



Blackman, J., Love, S., Sinclair, L. I., Cain, R. J., & Coulthard, E. J. (2022). APOE ϵ 4, Alzheimer's disease neuropathology, and sleep disturbance, in individuals with and without dementia. *Alzheimer's Research and Therapy*, 14(1), [47]. <https://doi.org/10.1186/s13195-022-00992-y>

Publisher's PDF, also known as Version of record

Link to published version (if available):
[10.1186/s13195-022-00992-y](https://doi.org/10.1186/s13195-022-00992-y)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the final published version of the article (version of record). It first appeared online via BMC at <https://doi.org/10.1186/s13195-022-00992-y>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: <http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

RESEARCH

Open Access



APOE ϵ 4, Alzheimer's disease neuropathology and sleep disturbance, in individuals with and without dementia

Jonathan Blackman¹, Seth Love², Lindsey Sinclair², Richard Cain² and Elizabeth Coulthard^{2*}

Abstract

Background: Apolipoprotein E epsilon 4 (*APOE- ϵ 4*) carrier status is an established risk factor for Alzheimer's disease (AD) dementia. It has also been linked with sleep disturbance in healthy older adults and increased insomnia risk. This association may be driven by the effect of *APOE- ϵ 4* on AD pathological change, itself associated with sleep abnormalities. To assess this relationship, we have evaluated post-mortem neuropathological findings in patients with and without cognitive impairment and AD pathology, who had extensive clinical assessment within 12 months of death.

Methods: This retrospective cohort study used UK Brain Banks Network data. Eligible subjects were aged over 50, with pre-mortem neuropsychiatry inventory scores of sleep disturbance (NPI-K), neurocognitive testing and functional cognitive status assessment (Clinical Dementia Rating scale). Neuropathological data included Thal phase, Braak stage and CERAD scores (measures of $A\beta$ plaque distribution, tangle distribution and neuritic plaque density, respectively) combined to form the National Institute on Aging Alzheimer's Association (NIA-AA) ABC score reflecting AD neuropathology. Participants with other significant intracerebral pathology or pathological features of non-AD dementia were excluded.

Multivariate linear regression was performed with NPIK Global Score (NPIK frequency score multiplied by severity score) as the dependent variable and *APOE- ϵ 4* heterozygosity or homozygosity as independent variables. Covariates included age, gender, *APOE- ϵ 2* status and ABC NPI measures reflecting depression and anxiety. Further models stratified by ABC score and functional cognitive status were also produced.

Results: Seven hundred twenty-eight records were identified. Two hundred two participants were included in the final analysis: mean (SD) age 84.0 (9.2) and MMSE 14.0 (11.8). Mean sleep disturbance scores were highest in ϵ 4 homozygosity ($n=11$), 4.55 (5.4); intermediate in ϵ 4 heterozygosity ($n=95$), 2.03 (4.0); and lowest in non- ϵ 4 carriers ($n=96$), 1.36 (3.3). Within the full sample, controlling for pathological status, age, gender, depression, anxiety and CDR-SOB status, *APOE- ϵ 4* homozygosity was associated with sleep disturbance (β 2.53, $p=0.034$). *APOE- ϵ 4* heterozygosity was similarly associated in individuals without dementia (β 1.21, $p=0.048$).

Conclusion: These findings lend weight to the hypothesis that *APOE- ϵ 4* affects sleep by mechanisms independent of AD pathological change. Evaluation of those mechanisms would enhance understanding of sleep disturbance pathways and potentially provide treatment targets.

Keywords: Alzheimer's, Dementia, Sleep, APOE-E4, Apolipoprotein, Cognitive impairment

*Correspondence: Elizabeth.coulthard@bristol.ac.uk

² Learning and Research, University of Bristol, Southmead, Bristol BS10 5NB, UK

Full list of author information is available at the end of the article



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Relative to the common $\epsilon 3$ allele of apolipoprotein E (*APOE* $\epsilon 3$), the $\epsilon 4$ allele is an established risk factor for the development of sporadic and late-onset familial Alzheimer's disease (AD) [1–3]. Within predominantly Caucasian populations, increasing allele dose is positively associated with AD risk, with $\epsilon 4$ heterozygosity conferring an odds ratio (OR) of approximately 3 and $\epsilon 4$ homozygosity an OR of approximately 14 [4]. *APOE* $\epsilon 4$ also lowers the age of onset in a similarly allele-number-dependent manner, with one allele advancing onset by 2–5 years and two by 5–10 years [5] although such relationships appear weaker in African-American populations [6–8].

Multiple mechanisms have been proposed through which *APOE* $\epsilon 4$ may exert these effects [9]. Apolipoprotein E4 (ApoE4) affects amyloid beta ($A\beta$) metabolism, predisposing to its extracellular deposition as amyloid plaques [10–12] and to more severe cerebral amyloid angiopathy [13–16]. Whilst effects on $A\beta$ are hypothesised to represent the dominant pathway, proteolytic ApoE4 cleavage resulting from stress or injury also predisposes to tau hyperphosphorylation and neurofibrillary tangle (NFT) formation [17]. ApoE4 has further been associated with disruption to glucose metabolism [18–20], blood-brain barrier integrity [21], cerebrovascular function [22], lipid transport [23], synaptic function [24] and inflammatory responses [25] as well as neuronal toxicity and α -synuclein/TDP-43 pathologies [26, 27].

Multiple studies have also linked *APOE* $\epsilon 4$ to sleep disturbance: specifically, objective sleep disturbance in healthy older adults [28], an increased risk of insomnia [29] and obstructive sleep apnoea/sleep-disordered breathing in both adults [30, 31] and children [32]. Improved sleep was reported to attenuate the negative effect of $\epsilon 4$ on incident AD [33]. Additionally, $\epsilon 4$ has been proposed as a mediator of the relationship between sleep and cognitive decline, both obstructive sleep apnoea (OSA) and *APOE* $\epsilon 4$ impairing cognitive performance [34–36]. However, whilst possession of $\epsilon 2$ reduces the odds of developing AD [37, 38], this allele has been linked with increased likelihood of OSA [39].

Sleep disturbance, whilst traditionally associated with established AD disease [40–42], is detectable prior to the emergence of symptoms [43–45] and plays a potentially causative role in AD pathogenesis [46–48]. Therefore, *APOE* $\epsilon 4$ could influence AD incidence and progression through the effects of this allele on sleep. Establishing this categorically is complicated by the influence of ApoE4 on the pathological hallmarks of AD themselves detectable decades prior to symptomatic presentation with cognitive impairment [49] and also associated with sleep disturbance. Hippocampal and Entorhinal Cortex

deposition of NFTs found in early Braak stages [50] have been associated with an increased likelihood of sleep disturbance [51]. AD pathology within the suprachiasmatic nuclei and the ventrolateral preoptic area has also been implicated in sleep disturbance [52, 53] with hippocampal $A\beta$ burden in otherwise healthy adults correlating significantly with impairments in non-random eye movement (NREM) slow wave activity generation and showed a trend towards deterioration in macro-architectural sleep parameters [54].

Here, we have tested the hypothesis that *APOE* $\epsilon 4$ allele count increases sleep disturbance in people with and without cognitive impairment, independently of its influence on the two major hallmark AD pathologies ($A\beta$ plaques and tau neurofibrillary tangles). We have controlled for the extent of AD pathological change by the gold standard of post-mortem neuropathological assessment [55] according the 2012 National Institute on Aging-Alzheimer's Association Guidelines [56] and have excluded individuals with other significant intracerebral pathology.

Methods

Participants

This retrospective cohort study used data obtained for participants in the Brains for Dementia Research (BDR) Programme (<https://www.brainsfordementiaresearch.org.uk/>) and held on the UK Brain Banks Network (UKBBN) database. The database holds demographic and neuropathological details of donated brains, processed and assessed according to detailed and comprehensive post-mortem protocols, as well as clinical assessments undertaken prior to post-mortem as part of the BDR project established in 2007. This links 5 brain banks across the UK (London, Oxford, Newcastle, Bristol and Manchester) with common protocols for consent, tissue handling and quality indicators. Volunteers were recruited via posters, radio adverts, presentations to groups/clubs and signposted via Alzheimer's Research UK and Alzheimer's Society charities. The population comprises many healthy participants with a positive family history of dementia and also participants with a diagnosis of dementia [57]. See Table 1 for inclusion and exclusion criteria.

A spectrum of histopathological findings is represented, ranging from healthy tissue to marked AD neuropathological changes, in individuals both with and without clinical AD dementia. Included participants had full *APOE* genotyping.

Outcome measure

Sleep disturbance was measured by component K of the neuropsychiatric inventory (NPI-K) [58]. These score

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
UK Brain Bank Network Participant Recorded Braak, Thal and CERAD pathological stage Each of the following within 12 months pre-mortem <ul style="list-style-type: none"> • Neuropsychiatry Inventory K measure of sleep disturbance • Clinical Dementia Rating (CDR) global score Age > 50	Significant intracerebral pathology other than Alzheimer's disease including the following: <ul style="list-style-type: none"> • Severe cerebrovascular disease (ischaemic and haemorrhagic) • Lewy body disease as defined by Braak LB stage > 0 • Neoplasia, epilepsy, CNS inflammation, trauma, vascular malformation, prion disease Pathological findings in keeping with dementia other than Alzheimer's dementia including Frontotemporal dementia, vascular dementia and Lewy body dementias

responses provided by an informant, caregiver or study partner including increased latency, increased wake time after sleep onset, wandering, early morning wakening, excessive daytime sleep and sleep-wake cycle disturbance. A global score was obtained by multiplying frequency and severity domains (see Table 2).

Neuropathologic data

Each participant had undergone post-mortem analysis of CERAD neuritic plaque stage, Thal Aβ plaque stage and Braak NFT stage allowing for calculation of the National Institute on Aging-Alzheimer's Association ABC Score [56]. The combination of A, B and C score determine the extent of AD neuropathological change, designated "Not", "Low", "Intermediate" and "High".

Statistical analysis

For data cleaning and analysis, we used R Studio v3.6.3 statistical software. Raw scores were used throughout. Demographic and clinical variables were tested across groups for normality and compared made using Kruskal-Wallis and Pearson chi-squared tests. All tests of significance were two-tailed with $\alpha = 0.05$.

Descriptive statistic was produced with unadjusted means of sleep disturbance by APOE ε4 status. These were calculated for the whole population before being stratified by NIAA-AA ABC score and CDR status. A fourth unadjusted comparison stratified the whole population into four phenotypically separate groups categorised by low CDR (0/0.5) or high CDR (1/2/3) and

low ABC score (none/low) or high ABC score (intermediate/high). These groups are termed 'Healthy' (low CDR and low ABC), 'Other Cognitive Impairment' (high CDR and low ABC), 'Alzheimer's Disease' (low CDR and high ABC) and 'Alzheimer's dementia' (high CDR and high ABC).

The primary outcome measure was determined by multivariate linear regression with NPI-K Sleep Disturbance Global Score as the dependent variable. Crude and adjusted analyses were performed including dummy variables reflecting APOE ε4 allele copy number, with 0 as reference. Covariates were introduced to an adjusted model to control for APOE ε2 allele number, age, gender, CDR sum of boxes (CDR-SOB) and neuropsychiatry inventory measures of depression and anxiety. Dummy variables were created to reflect NIAA-AA ABC neuropathological stages. All regression models were checked for multicollinearity with variance inflation factors < 10. The study is powered at 80% to detect an effect size of $f^2 = 0.088$ ($n = 202$, $\alpha = 0.05$).

As a post hoc sensitivity analysis, these regressions were repeated in groups stratified by NIAA-AA ABC score and CDR status.

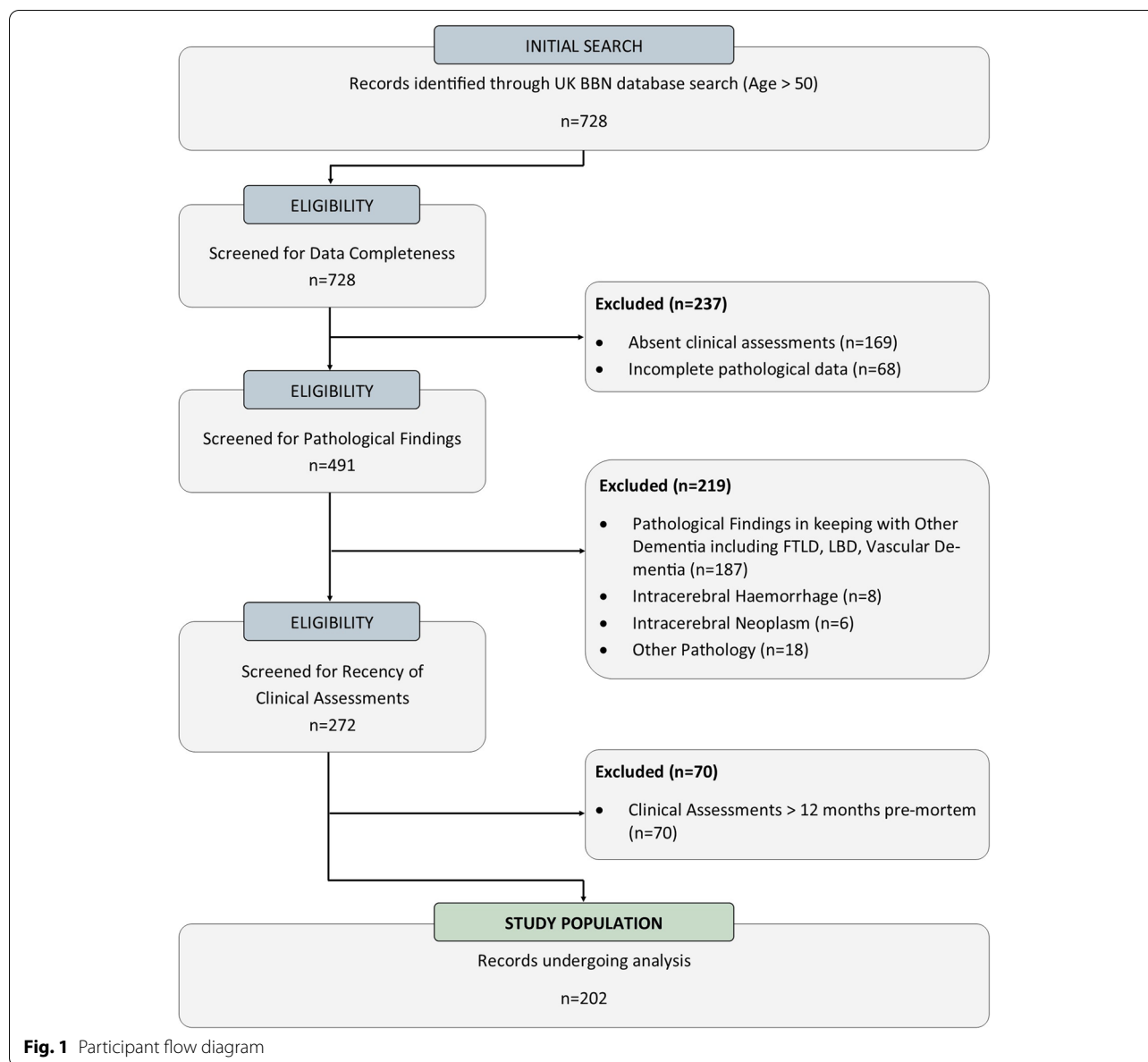
Results

Participant selection

Initial database search yielded $n = 728$ BDR cases, of which $n = 202$ fulfilled our criteria for analysis (See Fig. 1).

Table 2 Neuropsychiatric inventory measure of sleep disturbance (NPI)

Frequency score			Severity score		
1	Occasionally	Less than once per week	1	Mild	Night-time behaviours occur but they are not particularly disruptive
2	Often	About once per week	2	Moderate	Night-time behaviours occur and disturb the participant and the sleep of the caregiver, more than one type of night-time behaviour may be present
3	Frequently	Several times per week but less than every day	3	Marked	Night-time behaviours occur; several types of night-time behaviour may be present; the participant is very distressed during the night and the caregiver's sleep is markedly disturbed
4	Very frequently	Once or more per day			



Baseline demographics

Selected participants had a mean age of 84.0 years (SD = 9.2), 51.0% were male, mean CDR 1.8 (SD = 1.3) and mean Mini-Mental State Examination (MMSE) score 14.0 (SD = 11.8). Baseline demographics of the study population stratified by *APOE*- $\epsilon 4$ allele count (non- $\epsilon 4$ carriers $n = 96$, $\epsilon 4$ heterozygotes $n = 95$, $\epsilon 4$ homozygotes $n = 11$) are shown in Table 3. There were statistically significant differences in AD ABC stage, mean MMSE and mean CDR scores.

Sleep disturbance by *APOE* $\epsilon 4$ status

Crude sleep disturbance scores in the cohort stratified by $\epsilon 4$ are shown in Table 4. There were statistically significant increases in all neuropsychiatry inventory

measures of sleep disturbance between those with 2 vs 0 alleles. Severity, frequency and caregiver distress domains were also significantly higher in those with 2 vs 1 allele. There were increased caregiver distress scores only in those with 1 allele compared with 0.

Positive trends between $\epsilon 4$ allele number and increasing mean NPIK sleep disturbance score were across the full-cohort irrespective of stratification by CDR status, ABC score of neuropathological change and clinical classification (Fig. 2).

Primary analysis

Full multivariate linear regression revealed a statistically significant effect of *APOE* $\epsilon 4$ homozygosity on global

Table 3 Baseline demographics by APOE- $\epsilon 4$ status

	Non $\epsilon 4$ carrier <i>n</i> =96	$\epsilon 4$ heterozygosity <i>n</i> =95	$\epsilon 4$ homozygosity <i>n</i> =11	<i>p</i> value
Mean age (SD)	85.2 (9.1)	83.0 (9.3)	81.5 (8.5)	0.162*
Gender male no. (%)	48 (50.0)	49 (51.6)	6 (54.5)	0.948†
ABC stage				
None	16	3	0	<0.001†
Low	41	18	0	
Intermediate	15	23	4	
High	24	51	7	
Mean MMSE (SD)	16.1 (12.5)	12.2 (11.0)	9.0 (9.8)	0.063*
Mean CDR Global Score (SD)	1.6 (1.3)	2.0 (1.2)	2.8 (0.8)	0.002*
Mean CDR SOB	8.8 (8.0)	12.2 (6.8)	16.2 (5.1)	<0.001*

**p* values calculated by Kruskal-Wallis test

† Chi-squared Test

Table 4 Neuropsychiatry inventory sleep disturbance scores by APOE $\epsilon 4$ status

	Non- $\epsilon 4$ carrier <i>n</i> =96	$\epsilon 4$ Heterozygosity <i>n</i> =95	$\epsilon 4$ Homozygosity <i>n</i> =11	<i>p</i> value*		
				0 vs 1 $\epsilon 4$ Alleles	1 vs 2 $\epsilon 4$ Alleles	0 vs 2 $\epsilon 4$ Alleles
NPI K Global Score (SD)	1.36 (3.3)	2.03 (4.0)	4.55 (5.4)	0.236	0.107	0.024
NPI K Severity Score (SD)	0.42 (0.9)	0.57 (1.0)	1.27 (1.5)	0.135	0.034	0.013
NPI K Frequency Score (SD)	0.67 (1.4)	0.92 (1.6)	1.64 (1.9)	0.103	0.029	0.008
NPI K Caregiver Distress Score (SD)	0.39 (1.2)	0.53 (1.3)	1.00 (1.7)	0.003	0.007	<0.001

**p* values calculated by Wilcoxon rank-sum test

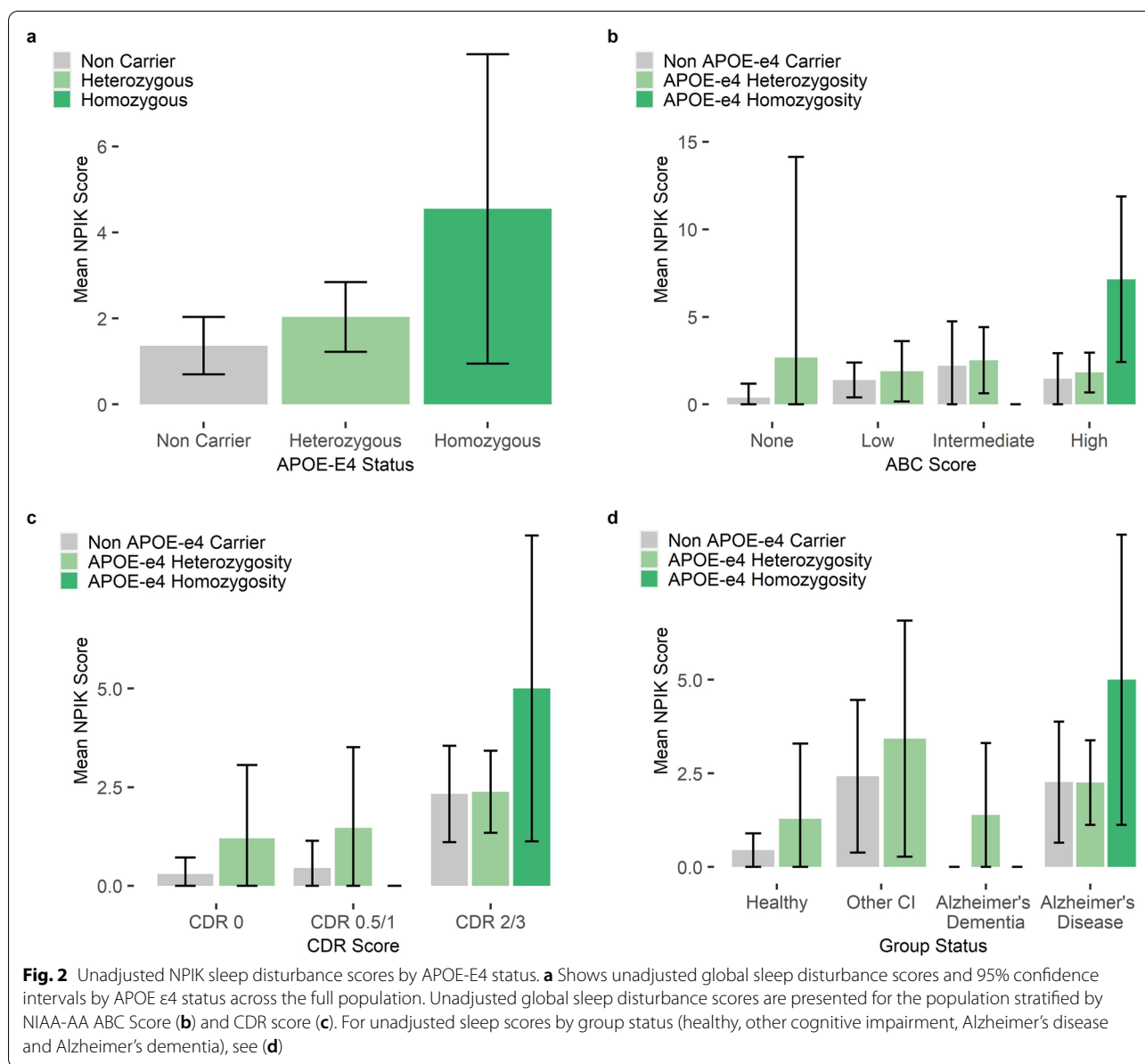
scores of sleep disturbance (β 2.53, $p=0.034$) controlling for AD pathological status, $\epsilon 2$ carrier status, age, gender, depression, anxiety and CDR-SOB status. A positive trend was found for $\epsilon 4$ heterozygosity in both crude (β 0.67, $p=0.221$) and adjusted (β 0.41, $p=0.471$) analyses, although neither reached statistical significance (see Table 5).

Further, multivariate regression testing additional models were performed post hoc (Supplementary Material Table 1). Whilst the effect size estimates for APOE $\epsilon 4$ status within these models differed, overall trends and statistical significance remained unaltered. To further assess the independent effects of APOE $\epsilon 4$ status, further multivariate regressions were performed after stratification of the cohort by neuropathological change and CDR status (Tables 6 and 7). Positive trends between APOE $\epsilon 4$ status and sleep disturbance were seen in all stratified groups. Sleep disturbance was significantly associated with $\epsilon 4$ heterozygosity in the group without clinical dementia (CDR 0/0.5) (β 1.28, $p=0.024$) and with $\epsilon 4$ homozygosity in the relatively cognitively impaired group (CDR 1/2/3) (β 2.95, $p=0.045$).

Discussion

In this large, community-based cohort, APOE $\epsilon 4$ homozygosity was independently associated with sleep disturbance after controlling for the extent of AD neuropathological change, age, gender and affective symptoms, in individuals both with and without dementia. Homozygosity conferred a 2.53 (± 1.18) mean point increase in NPI-K global sleep disturbance score. A non-significant trend towards an increased score was also noted with APOE $\epsilon 4$ heterozygosity, which conferred a 0.41-mean point increase in sleep disturbance score. Within the group without dementia (CDR 0/0.5), $\epsilon 4$ heterozygosity conferred a statistically significant increase in sleep disturbance score of 1.21 points.

Understanding of the relationship between ApoE status and sleep disturbance continues to evolve. Shortening of rapid-eye-movement (REM) sleep in individuals with MCI was significantly more apparent in carriers than non-carriers of the $\epsilon 4$ allele [59]. However, such differences extend beyond populations affected by cognitive impairment. Objective sleep disturbance in healthy adults as measured by polysomnography and actigraphy



was found to be independently associated with the presence of the $\epsilon 4$ allele [28]. Furthermore, in a study that controlled for demographic variables, the $\epsilon 4$ allele was associated with insomnia in those both with and without psychiatric disorders [29]. Improved sleep attenuated the increased risk of AD development conferred by possession of $\epsilon 4$, in particular modifying its effect on neurofibrillary tangle formation [33]. Conversely, $\epsilon 4$ carriers with dementia were found to have slower rates of sleep disturbance progression than non-carriers [60] albeit in a small cohort. Our findings support previous findings indicating that people with one or more *APOE* $\epsilon 4$ alleles are likely to have more impaired sleep but add to these

findings by controlling for the severity of Alzheimer's disease pathology as determined neuropathologically. There are a range of potential explanations for these findings:

Apo E4-mediated AD pathological change

APOE $\epsilon 4$ is thought to influence AD pathology [9] through enhanced $A\beta$ deposition [61], tau phosphorylation and neurotoxicity [62, 63], all of which may lead to sleep abnormalities [64]. For example, in participants with AD, *APOE* $\epsilon 4$ allele status influences CSF measures of tauopathy, itself associated with night-time behaviour disturbance [65]. We have found that $\epsilon 4$ influences sleep independently of $A\beta$ and tau stage. Hence, as well as its

Table 5 NPIK Global Sleep Disturbance Score—full population linear regression

	Crude analysis			Adjusted analysis		
	β	SE	<i>p</i>	β	SE	<i>p</i>
Full population n=202						
<i>APOE</i> $\epsilon 4$ Status ^a						
Heterozygous	0.67	0.54	0.221	0.41	0.57	0.471
Homozygous	3.18	1.20	0.008	2.53	1.18	0.034
NIA-AA ABC Stage ^b						
Low				0.51	0.94	0.590
Intermediate				0.07	1.04	0.943
High				-0.73	1.05	0.493
<i>APOE</i> $\epsilon 2$ carrier status						
Age				1.43	1.24	0.252
Male gender				-0.08	0.03	0.004
NPI-D Global Score (depression)				-0.53	0.50	0.293
NPI-E Global Score (anxiety)				0.01	0.14	0.928
CDR-SOB				0.19	0.13	0.145
				0.13	0.04	0.003

^a Baseline Reference of *APOE* $\epsilon 3/\epsilon 3$, $\epsilon 2/\epsilon 3$, and $\epsilon 2/\epsilon 2$

^b Baseline reference of NIA-AA ABC Score 'None'

Table 6 NPIK Sleep Disturbance Score—adjusted analysis stratified by neuropathological change^a

	β	SE	<i>p</i>
ABC score 0/1 ("None"/"Low"), n=80			
<i>APOE</i> $\epsilon 4$ status ^b			
Heterozygosity	0.97	0.75	0.200
Homozygosity	NA [‡]	NA [‡]	NA [‡]
ABC Score 2/3 ("Intermediate"/"High"), n=129			
<i>APOE</i> $\epsilon 4$ status ^b			
Heterozygous	0.42	0.83	0.609
Homozygous	2.85	1.40	0.045

^a Adjusted by age, gender, *APOE* $\epsilon 2$ status, NPI-D, NPI-E and CDR-SOB

^b Baseline reference *APOE* $\epsilon 3/\epsilon 3$, $\epsilon 2/\epsilon 3$ or $\epsilon 2/\epsilon 2$

[‡] No participants within the ABC 0/1 group with 2 *APOE* $\epsilon 4$ alleles

Table 7 NPIK Sleep Disturbance Score—adjusted analysis stratified by CDR status^a

	β	SE	<i>p</i>
CDR score 0/0.5, n=67			
<i>APOE</i> $\epsilon 4$ status ^b			
Heterozygous	1.21	0.60	0.048
Homozygous	0.13	2.17	0.952
CDR score 1/2/3, n=142			
<i>APOE</i> $\epsilon 4$ status ^b			
Heterozygous	0.10	0.80	0.897
Homozygous	2.77	1.93	0.048

^a Adjusted by age, gender, *APOE* $\epsilon 2$ status, NPI-D, NPI-E and NIA-AA ABC score

^b Baseline reference *APOE* $\epsilon 3/\epsilon 3$, $\epsilon 2/\epsilon 3$ or $\epsilon 2/\epsilon 2$

impact on these hallmark features of AD, *APOE* $\epsilon 4$ may also influence AD risk through other neurotoxic pathways and/or loss of neuroprotective functions [9] that have the potential to influence sleep quality (Fig. 3).

Apo E4-mediated effects on melatonin

In a study of 85 patients with AD, *APOE* $\epsilon 4$ homozygosity compared with heterozygosity was associated with significantly reduced post-mortem CSF melatonin (32pg/ml \pm 8 vs 71 \pm 7, *p*=0.02) [66]. Reduced melatonin has been linked to sundown syndrome in dementia [67, 68], and replacement improves symptoms according to systematic review [69]. However, melatonin is up to five times higher in healthy adults compared with those with AD [66, 67], and it is plausible that *APOE* $\epsilon 4$ may be associated with reduced melatonin via secondary mechanisms linked to AD severity as opposed to direct effects.

Apo E4-mediated sleep disordered breathing

APOE $\epsilon 4$ was reported to be directly associated with OSA and symptomatic sleep disordered breathing [31], possession of this allele being associated with an approximate doubling of risk for apnoea-hypoxic index > 15 [OR 2.0 (1.2–3.5)] in adults and separately in children [32]. Two main mechanisms for a causal relationship were proposed. Firstly, an $\epsilon 4$ -associated increase in respiratory/sleep centre tau or amyloid burden may drive centrally mediated sleep disordered breathing [31]. Alternatively, (or additionally) ApoE4 has a central role in lipid metabolism [70] mediating lipoprotein to cell surface receptor

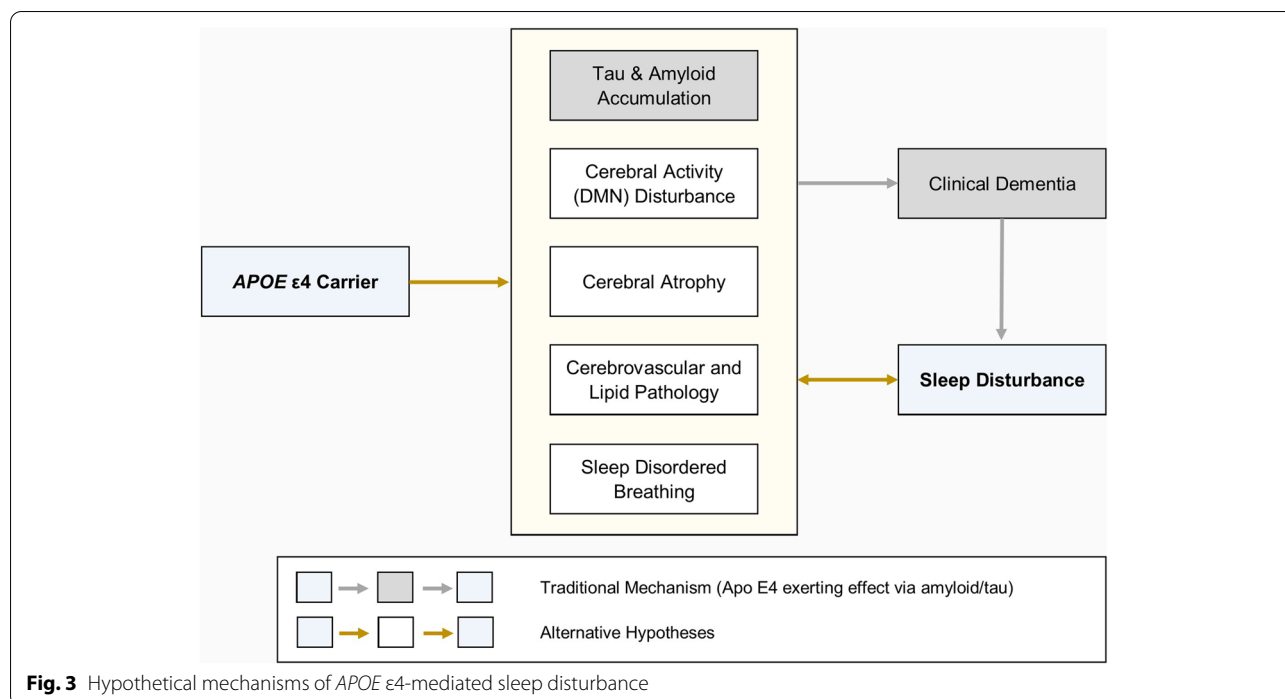


Fig. 3 Hypothetical mechanisms of *APOE* ε4-mediated sleep disturbance

binding, increasing plasma low-density lipoprotein (LDL) levels and accelerating atherogenesis [71]. Centrally mediated sleep disordered breathing is recognised in a wide range of cerebral pathologies [72], including cerebrovascular pathology that might be exacerbated by possession of ε4. A further plausible mechanism, given that *APOE* ε4 predisposes to metabolic syndrome [73] and increased insulin resistance [74] would be through secondary increased obesity; however, ε4 carriers on average have a lower body mass index than do ε3 or ε2 carriers [75, 76]. A systematic review found no support for a causal association between *APOE* ε4 allele and OSA [OR 1.13 (0.86–1.47)] [77], but the authors commented that the studies were heterogeneous, may not have accommodated important gene-gene interactions and may have been underpowered.

Apo E4-mediated cerebral atrophy

Previous work linked possession of ε4 with accelerated age-related cortical thickness loss [78, 79]. This itself was associated with self-reported sleep disturbance in healthy community dwelling adults [80] and reduced objectively measured total sleep time, random eye movement, N2 and N3 stages of sleep in alcohol-use disorder [81].

Apo E4 effects on functional cerebral activity

Baseline activity within the Default Mode Network (DMN)—the distributed network of brain regions more

active during rβ and characterised by high functional connectivity—is greater in *APOE* ε4 carriers than in non-carriers [82–84]. This overactivity was hypothesised to inhibit brain structures stimulating sleep initiation as described within the ‘failure to inhibit wakefulness’ hypothesis of sleep onset [85, 86]. Whilst the mechanism for this is uncertain, the findings extend to young adults aged 20–35, underlining a potential active role for ε4 outside of established AD pathology [83].

Study strengths and limitations

This study is subject to several limitations. Firstly, the sample, whilst deeply characterised, was limited by small numbers in the *APOE*-ε4 homozygous group and relatively small numbers within each neuropathological group within the heterozygous group limiting power to detect full effects. Linked to this, p values of ‘statistically significant’ findings were close to 0.05. Reassuringly, however, the sleep disturbance signal was positively correlated with allele number. Participants in the BDR cohort are mostly from less socially and economically deprived parts of the UK [57] and are not therefore fully representative of the general population in the UK. Medication history was not comprehensive enough for inclusion in our analysis and may represent a significant confounder with prescribed sleep medications ameliorating or masking symptoms. Systemic illness that could have impacted on sleep disturbance may not have been detected post-mortem.

The use of the neuropsychiatry inventory sleep disturbance score as principal outcome measure is a further potential weakness. Whilst broad and encompassing a heterogeneous range of disorders, it relies on caregiver report and is therefore potentially subject to bias, e.g., false negative reports of subtle changes. However, it is well-validated, widely used and its reliance on a semi-objective caregiver as opposed to subjective personal reports also has advantages. Outcome scores for this study were obtained within 12 months of death. At the more distant end of this scale, pathological changes could have evolved between clinical data collection and autopsy; however, recall bias from retrospective data collection is eliminated.

Strengths include the categorisation of participants and quantification of AD changes based on the gold standard of post-mortem neuropathology with application of strict exclusion criteria, allowing for the effects of AD pathology to be largely determined in isolation. Data collected as part of the BDR project is standardised and collected as part of a detailed and comprehensive protocol. The population also reflected a range of AD pathology, with 38.2% of the study population recording ABC Scores of 'Not' or 'Low'.

Conclusion

APOE $\epsilon 4$ homozygosity was associated with sleep disturbance, independent of AD pathological change and clinical functional status. Neuropathologically validated clinical studies often provide the first impetus in developing improved understanding of underlying mechanisms of neurological disease. There are a range of plausible mechanisms by which this effect of *APOE* $\epsilon 4$ may be exerted; further systematic testing of which would enhance understanding of sleep disturbance pathways and may subsequently provide treatment targets for this distressing symptom, also linked to AD progression.

Abbreviations

AD: Alzheimer's disease; *APOE*- $\epsilon 4$: Apolipoprotein E epsilon 4; BDR: Brains for Dementia Research; CDR: Clinical Dementia Rating; CDR-SOB: Clinical Dementia Rating—sum of boxes; CNS: Central nervous system; CSF: Cerebrospinal fluid; DMN: Default Mode Network; LB: Lewy body; MMSE: Mini-Mental State Examination; NIA-AA: National Institute on Aging and Alzheimer's Association; NPI-K: Neuropsychiatry Inventory Measure of Sleep Disturbance; NREM: Non-random eye movement; OR: Odds ratio; OSA: Obstructive sleep apnoea; SD: Standard deviation; TDP-43: Transactive response DNA binding protein-43; UK: United Kingdom.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13195-022-00992-y>.

Additional file 1. Full Population Linear Regression – Additional Models.

Acknowledgements

The Brains for Dementia Research (BDR) Programme (<https://www.brainsfordementiaresearch.org.uk/>) and UK Brain Banks Network (UKBBN) database for collecting and holding data used in this study.

Authors' contributions

Project conception, data analysis and write-up: JB. Project oversight and review: SL, EC and LS. Data preparation and management: RC. The authors read and approved the final manuscript.

Funding

JB receives funding from Alzheimer's Research UK (supported by the Margaret Jost Fellowship and the Don Thoburn Memorial Scholarship), and the David Telling Charitable Trust and EC has received funding from BRACE and ARUK (Bristol & Bath Network).

Availability of data and materials

The dataset used and analysed in this current study are available from the first author on reasonable request.

Declarations

Ethics approval and consent to participate

The Brains for Dementia Research project has been approved by Newcastle & North Tyneside 1 Research Ethics Committee to function as a research tissue bank. Access to the participant data was provided by the UK Brain Banks Network data access Committee and the Brains for Dementia Research data access committee. The participants provided their written informed consent to participate in the Brains for Dementia Research programme.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹North Bristol NHS Trust, Bristol, UK. ²Learning and Research, University of Bristol, Southmead, Bristol BS10 5NB, UK.

Received: 17 January 2022 Accepted: 20 March 2022

Published online: 30 March 2022

References

- Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology*. 1993;43(8):1467–72.
- Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261(5123):921–3.
- Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *APOE and Alzheimer Disease Meta Analysis Consortium*. *JAMA*. 1997;278(16):1349–56.
- Genin E, Hannequin D, Wallon D, Sleegers K, Hiltunen M, Combarros O, et al. *APOE* and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry*. 2011;16(9):903–7.
- Sando SB, Melquist S, Cannon A, Hutton ML, Sletvold O, Saltvedt I, et al. *APOE* epsilon 4 lowers age at onset and is a high risk factor for Alzheimer's disease; a case control study from central Norway. *BMC Neurol*. 2008;8:9.
- Sahota A, Yang M, Gao S, Hui SL, Baiyewu O, Gureje O, et al. Apolipoprotein E-associated risk for Alzheimer's disease in the African-American population is genotype dependent. *Ann Neurol*. 1997;42(4):659–61.
- Reitz C, Jun G, Naj A, Rajbhandary R, Vardarajan BN, Wang LS, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4,

- and the risk of late-onset Alzheimer disease in African Americans. *JAMA*. 2013;309(14):1483–92.
8. Tang MX, Stern Y, Marder K, Bell K, Gurland B, Lantigua R, et al. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. *JAMA*. 1998;279(10):751–5.
 9. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol*. 2013;9(2):106–18.
 10. Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, et al. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proc Natl Acad Sci U S A*. 1993;90(20):9649–53.
 11. Polvikoski T, Sulkava R, Haltia M, Kainulainen K, Vuorio A, Verkkoniemi A, et al. Apolipoprotein E, dementia, and cortical deposition of beta-amyloid protein. *N Engl J Med*. 1995;333(19):1242–7.
 12. Kok E, Haikonen S, Luoto T, Huhtala H, Goebeler S, Haapasalo H, et al. Apolipoprotein E-dependent accumulation of Alzheimer disease-related lesions begins in middle age. *Ann Neurol*. 2009;65(6):650–7.
 13. Rannikmäe K, Kalaria RN, Greenberg SM, Chui HC, Schmitt FA, Samarasekera N, et al. APOE associations with severe CAA-associated vasculopathic changes: collaborative meta-analysis. *J Neurol Neurosurg Psychiatry*. 2014;85(3):300–5.
 14. Shinohara M, Murray ME, Frank RD, DeTure M, Yamazaki Y, Tachibana M, et al. Impact of sex and APOE4 on cerebral amyloid angiopathy in Alzheimer's disease. *Acta Neuropathol*. 2016;132(2):225–34.
 15. Chalmers K, Wilcock GK, Love S. APOE epsilon 4 influences the pathological phenotype of Alzheimer's disease by favouring cerebrovascular over parenchymal accumulation of A beta protein. *Neuropathol Appl Neurobiol*. 2003;29(3):231–8.
 16. Love S, Chalmers K, Ince P, Esiri M, Attems J, Jellinger K, et al. Development, appraisal, validation and implementation of a consensus protocol for the assessment of cerebral amyloid angiopathy in post-mortem brain tissue. *Am J Neurodegener Dis*. 2014;3(1):19–32.
 17. Brecht WJ, Harris FM, Chang S, Tesseur I, Yu GQ, Xu Q, et al. Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. *J Neurosci*. 2004;24(10):2527–34.
 18. Small GW, Mazziotta JC, Collins MT, Baxter LR, Phelps ME, Mandelkern MA, et al. Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. *JAMA*. 1995;273(12):942–7.
 19. Jagust WJ, Landau SM, AS DN I. Apolipoprotein E, not fibrillar beta-amyloid, reduces cerebral glucose metabolism in normal aging. *J Neurosci*. 2012;32(50):18227–33.
 20. Zhao N, Liu CC, Van Ingelgom AJ, Martens YA, Linares C, Knight JA, et al. Apolipoprotein E4 impairs neuronal insulin signaling by trapping insulin receptor in the endosomes. *Neuron*. 2017;96(1):115–29.e5.
 21. Halliday MR, Pomara N, Sagare AP, Mack WJ, Frangione B, Zlokovic BV. Relationship between cyclophilin A levels and matrix metalloproteinase 9 activity in cerebrospinal fluid of cognitively normal apolipoprotein e4 carriers and blood-brain barrier breakdown. *JAMA Neurol*. 2013;70(9):1198–200.
 22. Schilling S, DeStefano AL, Sachdev PS, Choi SH, Mather KA, DeCarli CD, et al. APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. *Neurology*. 2013;81(3):292–300.
 23. Hanson AJ, Banks WA, Hernandez Saucedo H, Craft S. Apolipoprotein E genotype and sex influence glucose tolerance in older adults: a cross-sectional study. *Dement Geriatr Cogn Dis Extra*. 2016;6(1):78–89.
 24. Arendt T, Schindler C, Brückner MK, Eschrich K, Bigl V, Zedlick D, et al. Plastic neuronal remodeling is impaired in patients with Alzheimer's disease carrying apolipoprotein epsilon 4 allele. *J Neurosci*. 1997;17(2):516–29.
 25. Keene CD, Cudaback E, Li X, Montine KS, Montine TJ. Apolipoprotein E isoforms and regulation of the innate immune response in brain of patients with Alzheimer's disease. *Curr Opin Neurobiol*. 2011;21(6):920–8.
 26. Josephs KA, Whitwell JL, Weigand SD, Murray ME, Tosakulwong N, Liesinger AM, et al. TDP-43 is a key player in the clinical features associated with Alzheimer's disease. *Acta Neuropathol*. 2014;127(6):811–24.
 27. Wennberg AM, Tosakulwong N, Lesnick TG, Murray ME, Whitwell JL, Liesinger AM, et al. Association of apolipoprotein E epsilon 4 with transactive response DNA-binding protein 43. *JAMA Neurol*. 2018;75(11):1347–54.
 28. Drogos LL, Gill SJ, Tyndall AV, Raneri JK, Parboosingh JS, Naef A, et al. Evidence of association between sleep quality and APOE epsilon 4 in healthy older adults: a pilot study. *Neurology*. 2016;87(17):1836–42.
 29. Wang CC, Lung FW. The role of PGC-1 and Apoe4 in insomnia. *Psychiatr Genet*. 2012;22(2):82–7.
 30. Gottlieb DJ, DeStefano AL, Foley DJ, Mignot E, Redline S, Givelber RJ, et al. APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: the Sleep Heart Health Study. *Neurology*. 2004;63(4):664–8.
 31. Kadotani H, Kadotani T, Young T, Peppard PE, Finn L, Colrain IM, et al. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. *JAMA*. 2001;285(22):2888–90.
 32. Gozal D, Capdevila OS, Kheirandish-Gozal L, Crabtree VM. APOE epsilon 4 allele, cognitive dysfunction, and obstructive sleep apnea in children. *Neurology*. 2007;69(3):243–9.
 33. Lim AS, Yu L, Kowgier M, Schneider JA, Buchman AS, Bennett DA. Modification of the relationship of the apolipoprotein E epsilon 4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurol*. 2013;70(12):1544–51.
 34. Spira AP, Blackwell T, Stone KL, Redline S, Cauley JA, Ancoli-Israel S, et al. Sleep-disordered breathing and cognition in older women. *J Am Geriatr Soc*. 2008;56(1):45–50.
 35. O'Hara R, Schröder CM, Kraemer HC, Kryla N, Cao C, Miller E, et al. Nocturnal sleep apnea/hypopnea is associated with lower memory performance in APOE epsilon4 carriers. *Neurology*. 2005;65(4):642–4.
 36. Cosentino FI, Bosco P, Drago V, Prestianni G, Lanuzza B, Iero I, et al. The APOE epsilon4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. *Sleep Med*. 2008;9(8):831–9.
 37. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC Jr, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet*. 1994;7(2):180–4.
 38. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet*. 2007;39(1):17–23.
 39. Yyrum E, Balbay O, Annakkaya AN, Gulec Balbay E, Silan F, Arbak P. The relationship between obstructive sleep apnea syndrome and apolipoprotein E genetic variants. *Respiration*. 2015;89(3):195–200.
 40. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry*. 1992;49(8):651–68 discussion 69–70.
 41. Weldemichael DA, Grossberg GT. Circadian rhythm disturbances in patients with Alzheimer's disease: a review. *Int J Alzheimers Dis*. 2010;2010:1.
 42. Prinz PN, Peskind ER, Vitaliano PP, Raskind MA, Eisdorfer C, Zemczukov N, et al. Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. *J Am Geriatr Soc*. 1982;30(2):86–93.
 43. Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP, et al. Sleep quality and preclinical Alzheimer disease. *JAMA Neurol*. 2013;70(5):587–93.
 44. Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep*. 2013;36(7):1027–32.
 45. Sprecher KE, Kosciak RL, Carlsson CM, Zetterberg H, Blennow K, Okonkwo OC, et al. Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. *Neurology*. 2017;89(5):445–53.
 46. Mander BA, Winer JR, Jagust WJ, Walker MP. Sleep: a novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer's disease? *Trends Neurosci*. 2016;39(8):552–66.
 47. Fultz NE, Bonmassar G, Setsompop K, Stickgold RA, Rosen BR, Polimeni JR, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science*. 2019;366(6465):628–31.
 48. Ju YE, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nat Rev Neurol*. 2014;10(2):115–9.
 49. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119–28.
 50. Braak H, Alafuzoff I, Arzberger T, Kretschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. 2006;112(4):389–404.
 51. Ehrenberg AJ, Suemoto CK, França Resende EP, Petersen C, Leite REP, Rodriguez RD, et al. Neuropathologic correlates of psychiatric symptoms in Alzheimer's disease. *J Alzheimers Dis*. 2018;66(1):115–26.
 52. Wennberg AMV, Wu MN, Rosenberg PB, Spira AP. Sleep disturbance, cognitive decline, and dementia: a review. *Semin Neurol*. 2017;37(4):395–406.

53. Lu J, Greco MA, Shiromani P, Saper CB. Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *J Neurosci*. 2000;20(10):3830–42.
54. Mander BA, Marks SM, Vogel JW, Rao V, Lu B, Saletin JM, et al. β -amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci*. 2015;18(7):1051–7.
55. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener*. 2019;14(1):32.
56. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathological assessment of Alzheimer's disease. *Alzheimers Dement*. 2012;8(1):1–13.
57. Francis PT, Costello H, Hayes GM. Brains for dementia research: evolution in a longitudinal brain donation cohort to maximize current and future value. *J Alzheimers Dis*. 2018;66(4):1635–44.
58. Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. *Neurology*. 1997;48(5 Suppl 6):S10–6.
59. Hita-Yanez E, Atienza M, Gil-Neciga E, Cantero JL. Disturbed sleep patterns in elders with mild cognitive impairment: the role of memory decline and ApoE epsilon4 genotype. *Curr Alzheimer Res*. 2012;9(3):290–7.
60. Yesavage JA, Friedman L, Kraemer H, Tinklenberg JR, Salehi A, Noda A, et al. Sleep/wake disruption in Alzheimer's disease: APOE status and longitudinal course. *J Geriatr Psychiatry Neurol*. 2004;17(1):20–4.
61. Ellis RJ, Olichney JM, Thal LJ, Mirra SS, Morris JC, Beekly D, et al. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, Part XV. *Neurology*. 1996;46(6):1592–6.
62. Huang Y. Abeta-independent roles of apolipoprotein E4 in the pathogenesis of Alzheimer's disease. *Trends Mol Med*. 2010;16(6):287–94.
63. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2006;103(15):5644–51.
64. Lloret M-A, Cervera-Ferri A, Nepomuceno M, Monllor P, Esteve D, Lloret A. Is Sleep Disruption a Cause or Consequence of Alzheimer's Disease? Reviewing Its Possible Role as a Biomarker. *Int J Mol Sci*. 2020;21(3):1168.
65. de Oliveira FF, Miraldo MC, de Castro-Neto EF, de Almeida SS, Matas SLA, Bertolucci PHF, et al. Associations of neuropsychiatric features with cerebrospinal fluid biomarkers of amyloidogenesis and neurodegeneration in dementia with Lewy bodies compared with Alzheimer's disease and cognitively healthy people. *J Alzheimers Dis*. 2021;81(3):1295–309.
66. Liu RY, Zhou JN, van Heerikhuizen J, Hofman MA, Swaab DF. Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoprotein E-epsilon4/4 genotype. *J Clin Endocrinol Metab*. 1999;84(1):323–7.
67. Mishima K, Tozawa T, Satoh K, Matsumoto Y, Hishikawa Y, Okawa M. Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep-waking. *Biol Psychiatry*. 1999;45(4):417–21.
68. Volic L, Harper DG, Manning BC, Goldstein R, Satlin A. Sundowning and circadian rhythms in Alzheimer's disease. *Am J Psychiatry*. 2001;158(5):704–11.
69. de Jonghe A, Korevaar JC, van Munster BC, de Rooij SE. Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. *Int J Geriatr Psychiatry*. 2010;25(12):1201–8.
70. Huang Y, Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiol Dis*. 2014;72(Pt A):3–12.
71. Huang Y. Mechanisms linking apolipoprotein E isoforms with cardiovascular and neurological diseases. *Curr Opin Lipidol*. 2010;21(4):337–45.
72. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. *Sleep*. 1999;22(2):217–23.
73. El-Lebedy D, Raslan HM, Mohammed AM. Apolipoprotein E gene polymorphism and risk of type 2 diabetes and cardiovascular disease. *Cardiovasc Diabetol*. 2016;15:12.
74. Elosua R, Demissie S, Cupples LA, Meigs JB, Wilson PW, Schaefer EJ, et al. Obesity modulates the association among APOE genotype, insulin, and glucose in men. *Obes Res*. 2003;11(12):1502–8.
75. Tejedor MT, Garcia-Sobreviela MP, Ledesma M, Arbones-Mainar JM. The apolipoprotein E polymorphism rs7412 associates with body fatness independently of plasma lipids in middle aged men. *PLoS One*. 2014;9(9):e108605.
76. Volcik KA, Barkley RA, Hutchinson RG, Mosley TH, Heiss G, Sharrett AR, et al. Apolipoprotein E polymorphisms predict low density lipoprotein cholesterol levels and carotid artery wall thickness but not incident coronary heart disease in 12,491 ARIC study participants. *Am J Epidemiol*. 2006;164(4):342–8.
77. Thakre TP, Mamtani MR, Kulkarni H. Lack of association of the APOE epsilon 4 allele with the risk of obstructive sleep apnea: meta-analysis and meta-regression. *Sleep*. 2009;32(11):1507–11.
78. Espeseth T, Westlye LT, Fjell AM, Walhovd KB, Rootwelt H, Reinvang I. Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E epsilon 4. *Neurobiol Aging*. 2008;29(3):329–40.
79. Fennema-Notestine C, Panizzon MS, Thompson WR, Chen CH, Eyler LT, Fischl B, et al. Presence of ApoE epsilon4 allele associated with thinner frontal cortex in middle age. *J Alzheimers Dis*. 2011;26(Suppl 3):49–60.
80. Sexton CE, Storsve AB, Walhovd KB, Johansen-Berg H, Fjell AM. Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology*. 2014;83(11):967–73.
81. Zhang R, Tomasi D, Manza P, Shokri-Kojori E, Demiral SB, Feldman DE, et al. Sleep disturbances are associated with cortical and subcortical atrophy in alcohol use disorder. *Transl Psychiatry*. 2021;11(1):428.
82. Bondi MW, Houston WS, Eyler LT, Brown GG. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology*. 2005;64(3):501–8.
83. Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, et al. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci U S A*. 2009;106(17):7209–14.
84. Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, et al. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med*. 2000;343(7):450–6.
85. Espie CA, Broomfield NM, MacMahon KM, Macphee LM, Taylor LM. The attention-intention-effort pathway in the development of psychophysiological insomnia: a theoretical review. *Sleep Med Rev*. 2006;10(4):215–45.
86. Marques DR, Gomes AA, Clemente V, Moutinho dos Santos J, Castelo-Branco M. Default-mode network activity and its role in comprehension and management of psychophysiological insomnia: a new perspective. *New Ideas Psychol*. 2015;36:30–7.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

