, the sleep-*APOE* interaction remained significant after excluding individuals with these conditions (eTable 1 Model F).

Psychotropic medications can affect sleep and cognition. However, the sleep-*APOE* interaction was essentially unchanged after adjusting for use of antidepressants, sedative-hypnotics, and anxiolytics (eTable 1 Model G).

Total daily activity is associated with incident AD[33] and may plausibly affect sleep. In a model adjusted for total daily activity, the sleep-*APOE* interaction remained significant (eTable 1 Model H).

APOE Genotype, Sleep Consolidation, and Cognitive Decline

To ensure that our results were not an artifact of the diagnostic process, we considered the effects of *APOE* genotype and sleep consolidation on the annual rate of decline of composite cognitive function, a continuous outcome, using linear mixed models incorporating participant-specific estimates of intercepts and slopes to account for baseline cognitive differences. In the base model (eTable 2 Model A), global cognition declined by 0.130 units/year. The ε4 allele was associated with poorer baseline cognition and more rapid decline while better baseline sleep consolidation was associated with better baseline cognition and slower decline. In a model with sleep-*APOE* interaction terms (eTable 2 Model B), better baseline sleep consolidation attenuated the ε4 effect on both the baseline cognitive level and subsequent decline.

To illustrate these effects, we compared model predictions for hypothetical average $\varepsilon4^{-}$, and $\varepsilon4^{+}$ individuals with poor, median and good sleep consolidation (Figure 1D–F). Irrespective of sleep consolidation, the ε4 allele was associated with poorer baseline cognition and more rapid decline. However, better sleep consolidation attenuated these effects.

APOE Genotype, Sleep Consolidation, Neuropathological Findings, and Cognition

At the time of these analyses, 201 participants with actigraphy, *APOE* genotype, and longitudinal cognitive data had died and undergone autopsy. Characteristics of these subjects are shown in eTable 3. In this subset, we used linear and logistic regression models to examine the effect of sleep consolidation and *APOE* genotype on AD and non-AD pathology. Sleep consolidation was last quantified on average 17.9 months (SD 13.7) before death. Neither sleep consolidation nor *APOE* genotype was associated with infarcts at autopsy (eTable 5). The ε4 allele was associated with more Aβ pathology, and greater NP and NFT density (eTable 4), and a higher likelihood of having LB (eTable 5). Better sleep consolidation attenuated the effect of *APOE* genotype on NFT density, but not the other pathological findings (Table 3, eTable 4; eTable 5; Figure 3).

We used linear regression models to further examine the relationships between *APOE* genotype, sleep, Aβ pathology, and NFT density (Table 3). In separate models, both *APOE* genotype and Aβ pathology were associated with NFT density, and when combined in the same model, both remained significant, although the effect estimate for *APOE* genotype was attenuated (models A, B, D), statistically consistent with *APOE* genotype influencing NFT density through both amyloid-dependent and independent pathways. Addition of sleep to this model did not appreciably change the effect estimates, arguing against mediation or confounding (model E). However, there was a significant sleep-*APOE* interaction (model G) even after adjusting for Aβ pathology (model H), suggesting that sleep consolidation modifies the *APOE* effect on NFT density in a manner not statistically mediated by Aβ pathology.

Aβ and NFT pathology may link *APOE* genotype to cognition[29,34], and LB and infarcts may also affect cognition. We used linear regression models to examine if Aβ pathology, NFT density, infarcts, or LBs may account for the effect of sleep on the association between *APOE* genotype and cognition proximate to death. As expected, better sleep attenuated the effect of *APOE* genotype on cognition proximate to death (eTable 5 Model B). Inclusion of terms for presence of gross infarcts, presence of LB, and burden of Aβ pathology did not substantially change this (C–E) suggesting that these pathologies do not account for the effect of sleep on the association between *APOE* genotype and cognition. However, adding a term for NFT density attenuated the interaction effect (F) in a manner that did not change with inclusion of Aβ pathology in the model (G). This is statistically consistent with NFT density accounting for the effect of sleep on the association between *APOE* genotype and cognition.

DISCUSSION

In this study of nearly 700 older persons without dementia, better sleep consolidation substantially attenuated the negative impact of the ε4 allele on incident AD risk. This environment-gene interaction was not accounted for by variation in physical activity, co-morbid medical conditions, or psychotropic medications. In additional analyses of cognitive change over time we showed that this finding was not an artifact of the diagnostic process. Finally, better sleep consolidation attenuated the negative impact of the ε4 allele on NFT density at death, which accounted for its beneficial effects on the association between *APOE* and cognition proximate to death. These findings highlight a thus far unappreciated biological and clinical link between sleep, *APOE* biology, NFTs, and AD.

There is a well-established link between *APOE* genotype and AD risk[1–5]. Furthermore, several studies support a link between sleep, cognition, and dementia risk[8–10,21,24,35]. However the precise relationship between *APOE* genotype, sleep, and AD is unclear. Several studies suggest that the ε4 allele may potentiate sleep disturbance[11–13,15,36]. Others suggest that sleep disruption and *APOE* genotype may interact to worsen cognitive function[13,16,17]. In this study, sleep consolidation neither mediated nor confounded the association between *APOE* genotype and incident AD, suggesting that it is not in the causal pathway linking *APOE* genotype to AD risk. However, better sleep consolidation substantially attenuated the impact of *APOE* genotype on incident AD risk.

APOE genotype is thought to influence the development of NFTs and Aβ pathology[37], the pathological hallmarks of AD. Biomarker studies suggest that Aβ pathology accumulates early, before clinical symptoms, while tau pathology accumulates only after Aβ accumulation is established[38]. Considerable evidence suggests that *APOE* ε4 predisposes to pathological Aβ accumulation[39,40], possibly by reducing clearance[41]. Aβ aggregation may then drive tau pathology[42–44]. However, *APOE* ε4 may also directly promote tau pathology in an Aβ-independent manner. *APOE* ε4 knock-in mice have higher levels of hyperphosphorylated tau compared to ε3 knock-in mice[45]. Moreover, in both *in vitro* and transgenic mouse models, APOE4 fragments can induce neuronal NFT-like inclusions[46,47] even without amyloid pathology. APOE4 may preferentially activate glycogen synthase kinase (GSK) 3β compared to APOE3[48], leading to tau hyperphosphorylation.

Animal experiments suggest that sleep disruption may influence the accumulation of Aβ pathology[35]. Moreover, a recent cross-sectional study of cognitively asymptomatic individuals demonstrated an association between actigraphic sleep efficiency and CSF Aβ, a marker of cerebral Aβ pathology[49]. Markers of tau pathology were not assessed in this study. In the present study, better sleep consolidation attenuated the association between *APOE* genotype and postmortem AD pathology, specifically NFT density, which accounted

in part for its beneficial effect on the association between *APOE* genotype and cognition. These results add to the growing body of evidence supporting a link between sleep, genetic susceptibility, and AD pathology. Moreover, they invite further investigation of the role of sleep in pathways directly linking *APOE* to tau pathology, not only in AD but also in primary tauopathies. In our study, although *APOE* genotype was strongly associated with Aβ pathology at death, sleep consolidation was not, nor did it modify the impact of *APOE* genotype on Aβ pathology. Several factors may account for this apparent difference compared to previous animal[35] and human[49] studies supporting an effect of sleep disruption on Aβ pathology. First, our participants were older than in previous human studies, and Aβ pathology was assessed only at death. Therefore, our results do not exclude an association at earlier times and in younger individuals. Second, animal studies relating sleep disruption to Aβ pathology were carried out in strongly amyloidogenic models that may not be completely representative of sporadic human AD. Third, in our study only a subset of participants had died by the time of these analyses and it is possible that data from a larger number of deceased individuals may reveal more subtle effects of sleep consolidation on Aβ pathology.

Taken as a whole, our findings are compatible with two hypotheses. In the first, baseline sleep consolidation may be a marker of some other factor (e.g. a medical co-morbidity, subclinical neurodegeneration, or a genetic or environmental factor) that causally modifies the impact of *APOE* genotype on NFT pathology and AD. However, several observations argue against this. First, our results were unchanged after adjusting for a wide range of medical comorbidities. Second, in linear mixed effect models that allowed for differences in baseline cognitive function (a marker of baseline neurodegenerative burden), a significant sleep-*APOE* interaction was still seen. Third, our results were robust to the exclusion of subjects with MCI at baseline, who would have had the greatest baseline neurodegenerative burden. Even if this first hypothesis were true, it would suggest that actigraphic sleep assessment could be an inexpensive and automated means of risk stratifying $\varepsilon 4^+$ individuals. In the second hypothesis (eFigure 1), sleep causally modifies the impact of *APOE* genotype on NFT formation and AD. In this hypothesis, uninterrupted sleep protects against biological mechanisms liking the ε4 allele to NFT formation (an example of which might be GSK3β hyperactivation[48]). Under this hypothesis, interventions to improve sleep consolidation may be a potentially useful approach to attenuate the risk of NFT pathology and AD in $\varepsilon 4^+$ individuals. Future interventional studies are needed to help define the appropriate role for *APOE* genotyping, actigraphic sleep assessment, and sleep interventions in the clinical management of individuals at risk for AD.

This study has several limitations. First, sleep disorders, some of which may plausibly affect both sleep consolidation and cognition, were not specifically assessed. However, the expected prevalence of significant (apnea index >10) sleep apnea in community-dwelling elders aged 65–99 has been estimated at only 11%[50], and the expected prevalence of significant restless legs is estimated at only 2.7%[51]. We think that these numbers are probably too low to have had a major impact on our results. Nevertheless, future studies should investigate whether there are specific sleep-*APOE* interaction effects on AD risk and pathology in patients with sleep apnea and other sleep disorders, particularly given recently reported associations between sleep apnea, cognition, and dementia[10,52]. Second, our cohort consisted entirely of volunteers, mostly women, which may limit generalizability. Third, although actigraphy is widely used in the ambulatory measurement of sleep, it is not identical to polysomnography. However, we and others have previously shown good concordance between actigraphic and polysomnographic sleep metrics[53], including the metric k_{RA} used in this study[21]. Fourth, the subset of participants who died and underwent autopsy during the study period was different than that which did not, and one must be careful in generalizing the postmortem results to the whole study population. Finally, AD

pathology was examined only at death and we cannot comment on the effect of sleep consolidation and *APOE* genotype on the temporal trajectory of Aβ or NFT accumulation.

This study also has several strengths. Sleep consolidation was measured objectively and non-invasively in participants' usual environments avoiding disturbance of natural sleep behavior, and confounding by poor recall or misperception. Moreover, it used a rigorous, standardized, well-characterized, and well-validated cognitive test battery administered annually for up to 6 years, allowing a high degree of certainty regarding the diagnosis of AD and the measurement of cognition. Finally, AD pathology was systematically assessed in a uniform way in the same individuals who underwent *APOE* genotyping and examination of sleep and cognition, allowing us to take a unique integrative approach to linking genotype, sleep, neuropathological findings, cognition, and AD in old age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Lim has responsibility for the integrity of the work as a whole. He conceived of the study hypotheses and design, analyzed and interpreted the data, carried out statistical analysis, drafted the manuscript, and approved the final manuscript. He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Yu contributed to the analysis of the data, performed statistical analysis, revised the article critically for important intellectual content, and approved the final manuscript. Dr. Kowgier contributed to the analysis of the data, performed statistical analysis, revised the article critically for important intellectual content, and approved the final manuscript. Dr. Schneider obtained funding, contributed to the study design, oversaw acquisition, analysis, and interpretation of the neuropathological data, revised the article critically for important intellectual content, provided administrative, technical, or material support, provided supervision, and approved the final manuscript. Dr. Buchman obtained funding, contributed to the study conception and design, oversaw data acquisition, contributed to data interpretation, revised the article critically for important intellectual content, provided administrative, technical, or material support, provided supervision, and approved the final manuscript. Dr. Bennett has responsibility for the integrity of the work as a whole. He obtained funding, contributed to the study conception and design, oversaw data acquisition, contributed to data interpretation, provided administrative, technical, or material support, provided supervision, revised the article critically for important intellectual content, and approved the final manuscript.

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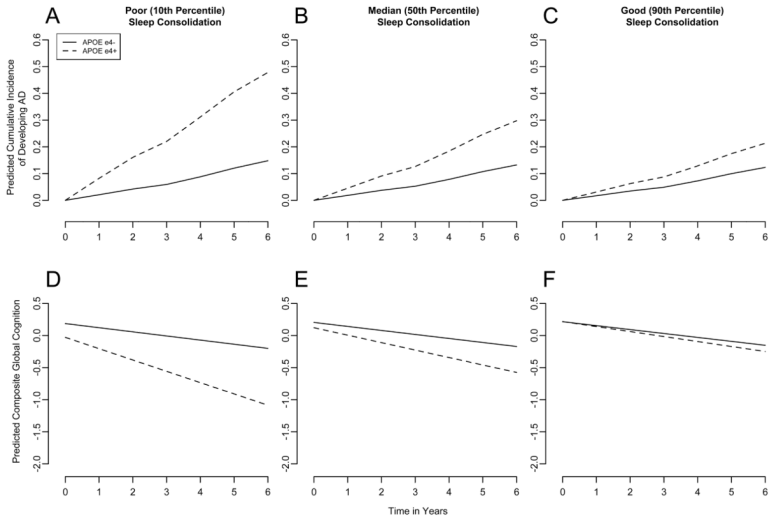

Figure 1. *APOE* Genotype, Sleep Consolidation, Cumulative Incidence of AD and Rate of Cognitive Decline

The model predicted cumulative incidence of AD and rate of cognitive decline based on the entire cohort are illustrated for hypothetical average *APOE* $\varepsilon 4^+$ and $\varepsilon 4^-$ participants with poor (A,D 10^{th} percentile), median (B,E 50^{th} percentile), and good (C,F 90^{th} percentile) sleep consolidation (k_{RA} = 0.037, 0.027 and 0.021).

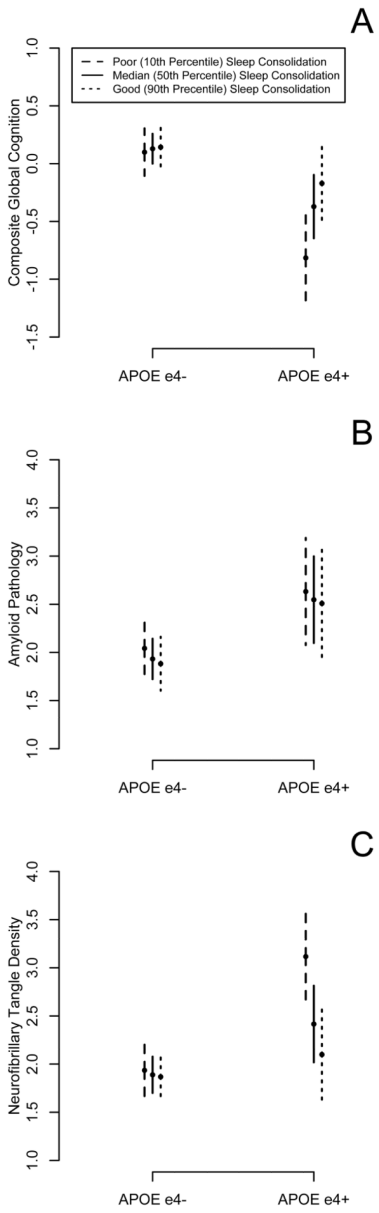

Figure 2. *APOE* Genotype, Sleep Consolidation, AD Pathology, and Cognitive Function Proximate to Death

The model predicted composite global cognitive function proximate to death (A), Aβ pathology at autopsy (B) and neurofibrillary tangle density at autopsy (C) based on deceased participants are illustrated for hypothetical average *APOE* $\varepsilon 4^{+}$ and $\varepsilon 4^{-}$ participants with poor (10^{th} percentile), median (50^{th} percentile), and good (90^{th} percentile) sleep consolidation. Vertical bars indicate 95% confidence intervals.

Table 1

Study Baseline Characteristics of Persons who Did or Did Not Develop Alzheimer Disease[a]

Characteristic	Developed AD (n=98)		Did not Develop AD (n=600)	
	APOE ε4⁻ (n=67)	*APOE* ε4⁺ (n=31)	*APOE* ε4⁻ (n=482)	*APOE* ε4⁺ (n=118)
Age (years)	87.5 (6.0)	84.2 (6.0)	81.3 (7.0)	80.0 (7.6)
Female, %	51/67 (76%)	22/31 (71%)	369/482 (77%)	94/118 (80%)
Education (years)	14.0 (2.9)	14.6 (2.7)	14.8 (2.9)	15.3 (2.9)
MMSE Score	25.6 (3.4)	26.0 (2.5)	28.3 (1.5)	28.3 (1.7)
Composite Global Cognition	−0.52 (0.56)	−0.34 (0.52)	0.27 (0.45)	0.23 (0.55)
Depressive Symptoms	1.9 (2.2)	1.39 (1.63)	0.98 (1.52)	1.01 (1.57)
Hypertension, %	44/67 (66%)	16/31 (51%)	286/482 (59%)	70/118 (59%)
Smoking, %	22/67 (33%)	10/31 (32%)	194/482 (40%)	50/118 (42%)
Diabetes, %	10/67 (15%)	4/31 (13%)	65/482 (13%)	7/118 (6%)
Stroke %	2/67 (3%)	3/31 (10%)	26/482 (5%)	10/118 (8%)
Peripheral Vascular Disease, %	17/67 (25%)	4/31 (13%)	64/482 (13%)	19/118 (16%)
Coronary Artery Disease, %	11/67 (16%)	2/31 (6%)	59/482 (12%)	14/118 (12%)
Congestive Heart Failure, %	3/67 (4%)	0/31 (0%)	28/482 (6%)	6/118 (5%)
Parkinson Disease, %	0/67 (0%)	0/31 (0%)	7/482 (1%)	1/118 (1%)
Days of Actigraphy	9.4 (0.8)	9.2 (0.7)	9.3 (0.9)	9.2 (0.8)
Total Daily Activity ($x10^5$ counts)	2.3 (1.2)	2.7 (1.5)	3.1 (1.6)	3.2 (1.6)
Sleep Consolidation k_{RA}	0.028 (0.007)	0.033 (0.011)	0.029 (0.007)	0.028 (0.008)

[*] All data presented as mean (standard deviation) unless otherwise indicated

Abbreviations: MMSE = mini mental state examination

Table 2

Effect of Degree of Sleep Consolidation and Presence/Absence of the *APOE* ε4 Allele on the Risk of Incident AD

	Effect on Risk of Incident AD			
Predictor	**Model A**	**Model B**	**Model C**	**Model D**
Sleep Consolidation	0.84 [0.71–1.00] p=0.05		0.84 [0.71–0.99] p=0.04	0.83 [0.63–1.10] p=0.19
APOE Genotype		2.21 [1.44–3.40] p=<0.001	2.22 [1.44–3.42] p<0.001	2.70 [1.51–4.83] p<0.001
Sleep Consolidation x *APOE* Genotype				0.67 [0.46–0.97] p=0.04

Hazard Ratio [95% Confidence Interval] p-values. Effects of sleep consolidation expressed per 1 standard deviation increase. Effects of *APOE* genotype expressed for presence vs. absence of the ε4 allele. All models adjusted for age at baseline, sex, and education