Evidence of association between sleep quality and *APOE* ϵ 4 in healthy older adults

A pilot study

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ABSTRACT

Background: It has been estimated that the prevalence of Alzheimer disease (AD) and related dementias will triple by 2035, unless effective interventions or treatments are found for the neurodegenerative disease. Understanding sleep changes as a marker for both AD risk and progression is a burgeoning area of investigation. Specifically, there is emerging evidence that both sleep disturbances and the *APOE* ϵ 4 allele are associated with increased dementia risk. Previous research has suggested that in AD, individuals carrying the *APOE* ϵ 4 allele have decreased sleep quality compared to individuals without the *APOE* ϵ 4 allele. This observational trial aimed to determine if healthy older adults with the risk allele (*APOE* ϵ 4+) have more sleep complaints or evidence of objective sleep disruption compared to healthy older adults without the risk allele (*APOE* ϵ 4–).

Methods: Within the larger Brain in Motion study, a subset of participants completed at-home polysomnography (PSG) and actigraphy sleep assessment. Subjective sleep complaints were determined using the Pittsburgh Sleep Quality Index.

Results: This investigation found a significant relationship between presence of *APOE* ϵ 4 allele and objective sleep disturbances measured by both actigraphy and PSG, but not subjective sleep complaints in a healthy population screened for dementia.

Conclusions: These data suggest that the influence of *APOE* ϵ 4 allele on objective sleep quality may precede subjective sleep complaints in individuals at increased risk for dementia. *Neurology*® 2016;87:1836–1842

GLOSSARY

A β = β -amyloid; **AD** = Alzheimer disease; **AHI** = apnea/hypopnea index; **BIM** = Brain in Motion; **MCI** = mild cognitive impairment; **PSG** = polysomnography; **PSQI** = Pittsburgh Sleep Quality Index; **WASO** = wake after sleep onset.

It is well-established that individuals who have probable Alzheimer disease (AD) and mild cognitive impairment (MCI) have sleep problems,^{1,2} manifesting as disturbed sleep-wake patterns.³ There is growing evidence that deposition of β -amyloid (A β) plaques within the brain, one of the hallmark pathologies of AD, is associated with increased sleep disturbances in patients with dementia⁴ and potentially those at risk of developing dementia. Within the cholinergic basal forebrain structures, accumulation of A β can occur in early adulthood.⁵ Notably, the basal forebrain is involved in both cognition⁶ and the regulation of sleep.⁷ In healthy adults, the burden of A β can be mitigated through clearance of the neurotoxic protein. Groundbreaking research has suggested that clearance of waste products, such as A β , is enhanced during normal sleep.⁸ In addition, deposition of A β is greater if sleep is disrupted,^{9,10} and while neurons are active.¹¹ Recent evidence has also suggested that higher A β burden in healthy older adults is associated with disrupted slow wave sleep.¹²

A variant of *APOE*, the ϵ 4 allele, is associated with an increased risk of AD and related dementias. In addition, there is evidence that maintenance of normal sleep-wake patterns,

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specifically fewer nighttime awakenings, attenuates the effects of the $\epsilon 4$ allele on cognitive decline in a population of patients with AD.¹³ Furthermore, cognitively intact middle-aged adults with levels of CSF A β_{42} less than 500 pg/mL have disrupted sleep compared to adults with higher levels of CSF A β_{42} .¹⁴ Specifically, midlife individuals who had a low amount of A β_{42} in their CSF had decreased sleep efficiency, more nighttime awakenings, and more daytime naps compared to healthy adults. Previous literature has suggested that levels of CSF A β decrease as individuals transition from healthy aging to mild cognitive impairment,¹⁵ and again in probable AD.^{16,17} Taken together, this literature suggests that individuals who are at higher risk for A β deposition in the brain are also at risk for disrupted sleep. This genetic risk may cause some individuals to enter a feed-forward loop where sleep problems cause an increase in A β deposition in the brain, which then further disrupts sleep circuitry in the brain.¹

This study aimed to investigate the potential relationship between both subjective and objective sleep quality and *APOE* genotype in a population of healthy, sedentary adults without dementia over the age of 55. We hypothesized that having at least one *APOE* $\epsilon 4$ allele will decrease both subjective and objective sleep quality compared to individuals without an *APOE* $\epsilon 4$ allele.

METHODS Participants. This investigation was completed as an ancillary study of the larger Brain in Motion (BIM) study, which is designed to investigate the effect of an aerobic exercise intervention on cognition in a population of healthy, sedentary older adults. Enrollment and study testing were completed between 2009 and 2015 for this cross-sectional study. All participants were generally healthy and screened for inclusion/exclusion criteria for the BIM study. For details, see Tyndall et al.¹⁸ The data used for this study were taken from their baseline assessment. Thirty-five participants were recruited from the parent study (table 1; mean age 65.1 years; 60% female). Four participants were excluded from the final polysomnography (PSG) analysis, resulting in a final sample size of 31; of those excluded, 3 refused to wear the PSG equipment and 1 experienced PSG equipment failure.

Standard protocol approvals, registrations, and patient consents. Ethics approval was granted by the University of Calgary Conjoint Health Research Ethics Board, and informed written consent was obtained from each participant following thorough explanation of the study.

In-home PSG. Unattended PSG recordings were conducted for a single night using the Embletta MPR PG (Natus Medical Inc., Pleasanton, CA) with an ST+ proxy unit attached to it. Each

Table 1 Participant demographics by *APOE* $\epsilon 4$ status

Demographics	APOE $\epsilon 4$ status, mean (SD)	
	$\epsilon 4-$ (n = 27)	$\epsilon 4+$ (n = 8)
Age, y	64.9 (5.0)	65.8 (5.1)
Sex, % female	66.7	37.5
Education, y	16.4 (3.4)	15.9 (1.5)
Body mass index, kg/m ²	26.9 (4.5)	26.5 (2.5)
Montreal Cognitive Assessment	27.5 (1.6)	27.1 (0.8)

participant was fitted with the PSG equipment at baseline by trained technicians in the patient's home. Respiratory monitoring included finger pulse oximetry, thoracic and abdominal effort measured using inductive plethysmography, and airflow using nasal pressure and an oronasal thermistor. Participants were also fitted for standard ECG. Leg movement was determined using 2 electrodes placed 2–4 cm apart vertically on the anterior tibialis muscle, and body position was derived using x, y, and z gravity sensors in the main body of the Embletta unit. Electrode placement for the EEG followed the standard 10–20 system.

Data were scored by a registered polysomnographic technologist (J.K.R.) to determine (1) sleep stage¹⁹; (2) apnea/hypopnea index (AHI), where an apnea is defined as at least a 90% decrease in the airflow channel for at least 10 seconds and a hypopnea is a decrease in the airflow channel of at least 30% for 10 seconds, accompanied by a 3% (or more) decrease in oxygen saturation or an arousal. An arousal is an abrupt shift in EEG frequency of at least 3 seconds preceded by 10 seconds of continuous sleep; (3) oxygenation; and (4) leg movements. From this, the following indices of sleep quality were obtained: (1) sleep period time, determined as the time measured between sleep onset and final awakening; (2) nighttime awakenings, measured as the number of times the individual awakened during the sleep period time. An awakening is defined as a return to an awake state for more than 15 seconds, characterized by alpha or beta EEG activity, an increase in tonic EMG activity, and REM; (3) wake after sleep onset (WASO), total time spent awake between sleep onset and final awakening; (4) sleep onset latency, the time period measured between “lights out” and first 30 seconds epoch of any sleep stage; (5) total sleep time, measured as sleep period time minus wake after sleep onset; and (6) sleep efficiency, the ratio of total sleep time to total recording time, multiplied by 100.

Actigraphy. The AW-2 Actiwatch (Minimitter; Philips Respironics, Murrysville, PA) is a small, lightweight, waterproof accelerometer, worn like a wristwatch, with a piezoelectric beam to detect all 3 axes of movement. The actigraph was worn on the nondominant wrist for a period of 2 weeks. The PSG was completed during the 2 weeks when each participant was wearing the Actiwatch, so that they overlapped for a single night. Actigraphs were assessed in 30-second epochs and sleep variables were calculated across the 14-day collection period. Data analysis was completed using the Actiware scoring algorithm, which compares activity counts for each epoch and those surrounding it to a threshold value, which we set at medium sensitivity (activity count of 40) on the Actiware program (Philips Actiware 6.0.4). For each participant, we calculated (1) total nocturnal sleep time (the hours/night spent asleep); (2) frequency and duration of awakenings after sleep onset by (3) sleep efficiency (% of time asleep); and (4) sleep latency (the number of minutes to fall asleep).

Table 2 Subjective sleep measures classified by *APOE* $\epsilon 4$ status

Pittsburgh Sleep Quality Index (PSQI) ^a	Range	<i>APOE</i> $\epsilon 4$ status, mean (SD)		η^2
		$\epsilon 4- (n = 27)$	$\epsilon 4+ (n = 8)$	
Total PSQI score	0–14	5.6 (3.1)	4.1 (2.3)	0.02
Sleep period time, min	345–600	484.7 (61.9)	483.8 (44.5)	0.05
Total sleep time, min	300–540	401.7 (87.7)	420.0 (53.2)	0.00
Sleep efficiency, %	63–100	83.2 (16.8)	87.1 (10.8)	0.00
Sleep latency, min ^{b,c}	2–60	14.2 (12.2)	12.9 (11.2)	0.00

^a Analyses corrected for age and sex.

^b Significant effect of sex within the analysis.

^c Significant effect of age within the analysis.

Subjective sleep questionnaire. Sleep quality was assessed using a retrospective self-report measure, the Pittsburgh Sleep Quality Index (PSQI).²⁰ The PSQI provides an estimate of the following sleep parameters across the last month: sleep quality; sleep onset latency; total sleep time; daytime sleepiness; sleep efficiency, the ratio of estimated total sleep time to total time spent in bed; sleep disturbances; and sleep medication use.

***APOE* genotyping.** Using standard protocols, genomic DNA was extracted from buffy coats obtained from whole blood samples (Gentra Puregene Blood Kit; Qiagen, Venlo, Netherlands). Samples underwent PCR amplification followed by Sanger sequencing (BigDye v1.1 Cycle Sequencing Kit; Applied Biosystems, Foster City, CA) on ABI 3130XL Genetic Analyzer (Applied Biosystems). Mutation Surveyor DNA Variant Analysis software (SoftGenetics, LLC; State College, PA) was used to identify *APOE* $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles by manually combining the alleles from the single nucleotide polymorphisms NM_000041.2:c.388T>C (p.Cys130Arg; rs429358) and c.526C>T (p.Arg176Cys; rs7414) as follows: at nucleotides 388 and 526 (amino acids 130 and 176), $\epsilon 2 = TT$ (CysCys), $\epsilon 3 = TC$ (CysArg), and $\epsilon 4 = CC$ (ArgArg). *APOE* $\epsilon 4+$ was identified as $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$, and *APOE* $\epsilon 4-$ was $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, and $\epsilon 3/\epsilon 3$.

Data analysis. All statistical analyses were completed using SPSS 21.0 (Chicago, IL). All data were checked for outliers and normality before analyses were initiated. Unattended PSG at home and actigraphy were used to objectively measure sleep, and a retrospective questionnaire, the PSQI, was used to assess subjective sleep quality. Mixed effect analysis of

covariance controlling for age and sex was utilized to determine if there were differences in the objective and self-reported sleep in individuals who were *APOE* $\epsilon 4+$ ($n = 8$) compared to those who were *APOE* $\epsilon 4-$ ($n = 27$). Analysis of observed power η^2 is reported for all between-subject comparisons, using the categorical magnitude sizes presented by Cohen (1988) for an analysis of variance/covariance (small = 0.01; medium = 0.06; large = 0.14).²¹

RESULTS Differences in between group (*APOE* $\epsilon 4+$, *APOE* $\epsilon 4-$) demographic outcomes were assessed using independent t tests for continuous variables and χ^2 tests for categorical variables. There were no significant group differences on age, sex, years of education, or dementia screening scores (table 1). Previous literature has suggested that age and sex can influence both objective and subjective sleep parameters and are included as covariates in all analyses.²²

Overall, the analyses showed significant differences between the *APOE* $\epsilon 4$ genotype group's objective sleep parameters using PSG and actigraphy, but not in the self-reported sleep disturbances. When controlling for age and sex, there were no significant differences in self-reported sleep parameters measured by the PSQI (table 2). Objective sleep measured using PSG and actigraphy showed significantly worse sleep in individuals who had the high-risk *APOE* $\epsilon 4$ genotype ($\epsilon 4+$) compared to those who did not have the high-risk allele. For a summary of the *APOE* $\epsilon 4$ genotype group differences on objective sleep measures by actigraphy, see table 3. Specifically, *APOE* $\epsilon 4+$ individuals had a shorter duration of sleep ($p = 0.01$), but not significantly less time spent in bed (table 2). In addition, individuals with an *APOE* $\epsilon 4$ allele had significantly more time spent awake after sleep onset (WASO) measured by PSG ($p = 0.006$), and lower sleep efficiency measured with both actigraphy ($p = 0.019$) and PSG ($p = 0.003$) (figure).

There were some differences in the sleep architecture between groups. *APOE* $\epsilon 4+$ individuals had significantly less stage 1 ($p = 0.033$), stage 2 ($p < 0.01$), and REM sleep ($p = 0.046$) compared to *APOE* $\epsilon 4-$ individuals, while no differences were seen in the duration of slow wave sleep when correcting for both age and sex (tables 4 and 5). Within our data, the differences seen between groups in stage 1 and REM sleep are not clinically significant. To account for differences in the amount of time spent sleeping between groups, additional analyses were completed looking at between-group differences on percentage of total sleep time spent in each sleep stage. When correcting for sex and age, *APOE* $\epsilon 4+$ individuals had a significantly lower percentage of total sleep time spent in stage 2 ($p = 0.034$), but significantly more time spent in REM sleep ($p = 0.012$). However, the

Table 3 Actigraphy objective sleep parameters classified by *APOE* $\epsilon 4$ status

Actigraphy ^a	Range	<i>APOE</i> $\epsilon 4$ status, mean (SD)		η^2
		$\epsilon 4- (n = 27)$	$\epsilon 4+ (n = 8)$	
Sleep period time, min	399–563	485.2 (43.0)	510.4 (39.5)	0.09
Total sleep time, min	347–501	437.2 (35.9)	427.2 (35.5)	0.01
Sleep efficiency, % ^b	75–95	89.7 (3.3)	84.6 (6.5)	0.20
Sleep latency, min	4.0–33.8	12.1 (7.3)	16.3 (9.0)	0.09
Awakenings index	1.3–7.0	3.9 (1.4)	4.6 (1.2)	0.04
WASO, min	9.4–70.9	30.6 (14.0)	35.4 (10.0)	0.03

Abbreviation: WASO = Wake after sleep onset.

^a Analyses corrected for age and sex.

^b $p < 0.01$.

Figure Objective and subjective sleep efficiency measurement in individuals with the *APOE* ϵ 4 allele

(A) *APOE* ϵ 4 allele (ϵ 4+) was associated with significantly lower sleep efficiency when measured using in-home polysomnography when correcting for age and sex ($p = 0.003$), (B) but not when measured with the retrospective self-report measure (Pittsburgh Sleep Quality Index). ** $p < 0.01$.

Table 4 Polysomnography sleep parameters, sleep disturbances, and sleep architecture classified by *APOE* ϵ 4 status

Sleep descriptives	Range	APOE ϵ 4 status, mean (SD)		η^2
		ϵ 4 - (n = 24)	ϵ 4 + (n = 7)	
Sleep period time, min	353-581	490.1 (57.9)	460.3 (25.4)	0.04
Total sleep time, min ^a	257-509	441.3 (50.7)	352.1 (66.7)	0.32
Sleep efficiency, % ^b	50.3-95.6	87.8 (3.2)	73.8 (17.0)	0.38
Sleep latency, min	1-77.3	13.8 (13.2)	20.8 (25.7)	0.05
Arousal and awakening index	1.9-7.8	5.0 (1.2)	5.9 (1.7)	0.08
WASO, min ^b	10.4-187.4	48.5 (17.5)	108.1 (73.9)	0.36
Sleep architecture by % of total sleep time ^c				
N1, % ^d	8-31	15.0 (5.4)	14.7 (5.2)	0.01
N2, % ^{d,e}	49.9-78.4	64.2 (6.4)	58.8 (6.8)	0.16
Slow wave sleep, % ^f	0-11.8	2.7 (3.2)	4.3 (4.5)	0.10
REM, % ^e	11.6-27.50	18.1 (3.5)	22.2 (3.4)	0.01
Sleep disturbances and arousals ^c				
Mean PSG stage changes	84-227	148.1 (39.0)	133.9 (44.6)	0.02
Apnea and hypopnea index	1.5-54.4	14.7 (12.6)	9.7 (6.7)	0.03
% With sleep apnea (AHI >15)	n/a	51.9	37.5	0.02
Mean pulse O ₂ saturation across sleep time	89.7-97.0	92.4 (1.6)	92.4 (1.3)	0.00
Time spent with pulse O ₂ saturation <90%, min	0-78.8	16.4 (20.7)	15.3 (28.1)	0.00
Periodic Limb Movement Index ^g	0-95.9	7.9 (9.7)	21.9 (36.9)	0.09

Abbreviations: AHI = apnea/hypopnea index; PSG = polysomnography; WASO = wake after sleep onset.

^a $p < 0.01$.

^b $p < 0.001$.

^cAnalyses corrected for age and sex.

^dSignificant effect of sex within the analysis.

^e $p < 0.05$.

^fSignificant effect of age within the analysis.

^gOne participant was an outlier on limb movements; upon removal from the analysis, the comparison between *APOE* ϵ 4 status groups remained nonsignificant.

increase in amount of time spent in REM sleep is not clinically significant, as both groups are still close to normative data for individuals between the ages of 60 and 69.²³ In addition, there was an almost, but not quite, significant increase in the amount of time spent in slow wave sleep by *APOE* ϵ 4+ compared to *APOE* ϵ 4- individuals ($p = 0.09$). Finally, there were no differences between groups on arousal index, respiratory disturbance index, apnea and hypopnea index in REM or non-REM sleep, mean blood oxygen saturation, time spent below a blood oxygen saturation of 90%, or periodic limb movement index ($ps > 0.05$). One participant was a significant positive outlier on periodic limb movement index, and when removed from the analysis the group comparison remained nonsignificant.

DISCUSSION Within our data, we have observed significantly worse objective sleep quality in *APOE* ϵ 4+ individuals without an increase in subjective sleep complaints. The differences in sleep efficiency observed appear to be due to an increase in the amount of time spent awake after sleep onset, without an increase in the number of awakenings. This suggests that *APOE* ϵ 4+ individuals are having the same number of sleep disturbances, but may be staying awake for a longer duration compared to *APOE* ϵ 4- individuals. Overall, these data suggest that *APOE* ϵ 4+ individuals without dementia may be experiencing a decrease in time spent asleep, decreased sleep efficiency, and increased WASO without recognizing their sleep quality is impaired. In our cohort, individuals who are *APOE* ϵ 4+ did not have a significantly different frequency of arousals, leg movements, or respiratory disturbances. While our population is normal healthy adults, it is widely recognized that

Table 5 Characteristics of the *APOE* $\epsilon 4$ + participants

Participant	Age, y	Sex	Years of education	Body mass index	Total cholesterol, mmol/L	Blood pressure, SBP/DBP
1	60	Male	17.5	26.26	5.67	110/70
2	61	Male	14	26.22	5.43	127/75
3	64	Female	16	26.04	5.07	128/70
4	76	Male	14	29.87	5.17	124/66
5	68	Male	16	28.80	5.45	148/90
6	68	Male	18	28.45	5.59	124/71
7	67	Female	15	22.53	5.67	156/79
8	68	Female	17	23.80	5.36	147/78

Abbreviations: DBP = diastolic blood pressure; SBP = systolic blood pressure.

having an *APOE* $\epsilon 4$ allele increases the risk of dementia, specifically AD.

Currently there is minimal research investigating the effects of *APOE* $\epsilon 4$ genotype on sleep in otherwise healthy older adults. However, the effect of AD on sleep has been well-characterized. In addition to behavioral and cognitive deficits, individuals with AD show greater sleep abnormalities than would be expected based on age alone.^{24,25} Primary findings indicate that individuals with AD have decreased sleep efficiency, increased stage 1 sleep, more nighttime awakenings, and decreased slow wave sleep and REM sleep.^{1,24–29} Within our population of healthy adults at genetic risk for AD, we saw a decrease in sleep efficiency, which is similar to changes seen in individuals diagnosed with MCI and AD. We also saw a significant increase in the time and percentage of sleep spent in REM; however, the total difference in REM sleep between the 2 groups is a few minutes. This finding is not clinically significant, and based upon the normative data is still within the normal values for older adults. Taken together, these data highlight the need for future investigation of sleep across aging, specifically focusing on the transition from healthy aging to dementia.

Objective sleep disturbance, without subjective sleep complaints, may be evidence of prodromal disease resulting in changes to the underlying pathways controlling sleep. Previous research has suggested that individuals with MCI have worse objective and subjective sleep compared to healthy older adults.³⁰ In a cohort of healthy middle age and older adults, the relationship between subjective sleep complaints on the PSQI and objective sleep measures by PSG was poor.²⁰ When split into empirical clusters based on K-analysis of subjective sleep complaints, psychological factors such as perceived stress and anxiety ratings predicted group membership more strongly than objective measures from PSG or actigraphy.²⁰ This investigation did not provide information on whether older adults

were more likely to overestimate or underestimate their sleep quality. Within our sample, we did not observe any significant relationships between subjective sleep and sleep outcomes using PSG or actigraphy. Additional research is needed to determine if objective changes in sleep quality may be occurring prior to subjective complaints in older adults who are cognitively intact but have the high-risk *APOE* $\epsilon 4$ allele.

Taken together, these data lead to the following candidate mechanisms for future exploration. First, a contributing mechanism underlying *APOE* $\epsilon 4$ allele risk for dementia may be increased risk for disordered sleep. There is some evidence for this hypothesis in other age-related diseases, with the *APOE* $\epsilon 4$ allele being associated with an increased risk of obstructive sleep apnea and hypopnea.³¹ However, within our data, there were no significant differences in the percentage of participants who fit criteria for sleep apnea based upon the AHI. Alternatively, older adults with a high genetic risk for developing AD may show changes in their sleep before other symptoms of disease, possibly due to greater A β burden. Recent research suggests that deposition of A β in the brain will be in the basal forebrain, a structure involved in sleep regulation⁷ and implicated in AD progression.⁶ There is a possibility that disruptions in non-REM sleep and sleep efficiency are indications of early disease process within the brain, specifically accumulation of A β in brain areas involved in sleep regulation. Alternatively, these early disruptions in sleep architecture may be the impetus for development of disease where disruptions in glymphatic clearance of waste initiate the buildup of A β plaques and tau tangles. Additional research is needed to determine the direction of this relationship and if the presence of the *APOE* $\epsilon 4$ allele instigates entry into a feed-forward loop where sleep problems increase A β deposition (or reduce A β clearance via impaired circulation) in the brain, which then further disrupts sleep brain circuitry.

Our study has some limitations that should be considered. First, due to the small sample size, this investigation should be thought of as a hypothesis-generating rather than hypothesis-confirming analysis. Due to the small sample size, it is also not possible to eliminate the possibility of heterogeneity within the sample. This investigation adds an interesting and novel observation to the larger literature on the influence of genetic risk on dementia, sleep, and cognitive function in older adults. Despite our small sample size, a power calculation confirmed we have the power to observe a large (i.e., 0.8) effect size. In addition, the effect sizes observed on objective measures of sleep quality (i.e., PSG and Actigraphy Sleep Efficiency) have large observed effect sizes, $\eta^2 > 0.14$. Another potential limitation is that PSG may disrupt sleep. However, all of our participants were fitted

with the same equipment so the disruptions should not have affected one group more than the other.

One of the greatest strengths of this study is that we have a multimodal approach to assessing sleep, utilizing the gold standard for objective sleep quantification PSG as our benchmark. In addition, we used actigraphy assessment to collect a highly validated estimate of sleep quality across a 14-day period. Actigraphy is not the gold standard but generally has 95% concordance with PSG recordings. The concordance between actigraphy and the PSG measurement of sleep efficiency was good when comparing sleep across only the night of PSG recording for the actigraphy data and the one-night PSG measurement ($r = 0.39$, $p = 0.035$) within our data. Finally, to assess subjective sleep complaints, we collected data using the PSQI, a well-validated self-reported measure of sleep across the last month.²⁰ These 3 measures were chosen for their construct validity, clinical application, and overlap in key outcomes measures, such as sleep efficiency.

With the rising number of older adults, we should prioritize the goal of delaying or stopping the onset of incident dementia. Currently, the economic and personal burden of dementia caretaking is high, with the Alzheimer's Association estimating costs in the United States to approach \$1.1 trillion, representing a 5-fold increase in both health care and out-of-pocket spending.³² Beyond the economic repercussions, dementia has a devastating effect of quality of life for both patients and their caregivers.³³ Finding ways to reduce these burdens would be important on both an individual and public health level. In addition, improving sleep in the older adult population has been linked with improved quality of life, regardless of health status.^{34,35} One of the most effective interventions to improving sleep within the older adult population is aerobic exercise.^{36–38} Future studies should focus on the ability of an exercise intervention to potentially improve sleep in older adults who are *APOE* $\epsilon 4+$, since our data suggest that individuals who are *APOE* $\epsilon 4+$ may be experiencing worse sleep quality than *APOE* $\epsilon 4-$ older adults.

AUTHOR CONTRIBUTIONS

M.J.P., P.J.H., and G.A.E. designed and conceived the Brain in Motion ancillary sleep study. L.L.D. prepared the first draft of the manuscript and completed statistical analyses with guidance from P.J.H. and M.J.P. S.J.G. and K.S.G. were involved in data collection and J.K.R. completed the analysis and interpretation of the polysomnography data. Collection of genetic data was completed by A.V.T. under the direction of J.S.P. Analysis of the actigraphy data was completed jointly by K.S.G., A.N., and L.L.D. Interpretation of the data was jointly completed by L.L.D., P.J.H., G.A.E., and M.J.P. M.J.P. supervised L.L.D. (Alberta Innovates—Health Solution Postdoctoral Fellow), S.J.G. (MSc student), K.S.G. (Research Assistant), and A.V.T. (Alzheimer Society of Canada Doctoral Scholar). All authors reviewed and edited the manuscript across the development of this investigation.

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