Longitudinal association of apolipoprotein E and sleep with incident dementia

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Abstract

INTRODUCTION: Few longitudinal studies have explored the association between *ApoE* status, sleep disturbances and incident dementia among middle-aged participants.

METHODS: Cox regression analyses explored the association of sleep duration, insomnia, and daytime napping with incident all-cause dementia and their interaction with *ApoE* genetic risk among 397,777 middle-aged adults.

RESULTS: During a median of 10.8 years follow-up, sleeping more or fewer than 7 hours was associated with a higher dementia risk (hazard ratio [HR] for 5 vs 7 hours: 1.35, 95% confidence interval [CI]: 1.11–1.64; HR for 9 vs 7 hours: 1.59; 95% CI: 1.37–1.85) as was daytime napping (HR for often/all of the time vs never/rarely: 1.67; 95% CI: 1.37–2.03). Stratified analyses revealed that effects of sleep disturbances were similar across all *ApoE* genetic risk groups.

DISCUSSION: Short and long sleep duration, and daytime napping in middle-aged individuals are associated with the development of dementia in later life. Sleep duration and quality are important for everyone regardless of their genetic risk by *ApoE* genotype.

KEYWORDS: sleep duration, insomnia, daytime napping, APOE, dementia, longitudinal design, Cox regression, UK Biobank

1. Introduction

Dementia is one of the leading causes of disability, affecting around 50 million people worldwide[1]. It is known that both genetic and lifestyle factors play a role in the development of dementia. The ε4 allele of the Apolipoprotein E gene (*ApoE*) is known to be the most impactful genetic risk factor for late-onset Alzheimer's disease[2,3,4], and has been identified as a risk factor for other dementia subtypes as well[5,6]. In populations with European ancestry, the *ApoE* ε4/ε4 genotype has been linked to a 14-fold increase in risk for Alzheimer's disease, compared to the most common ε3/ε3 genotype[2]. The ε2/ε2 genotype on the other hand, has been found to confer decreased risk[2]. While genotypes are currently unmodifiable, a recent study[7] suggests that risk associated with genotypes may be offset by following a favourable lifestyle. As there are currently no disease-modifying therapies available for dementia, it is important to find and address modifiable lifestyle factors that can delay or prevent dementia onset[8].

One potentially modifiable risk factor is sleep. Waking up too early, difficulty falling or staying asleep and excessive nighttime or daytime sleeping are common and of growing concern in the population[9]. Prospective studies report short sleep duration[10,11], long sleep duration[11,12] and daytime napping[13,14,15] to be associated with cognitive decline and increased dementia risk. Recent meta-analyses show a U-shaped relationship between sleep duration and incident dementia, with lowest risk among those sleeping 7 hours a night[16,17]. Evidence for insomnia is more inconsistent, as some report an association with increased dementia risk[18,19], some report no association[20,21], and one meta-analysis showed insomnia to be associated with increased risk of all-cause dementia in studies with short follow-ups (<10 years) but not in studies with long follow-ups (>10 years)[16].

In fact, the majority of evidence on the association between sleep disturbances and incident dementia comes from studies that are either cross-sectional or have a follow-up of

<10 years[22,23]. Given that neurodegenerative changes that may contribute or be the cause of sleep disturbances can take place decades before dementia onset[24], there is a lack of longer-term longitudinal data. Another limitation in current evidence is that the majority of studies examine participants past middle-age (>65)[22], and the relationship found between sleep disturbances and dementia may be due to the early changes linked to dementia progression. Further, the role of *ApoE* in the association of sleep with dementia needs consideration, as the *ApoE* ε4 allele is associated with both dementia and sleep disturbances[25,26]. It would be plausible for *ApoE* status and sleep to interact on dementia risk, but few studies have investigated a possible interaction effect. These studies have found inconsistent results and have been limited by elderly samples[27,28], short follow-ups[27] and sex-specific samples[29].

The purpose of this study was to investigate the association of *ApoE* and sleep with incident dementia in middle-aged participants using data from a large population-based cohort. First, we aimed to examine whether short and long sleep duration, insomnia and excessive daytime napping are associated with an increased risk of developing all-cause dementia. And second, we examined whether *ApoE* status modifies the relationship between sleep duration and dementia; insomnia and dementia; and daytime napping and dementia. To our knowledge, this is the first analysis of a longer-term large single cohort study investigating the association between *ApoE* genotype, sleep in middle-aged participants and incident dementia and adds to the literature aiming to identify individuals who could most benefit from preventative strategies targeted at sleep.

2. Methods

2.1. Study Population

The UK Biobank is a population-based cohort of 502,538 adults recruited between 2006 and 2010[30]. Participants attended one of the 22 centers across England, Scotland and

Wales for baseline assessments for phenotyping, biological sample collection, self-reported questionnaires and nurse interviews. Participants also provided consent to linkage of electronic health records from primary care, hospital attendances and death certification to their study data. Information on the data collected has been published[30] and is available on the UK Biobank website.

Ethics approval for the UK Biobank study was obtained from the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee. Participants provided informed consent through electronic signature at baseline. We applied for and were given permission to use UK Biobank data under study number 40055.

We restricted our analyses to those with data available across all variables and excluded participants with self-reported 'dementia, Alzheimer's disease, or cognitive impairment' at baseline or dementia identified via primary care, hospital admission or death register records at or within two years of baseline assessments.

2.2. ApoE genotyping and risk

UK Biobank genotyping was performed using the Affymetrix UK BiLEVE Axiom Array and the Affymetrix UK Biobank Axiom Array[31]. Both arrays include the Single Nucleotide Polymorphisms (SNPs) rs7412 and rs429358 which dictate the protein isoform generated from the *ApoE* gene (Table A.1). UK Biobank undertook SNP quality control in several stages for a large number of batches, increasing data consistency[31]. Since the SNP data was unphased, there was one (low frequency) combination of alleles where the genotype could not be unambiguously inferred (Table A.2).

Extensive evidence suggests that compared to the most common 'risk neutral' ε3 allele of the *ApoE* gene, the ε2 allele offers neuroprotective effects, whereas the ε4 allele is

associated with a higher risk of developing Alzheimer's disease and is associated with non-Alzheimer's neuropathology as well[3,4,5,32]. Based on this evidence, participants' genetic risk by *ApoE* status was categorised into low (ε2/ε2, ε1/ε2, ε2/ε3), neutral (ε3/ε3), intermediate (ambiguous ε2/ε4 or ε1/ε3), somewhat high (ε3/ε4) and high risk (ε4/ε4) categories in accordance with SNPedia[33] categorisation.

2.3. Sleep Measures

Sleep measures were assessed at baseline via self-reported electronic touch-screen questionnaires. Sleep duration was assessed with the question: 'About how many hours sleep do you get in every 24 hours? Please include naps.' To allow for a non-linear relationship between sleep duration and dementia, sleep duration was categorized into ≤5, 6, 7, 8 and ≥9-hour categories based on the median values of the data. Seven hours was chosen as the reference category, as this was the median in the data and has been associated with the lowest risk of dementia[17]. Insomnia was assessed with the question: 'Do you have trouble falling asleep at night or do you wake up in the middle of the night?'. Response options were: never/rarely, sometimes and usually, where never/rarely was chosen as the reference category. 'Daytime napping was assessed with the question: 'How likely are you to doze off or fall asleep during the daytime when you don't mean to? e.g. when working, reading or driving'. Response options were: never/rarely, sometimes, often and all of the time. Three categories were constructed: never/rarely, sometimes and often/all of the time, where never/rarely was chosen as the reference category.

2.4. Ascertainment of Incident Dementia

All-cause incident dementia was ascertained through self-report and ICD-9/10 diagnostic codes in linked primary care data, hospital inpatient and death register records.

Across UK Biobank and all three linked databases, the positive predictive value for all-cause dementia has been found to be 82.5%[34].

2.5. Demographic and clinical characteristics

Demographic and other characteristics were collected at baseline through physical measurements and self-reported electronic questionnaires (Table A.3) and included sex; age; education, categorised as higher (college or university degree), upper secondary (secondary education's second or final stage), lower secondary (secondary education's first stage), vocational (professional qualification), and other; ethnic background categorised as White and non-White; socioeconomic status (quintiles derived from Townsend deprivation index combining information on employment, social class, housing and car availability); body mass index as a continuous covariate; smoking status, categorized as never, previous and current; alcohol drinker status, categorized as never, previous and current; diabetes as a binary covariate; physical inactivity (binary covariate based on World Health Organization's recommendation on metabolic equivalent minutes of moderate/vigorous activity per week[35], <600=inactive, ≥600=active); history of major depression disorder as a binary covariate; and number of medications taken as an indicator of medical comorbidity as a continuous covariate.

2.6. Statistical Analyses

Baseline characteristics of the sample were summarised for those with and without incident dementia status as mean and standard deviation for continuous variables and as frequencies and percentages for categorical variables. Longitudinal associations were examined with multivariable Cox proportional hazard regression models. Separate statistical models were fitted for each of *ApoE* genetic risk, sleep duration, insomnia and daytime

napping with time to incident all-cause dementia as the outcome in each. Participants were considered at risk for dementia from the date they were recruited (2006-2010). They were followed up until whichever came first: date of first diagnosis, date of death, date lost to follow-up or the last date of the study (19th of November 2019).

Covariates were chosen a priori from the literature on the basis of their potential to confound the relationship between sleep and dementia[8,36,37,38]. Variables assumed to potentially contribute to the development of dementia and related to sleep disturbances, such as cardiovascular diagnoses were not adjusted for because of the possibility of being on the causal pathway.

All models were first fitted minimally adjusted for sex, age and educational level and then further adjusted for ethnic background, socioeconomic status, body mass index, smoking status, alcohol drinker status, diabetes, physical inactivity, depression and number of medications taken. Finally, adjusting for all covariates, we refitted each model including an interaction term between genetic risk and the sleep measure of interest. All analyses were carried out using Stata SE, version 15.1 (StataCorp) and all main analyses were pre-specified.

To investigate the possibility of reverse causality, the associations of sleep measures and incident dementia were examined in sensitivity analyses excluding participants who developed dementia within 6 years of baseline assessments and in analyses stratified by age at recruitment (middle-aged [<65 years] or older adults [≥65 years]). Additional analyses stratified by sex were also performed. Schoenfeld residuals were used to perform a check for proportionality of hazards in all fully adjusted main models.

2.7. Missing Data

There were missing data on *ApoE* genotype (17.8%), sleep duration (0.8%), insomnia (0.3%), daytime dozing (0.8%), ethnic background (0.6%), socioeconomic status (0.1%),

education (2.0%), body mass index (0.6%), smoking status (0.6%), alcohol drinker status (0.3%), diabetes (0.3%) and number of medications taken (0.2%). Cumulatively, 20.8% of the sample were missing data on at least one variable. The proportion of missing *ApoE* data did not differ considerably between those who later developed dementia (18.6%) and those who did not develop dementia (17.8%). As missingness was mostly related to *ApoE* genotype and was probably due to poor quality samples[31] and thus likely to be missing at random, a complete-case analysis was conducted.

3. Results

The UK Biobank assessed 502,538 participants at baseline. After excluding participants with dementia at baseline or diagnosed within two years from baseline assessment (n = 277) and those without complete case data (n = 104,488), 397,773 participants were included in the analyses (Fig. A.1). Baseline characteristics of the participants are presented in Table 1. Over 4,213,895 person-years follow-up time (median 10.8, range 0.1–12.9 years), 1823 (0.46%) incidences of all-cause dementia occurred in the 397,777 participants, equivalent to 4.6 cases per 1000 population. Overall, participants' mean age at baseline was 56.5 (SD 8.1, range 38–73), the majority were women (54.8%) and of White ethnicity (94.5%).

3.1. Genetic risk and dementia

Risk of incident dementia increased across *ApoE* genetic risk categories after adjustment for age, sex and education (Table 2). Additional adjustment for sleep measures and potential confounders did not change these results, indicating that the effect of genetic risk by *ApoE* on incident dementia was independent of sleep duration, insomnia and daytime napping.

3.2. Sleep duration and dementia risk

A U-shaped relationship between sleep duration categories and risk of dementia was observed (Table 3). After adjustment for age, sex and education, participants in the ≤5-hour sleep category had a 69% increase in the rate of dementia incidence (HR: 1.69; 95% CI: 1.40–2.04), whereas participants in the ≥9 sleep category had a 76% increase in the rate of dementia incidence (HR: 1.76; 95% CI: 1.52–2.05) compared to participants in the 7-hour sleep category. Although further adjustment for potential confounders slightly attenuated these effect estimates, there was still evidence to suggest that sleep duration was associated with dementia risk independent of genetic risk and the covariates adjusted for, with the exception that 6 hours was no longer associated with an increased dementia rate (HR: 1.12; 95% CI: 0.97–1.28).

3.3. Insomnia and dementia risk

After adjustment for age, sex and education, participants experiencing insomnia sometimes, had a 28% reduction in the rate of dementia incidence, whereas those experiencing insomnia usually had a 23% reduction compared to those experiencing insomnia never/rarely (HR: 0.72; 95% CI: 0.64–0.81 and HR: 0.77; 95% CI: 0.68–0.87, respectively; Table 3). Further adjustment increased these effect estimates and their precision suggesting that insomnia was associated with reduced dementia risk independent of genetic risk and the covariates adjusted for.

3.4. Daytime napping and dementia risk

The risk of developing dementia increased in a dose-response manner across daytime napping categories (Table 3). After adjustment for age, sex and education, participants napping sometimes had a 15% increase in the rate of dementia incidence (HR: 1.15; 95% CI:

1.04–1.27), whereas those who napped often/all of the time had over double the rate (HR: 2.07; 95% CI: 1.71–2.51) compared to those who napped never/rarely. Full adjustment attenuated the effect estimates, but there was still evidence to suggest that daytime napping was associated with dementia risk independent of genetic risk and the covariates adjusted for. After full adjustment, napping sometimes was no longer associated with an increased dementia risk compared to napping never/rarely (HR: 1.07; 95% CI: 0.96-1.18).

3.5. Sensitivity analyses

We performed sensitivity analyses exploring the effects of sleep measures on incident dementia excluding participants (n = 746) who developed dementia within 6 years of baseline assessment. The results followed the same pattern as the main analyses although with less precision due to a reduced number of dementia cases (Table A.4). The patterns of results were similar when stratified by age but differed slightly when stratified by sex (Table A.5; Table A.6). Specifically, the effects of sleeping 5 hours compared to 7 hours on dementia incidence were stronger among men than women (HR: 1.57; 95% CI: 1.20–2.05 and 1.17; 95% CI: 0.89–1.53, respectively), as were the effects of sleeping 9 hours compared to 7 hours (HR: 1.70; 95% CI: 1.39–2.08 and HR: 1.49; 95% CI: 1.19–1.87, respectively).

3.6. Interaction between genetic risk and sleep factors on dementia risk

To maintain statistical power for the interaction and subgroup analyses, sleep duration was recategorized into ≤6 hours, 7 and ≥8 hours of sleep, and genetic risk by *ApoE* into lower (ε1/ε2, ε2/ε3, ε2/ε2), neutral (ε3/ε3) and higher risk (ambiguous ε2/ε4 or ε1/ε3, ε3/ε4, ε4/ε4). Although the ε2 confers lower risk, the ε2/ε4 genotype was categorized into higher risk and not neutral risk, as it has been found to confer a higher risk for Alzheimer's disease than the ε3/ε3 genotype (OR: 2.6; 95% CI: 1.6–4.0)[2].

There was weak evidence of an interaction between *ApoE* and sleep duration on incident dementia (*P* = .0211; Table A.7). Analyses stratified by *ApoE* categories showed that the patterns of sleep duration's effects were similar in all three genetic risk categories, with the exception of ≤6 hours in low genetic risk group, which seems to drive the interaction (Fig. 1.).

There was no evidence of an interaction between insomnia and *ApoE* status (*P* = .6005), suggesting that the effects of insomnia on dementia incidence did not vary on the basis of *ApoE* categories (Table A.7; Fig.2).

There was weak evidence of an interaction between daytime napping and *ApoE* status (*P* = .0294; Table A.7). Analyses stratified by *ApoE* categories showed that the pattern of daytime napping's effects were similar in all three genetic risk categories, with the exception of the sometimes category in the higher genetic risk group, which seems to drive the interaction (Fig. 3.).

The proportionality of hazards assumption was satisfied for models of sleep duration (*P* = .15) and insomnia (*P* = .21), but there was weak evidence that it was not met for daytime napping (*P* = .03).

4. Discussion

4.1 Summary of main findings

ApoE status, sleep duration, insomnia and daytime napping were independently associated with incident all-cause dementia. Sleeping ≤5 and ≥8 hours, compared to 7 hours, as well as napping often or all of the time during daytime, compared to never or rarely was associated with a higher dementia risk. Contrary to expectation, experiencing insomnia sometimes or usually, compared to never or rarely, was associated with a lower dementia risk. Further, we found weak statistical evidence of an interaction between *ApoE* and sleep

duration, and between *ApoE* and daytime napping, but the patterns of results were similar across all genetic risk group categories. The effects of sleep duration and daytime napping on dementia risk are therefore better explained by the main effects, indicating that sleep duration and quality are important for everyone.

4.2. Comparison with previous literature

The findings complement longitudinal studies reporting short and long sleep duration and excessive daytime napping to increase dementia risk[10,11,12,13,14,15,39,]. Recent meta-analyses report a U-shaped relationship between sleep duration and dementia[16,17], and an association between daytime napping and increased dementia risk[21]. This study confirmed and extended these findings within a larger sample of middle-aged participants and over a longer follow-up period than most studies included in these three meta-analyses.

Notable studies with long follow-ups and middle-aged participants include the Kuopio Ischaemic Heart Disease study[29] on 2386 men with a median of 21.9 years follow-up, where neither sleep duration or daytime tiredness were associated with incident dementia, and no joint effects were found of 'sleep disturbance' and *ApoE* ε4 in a subsample. Our findings are more in line with a recent Whitehall II study[10] on 7959 participants with a follow-up of 25 years, which found sleeping 6 hours or less to be associated with a higher dementia risk. However, no interaction effects were tested for *ApoE* status and sleep duration, and long sleep duration was not found to be associated with higher dementia risk, potentially reflecting lack of power due to a low number of participants with long sleep duration. Our study extends these findings within a larger sample with more participants in the 'long sleep' category and by examining the effect of *ApoE* in the association between sleep and dementia.

Previous longitudinal studies assessing insomnia and dementia have found inconsistent results. A recent meta-analysis[16] with 23 studies examining the longitudinal association

between insomnia and cognitive disorders revealed insomnia to be associated with all-cause cognitive disorders. However, the results were non-significant among studies with longer follow-ups (>10 years), possibly reflecting reverse causality among studies with shorter follow-ups. Heterogeneity was also detected between studies, possibly due to differing definitions of insomnia. Our study captured only difficulty falling or maintaining sleep, which is only one subcomponent of insomnia[40] and not a good indicator of sleep duration or quality as people may have difficulty falling asleep due to stresses from complex and demanding jobs. As insomnia has been associated with job strain[42] and greater job demands predict lower dementia risk[41], it is likely, that the protective effect of insomnia found in our study is due to unmeasured confounding. Future longitudinal studies with long follow-ups with comprehensive definitions of insomnia that adjust for covariates that could explain the effects found in our study are needed to understand the role of insomnia in dementia risk.

The underlying mechanisms by which short sleep duration increase dementia risk could be explained by greater ventricular enlargement[43], less efficient metabolic clearance of pathogenic proteins which predominantly occurs during sleep[44] and increased amyloid beta production as a result of sleep deprivation[45]. The mechanisms by which long sleep duration increases dementia risk are less understood, but it has been found that long sleep duration is associated with increased inflammation[46]. It is also possible that those sleeping a lot at night have poor sleep quality and compensate by sleeping longer or they may have other health conditions that mean they sleep longer. Daytime napping, on the other hand, is likely to indicate poor quality sleep at night or other ill health so its association with dementia risk is expected. It is also possible that sleep disturbances result from dementia-related pathology starting decades before clinical dementia onset, or that sleep disturbances are directly caused by high genetic liability for dementias[47]. Nonetheless, as current evidence points to a bidirectional relationship between sleep and pathophysiological changes in dementia[48],

addressing sleep disturbances and encouraging good sleep hygiene could potentially delay the onset of clinical dementia. Additionally, as our sensitivity analyses indicated that short and long sleep duration had a greater impact on dementia risk among men than among women, future research is warranted to explore the mechanisms underlying these potential sex differences to inform future preventative strategies.

4.3. Strengths and limitations

This study's strengths include the large sample size, extended follow-up from middle age to older age and adjustment for a large number of potential confounders. Despite the strengths, the study has several limitations. Although the positive predictive value of ascertaining all-cause dementia cases using the UK Biobank data is high[34], some cases are likely to have been missed. We did not examine the relationship of sleep disturbances and *ApoE* with different dementia subtypes, and future research will benefit from examining whether differences exist between dementia subtypes. The UK Biobank cohort is healthier and better educated than the general population with a lower dementia incidence compared to previous cohorts[49,50], and consists mostly of individuals of European ancestry and of White ethnicity. Although valid exposure-disease associations can be made, future research examining whether these results generalize to individuals from more diverse backgrounds is needed. Sleep disturbances were assessed with single questions, their evolution was not investigated, and the self-reported data could have introduced reporting bias. However, the study highlights the feasibility of using self-reported questionnaires to detect individuals with sleep disturbances. Further, although missing data is likely to be missing at random, the possibility of selection bias remains. There is a possibility of misclassification regarding *ApoE* categorization as distinguishing between ε2/ε4 and ε1/ε3 genotypes was not possible. However, as the ε1 is extremely rare[33,51] and the frequency of participants with the

ambiguous ε2/ε4 or ε1/ε3 genotype was only 2.53%, miscategorisation would have not had a large effect on the results. Although analyses were adjusted for potential confounders, median follow-up was 10.8 years and sensitivity analyses followed the same pattern as the main analyses, the possibility of unmeasured confounding and reverse causation remains. We expect the protective effect of insomnia found in our study to be due to unmeasured confounding by complex and demanding jobs, but as we were unable to draw this evidence from our data, this aspect should be further explored in future research. And finally, as the models assessing daytime napping violated the assumption of proportionality of hazards reducing the power of those findings, the results should be interpreted with this in mind.

4.4. Implications

To date, this study was one of the largest longitudinal studies to investigate the association between *ApoE* status, sleep and incident dementia, and has dealt with some of the limitations of previous literature. The study highlights the importance of sleep quality and quantity in the middle-aged general population. Preventative measures targeted at sleep disturbances should be considered to delay or prevent dementia onset. Further research is needed to understand the underlying mechanisms by which sleep disturbances increase dementia risk to allow the development of effective preventative strategies. Particularly, prospective research with comprehensive sleep measures and dementia biomarkers is needed, as well as research aimed to understand the role of insomnia with dementia risk.

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Fig. 1. Risk of incident dementia according to sleep duration category within each genetic risk category.

Fig. 2. Risk of incident dementia according to insomnia category within each genetic risk category.

Fig. 3. Risk of incident dementia according to daytime napping category within each genetic risk category.

Table 1. Baseline characteristics according to dementia status.

		Incident Dementia (*n* = 1823)	**No Incident Dementia (*n* = 395,950)**
Characteristic		**M (SD)**	**M (SD)**
Age, years		64.5 (4.6)	56.4 (8.1)
		n* (%)	***n* (%)**
Sex (female)		854 (46.9)	217,033 (54.8)
Ethnic background (White)		1743 (95.6)	374,197 (94.5)
Education†			
	Higher	367 (20.1)	133,396 (33.7)
	Upper secondary	157 (8.6)	45,209 (11.4)
	Lower secondary	378 (20.7)	106,231 (26.8)
	Vocational	267 (14.7)	46,408 (11.7)
	Other	654 (35.9)	64,706 (16.3)
Socioeconomic status quintile‡			
	1 (least deprived)	342 (18.8)	81,642 (20.6)
	2	347 (19.0)	80,774 (20.4)
	3	349 (19.1)	79,733 (20.14)
	4	343 (18.8)	78,989 (20.0)
	5 (most deprived)	442 (24.3)	74,812 (18.9)
Smoking status			
	Never	834 (45.8)	219,196 (55.4)
	Previous	785 (43.1)	139,001 (35.11)
	Current	204 (11.2)	37,753 (9.5)
Alcohol drinker status			
	Never	141 (7.7)	16,766 (4.2)
	Previous	127 (7.0)	13,499 (3.4)
	Current	1555 (85.3)	365,685 (92.4)
Diabetes (yes)		260 (14.3)	19,339 (4.9)
Physical inactivity (yes)§		298 (16.4)	38,940 (9.8)
History of depression (yes)		78 (4.3)	25,945 (6.6)
Genetic risk by *ApoE*¶			
	Low	122 (6.7)	50,672 (12.8)

	Neutral	693 (38.0)	232,802 (58.8)
	Intermediate	47 (2.6)	10,001 (2.5)
	Somewhat high	748 (41.0)	93,255 (23.55)
	High	213 (11.7)	9,220 (2.3)
Sleep duration			
	≤5 hours	140 (7.7)	21,179 (5.4)
	6	320 (17.6)	75,545 (19.1)
	7	518 (28.4)	154,689 (39.1)
	8	577 (31.7)	114,921 (29.0)
	≥9	268 (14.7)	29,616 (7.5)
Insomnia			
	Never/rarely	492 (27.0)	96,031 (24.3)
	Sometimes	798 (43.8)	189,736 (47.9)
	Usually	533 (29.2)	110,183 (27.8)
Daytime napping			
	Never/rarely	1 187 (65.1)	301,966 (76.3)
	Sometimes	522 (28.6)	83,341 (21.1)
	Often/all of the time	114 (6.3)	10,757 (2.7)
		M (SD)	**M (SD)**
Body Mass Index		27.5 (4.8)	27.3 (4.7)
Number of medications taken		4.5 (3.8)	2 .4 (2.6)

*Percentages may not sum up because of rounding.
†Higher education defined as university/college degree; upper secondary as A levels/AS levels or equivalent; lower secondary as O-levels/GCEs/CSEs or equivalent; vocational as NVQ/HND/HNC or equivalent or other professional qualification.
‡Socioeconomic status assessed with the Townsend deprivation index which combines information on employment, social class, housing and car availability. 5th quintile most deprived category.
§Physical inactivity defined as <600 metabolic equivalent minutes (MET) of moderate/vigorous activity per week; physical activity defined as ≥600 MET based on World Health Organization's recommendation[35].
¶Genetic risk categories defined based on Single Nucleotide Polymorphisms. Low category defined as ε2/ε2, ε1/ε2, ε2/ε3; neutral as ε3/ε3; intermediate as ambiguous ε2/ε4 or ε1/ε3; somewhat high as ε3/ε4; and high as ε4/ε4.

Table 2. Risk of incident dementia according to *ApoE* genetic risk.

				Model 1*			**Model 2†**		
	No of dementia cases	**PYAR per 100,000**	**Incidence rate per 100,000 PYAR**	**HR (95 % CI)**	***P* value**	**Global *P* value**	**HR (95 % CI)**	***P* value**	**Global *P* value**
***ApoE* risk**									
Low (*n* = 50,794)	122	5.4	22.6	0.80 (0.66–0.97)	0.021		0.81 (0.67–0.99)	0.037	
Neutral (*n* = 233,495)	693	14.7	47.0	1 (Reference)			1 (Reference)		
Intermediate (*n* = 10,048)	47	1.1	44.2	1.57 (1.17–2.12)	0.003	<.001	1.59 (1.18–2.13)	0.002	<.001
Somewhat high (*n* = 94,003)	748	10.0	75.2	2.73 (2.46–3.03)	<.001		2.74 (2.47–3.04)	<.001	
High (*n* = 9433)	213	1.0	214.6	8.00 (6.86–9.33)	<.001		7.80 (6.69–9.10)	<.001	

Abbreviation: HR, hazard ratio. PYAR, person-years at risk.
*Model 1: Cox proportional hazards regression adjusted for age, sex and education.
†Model 2: Cox proportional hazards regression adjusted for Model 1, ethnic background, socioeconomic status, body mass index, smoking status, alcohol status, diabetes, physical inactivity, history of depression, number of medications taken, sleep duration, insomnia and daytime napping.

Table 3. Risk of incident dementia according to sleep duration, insomnia and daytime napping.

				Model 1*			Model 2†		
	No of dementia cases	**PYAR per 100,000**	**Incidence rate per 100,000 PYAR**	**HR (95 % CI)**	**P value**	**Global P value**	**HR (95 % CI)**	**P value**	**Global P value**
Sleep duration									
≤5 (*n* = 21,319)	140	2.2	62.5	1.69 (1.40–2.04)	<.001		1.35 (1.11–1.64)	.002	
6 (*n* = 75,865)	340	8.0	42.4	1.20 (1.04–1.38)	.010		1.12 (0.97–1.28)	.125	
7 (*n* = 155,207)	518	16.5	31.4	1 (Reference)		<.001	1 (Reference)		<.001
8 (*n* = 115,498)	577	12.2	47.1	1.22 (1.08–1.37)	.001		1.22 (1.08–1.37)	.001	
≥9 (*n* = 29,884)	268	3.1	85.7	1.76 (1.52–2.05)	<.001		1.59 (1.37–1.85)	<.001	
Insomnia									
Never/rarely (*n* = 96,523)	492	10.2	48.0	1 (Reference)			1 (Reference)		
Sometimes (*n* = 190,534)	798	20.2	39.5	0.72 (0.64–0.81)	<.001	<.001	0.70 (0.63–0.79)	<.001	<.001
Usually (*n* = 110,716)	533	11.7	45.6	0.77 (0.68–0.87)	<.001		0.67 (0.59–0.75)	<.001	
Daytime napping									
Never/rarely (*n* = 303,153)	1187	32.2	36.9	1 (Reference)			1 (Reference)		
Sometimes (*n* = 83,863)	522	8.8	59.2	1.15 (1.04–1.27)	.009	<.001	1.07 (0.96–1.18)	.225	<.001
Often/all of the time (*n* = 10,757)	114	1.1	101.5	2.07 (1.71–2.51)	<.001		1.67 (1.37–2.03)	<.001	

Abbreviation: HR, hazard ratio. PYAR, person-years at risk.

*Model 1: Cox proportional hazards regression adjusted for age, sex and education.

†Model 2: Cox proportional hazards regression adjusted for Model 1, ethnic background, socioeconomic status, body mass index, smoking status, alcohol status, diabetes, physical inactivity, history of depression, number of medications taken and *ApoE* genetic risk.