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RESEARCH ARTICLE

Insomnia and risk of dementia in a large population-based study with 11-year follow-up: The HUNT study

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Summary

Despite evidence suggesting that insomnia is associated with the risk of dementia and cognitive dysfunction, studies have shown mixed results. Dementia has a long prodromal phase, and studies with long follow-up are required to avoid reverse causality. In our 11-year follow-up study, we assessed whether probable insomnia disorder (PID) based on diagnostic criteria, and insomnia symptoms were associated with risk of all-cause dementia, Alzheimer's disease (AD) and cognition, measured with the Montreal Cognitive Assessment scale. We also examined if Apolipoprotein E genotype modified any associations with dementia through interaction. We analysed data from 7492 participants in the Norwegian Trøndelag Health Study. PID was not associated with all-cause dementia (odds ratio = 1.03, 95% confidence interval = 0.74–1.43), AD (odds ratio = 1.07, 95% confidence interval = 0.71–1.60) or Montreal Cognitive Assessment score (regression coefficient = 0.37, 95% confidence interval = −0.06 to 0.80). The insomnia symptom "difficulties maintaining sleep" was associated with a lower risk of all-cause dementia (odds ratio = 0.81, 95% confidence interval = 0.67–0.98), AD (odds ratio = 0.73, 95% confidence interval = 0.57–0.93), and better Montreal Cognitive Assessment score, mean 0.40 units (95% confidence interval = 0.15–0.64). No interaction with Apolipoprotein E genotype was found. PID and insomnia symptoms did not increase the risk of dementia in our study. More research with longer follow-up is needed, and future studies should explore if the associations to dementia risk vary across insomnia subtypes.

KEYWORDS
cohort studies, disturbed sleep, DSM-5, epidemiology, HUNT study, major neurocognitive disorder

1 | INTRODUCTION

In the coming decades, the global population of people with dementia is expected to increase substantially due to demographic changes stemming from population aging (Livingston et al., 2020). In Norway in particular, the number of people with dementia is expected to more than double within the next 30 years (Gjøra et al., 2021). Because only approximately 40% of dementia cases can theoretically be prevented or postponed by modifying 12 health- and lifestyle-related risk factors (Livingston et al., 2020), the identification and treatment of additional risk factors are crucial to reduce the risk of dementia. Awareness of potential interactions between modifiable risk factors and genes associated with dementia could also improve future personalized risk assessment and prevention strategies (Eid et al., 2019).

Disturbed sleep is arguably a risk factor for dementia (Livingston et al., 2020), although not included in the 12 modifiable risk factors above. Sleep problems are common among people with dementia, and thought to result from pathophysiological neurodegeneration in areas of the brain involved in sleep regulation (Yaffe et al., 2014). In recent years, a bidirectional association has been hypothesized, suggesting that disturbed sleep might both be a cause and a consequence of dementia (Yaffe et al., 2014). The hypothesis that sleep disturbance is a risk factor for dementia is supported by studies showing accumulation of beta-amyloid, a hallmark of Alzheimer's disease (AD), in the central nervous system in response to sleep deprivation (Shokri-Kojori et al., 2018). The association could also be driven by systemic inflammation, which increases in the presence of sleep disturbances, and is thought to be an early event in the preclinical course of AD (Irwin & Vitiello, 2019).

Accumulating evidence suggests that insomnia-related sleep complaints are associated with an increased risk of AD (Osorio et al., 2011; Shi et al., 2018; Yaffe et al., 2015), all-cause dementia (Chen et al., 2012; de Almondes et al., 2016; Hung et al., 2018; Sindi et al., 2018) and cognitive decline (Brachem et al., 2020; Cricco et al., 2001; Jelicic et al., 2002; Johar et al., 2016). In a large, registered-based study involving 179,738 male military veterans in the USA, people with insomnia had a 26% increased risk of developing AD during the study's 8-year follow-up period (Yaffe et al., 2015). Insomnia has additionally been shown to double the risk of all-cause dementia over the course of a 3-year follow-up period (Chen et al., 2012; Hung et al., 2018), and a hazard ratio of 1.24 for all-cause dementia was found among people with midlife insomnia who were followed for 21 and 32 years (Sindi et al., 2018). Moreover, an increased risk of dementia was detected among people with short sleep duration, a plausible consequence of insomnia, in a recent study with a 25-year follow-up period (Sabia et al., 2021). At the same time, null findings have also been reported (Elwood et al., 2011; Foley et al., 2001), and one study even found an inverse association between the risk of dementia and the number of insomnia symptoms (Jaussent et al., 2012). Regarding cognition, studies have shown that insomnia is associated with simultaneous impaired cognitive performance (Brownlow et al., 2020; Wardle-Pinkston et al., 2019), and that some insomnia symptoms increase the risk of later cognitive decline (Brachem et al., 2020; Cricco et al., 2001; Jelicic et al., 2002; Johar et al., 2016). However, reviews report that overall results are inconsistent (Brownlow et al., 2020; Sexton et al., 2020; Wardle-Pinkston et al., 2019).

A diagnosis of insomnia is solely based on self-reported symptoms (Riemann et al., 2017), and heterogenous findings in previous studies may result from the lack of an objective sleep measure. Inconsistent definitions of insomnia may also contribute to the conflicting findings. While some authors define people as having insomnia if they report isolated insomnia symptoms (Cricco et al., 2001; Elwood et al., 2011; Jaussent et al., 2012; Osorio et al., 2011; Sindi et al., 2018), others use health records or registers to detect people with a clinical diagnosis of insomnia (Chen et al., 2012; Hung et al., 2018; Yaffe et al., 2015). A clinical diagnosis of insomnia requires daytime functional impairment in addition to the nocturnal insomnia symptoms (Patel et al., 2018; Riemann et al., 2017). Different follow-up periods may also lead to heterogeneous results. Because dementia pathophysiology begins several years before its clinical symptoms manifest (Cunningham et al., 2015), studies with short follow-up periods and cross-sectional designs may be hampered by reverse causality.

In our 11-year follow-up study, we aimed to assess whether insomnia according to diagnostic criteria, and insomnia symptoms are associated with the risk of all-cause dementia, AD and cognition. Our secondary aim was to assess if the ε4 allele of the Apolipoprotein E gene (ApoE-ε4), the most common genetic risk for late-onset AD, modified any associations with dementia through interaction. We hypothesized that insomnia increases the risk of both future dementia and impaired cognitive performance, and that the increased dementia risk may be especially pronounced among people carrying ApoE-ε4.

2 | METHODS

2.1 | Ethics

The Regional Committee for Medical and Health Research Ethics in Norway (REK North, No. 142334) approved the study. Participants provided their informed written consent to participate; however, if a participant was unable to consent, then the closest proxy provided their written consent.

2.2 | The Trøndelag health study

For our study, we used data from the Trøndelag Health Study (HUNT), a comprehensive population-based health study from the former county of Nord-Trøndelag in central Norway. Of the four waves of the HUNT study conducted since 1984, our data were collected from HUNT3 (2006–2008) and HUNT4 70+, a sub-study of HUNT4 (2017–2019) aimed at people aged ≥ 70 years (Gjøra et al., 2021). The HUNT study is thoroughly described elsewhere (Åsvold et al., 2022; Krokstad et al., 2013).

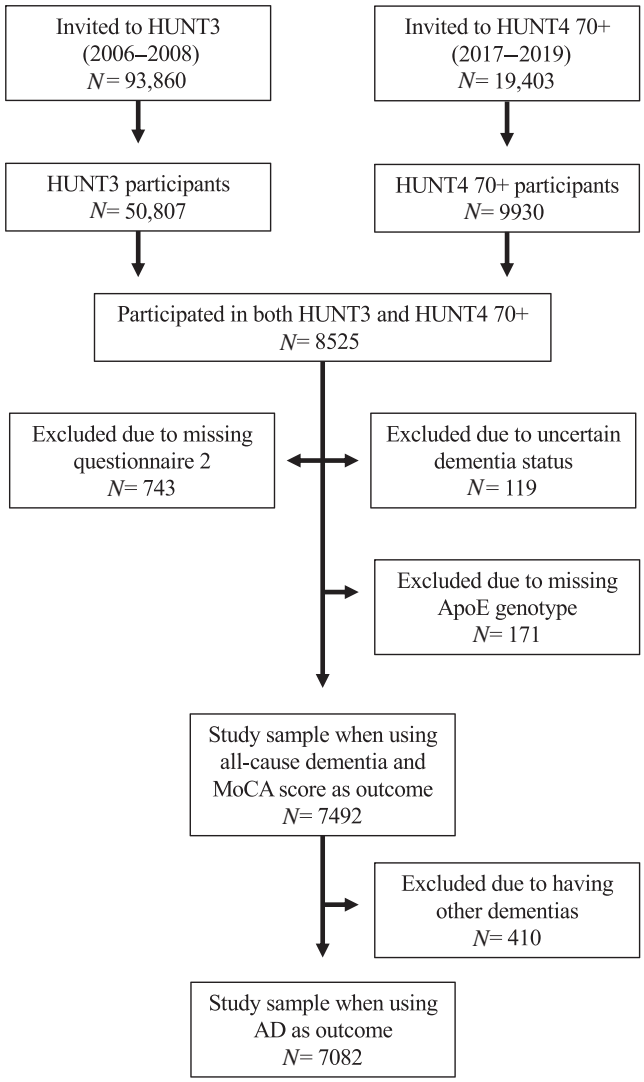

FIGURE 1 Flow of the sample. AD, Alzheimer's disease; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; EMA, early morning awakenings; MoCA, Montreal Cognitive Assessment; PID, probable insomnia disorder, according to DSM-5 criteria

2.3 | Sample

Out of the 93,860 people invited to participate in HUNT3, 50,807 (54.1%) participated. The corresponding numbers for HUNT4 70+ were 19,403 invitees and 9930 (51.2%) participants. People who participated in both HUNT3 and HUNT4 70+ ($n = 8525$) were eligible for inclusion in our study. Participants who had not completed Questionnaire 2 in HUNT3 (Krokstad et al., 2013; $n = 743$) were excluded, as this questionnaire contained all the data on sleep variables. We also excluded participants with uncertain dementia status ($n = 119$) or missing data regarding Apolipoprotein E genotype (ApoE; $n = 171$), which left an initial sample of 7492 participants. In analyses in which AD was used as an outcome, participants with other types of dementia ($n = 410$) were excluded from analyses, which left a sample of 7082 (Figure 1).

2.4 | PID and insomnia symptoms

We used the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) definition of insomnia symptoms and insomnia disorder. According to the *DSM-5*, people with diagnostic insomnia disorder report having difficulties initiating sleep (DIS), difficulties maintaining sleep (DMS) or early morning awakenings (EMA) at least three times a week for a minimum of 3 months, which results in daytime functional impairment (Patel et al., 2018). We used the following four questions from HUNT3 to identify DIS, DMS, EMA and daytime functional impairment in the sample: "How often in the last 3 months have you: (1) had difficulties falling asleep at night? (i.e. DIS); (2) woken up repeatedly during the night? (i.e. DMS); (3) woken too early and couldn't go back to sleep? (i.e. EMA); (4) felt sleepy during the day? (i.e. daytime functional impairment) ". Response options were: (A) "Never/seldom"; (B) "Sometimes"; and (C) "Several times a week". Participants were defined as having DIS, DMS or EMA (i.e. insomnia symptoms) if they reported experiencing the symptom several times a week. In accordance with DSM-5, participants defined as having DIS, DMS and/or EMA were also classified as having probable insomnia disorder (PID) if they reported experiencing concurrent daytime sleepiness several times a week (Uhlig et al., 2014). All sleep characteristics were self-reported.

2.5 | Dementia and cognition

The process of diagnosing people with dementia in the HUNT4 70+ population has been described in detail in a recently published article (Gjøra et al., 2021). Experienced medical doctors diagnosed dementia using the *DSM-5* criteria for major neurocognitive disorder (i.e. dementia) with reference to all available information on cognition, level of functioning, neuropsychiatric symptoms, comorbidity and symptom course using information from interviews with the participant and their next-of-kin. Participants with dementia were further classified as having subtypes of dementia, including AD. The standard cognitive assessment comprised the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) and the Word List Memory Task (WLMT) from the Consortium to Establish a Registry of Alzheimer's Disease (Morris et al., 1989). The MoCA is a brief screening tool used to measure cognitive function in eight domains that generates total scores ranging from 0 to 30, with higher scores indicating better cognition. The WLMT, a test for immediate and delayed recall, was conducted on all participants with a MoCA score > 21 to increase sensitivity for mild memory difficulties. For nursing home residents who were considered to have moderate to severe dementia, the Severe Impairment Battery-8 (SIB-8; Schmitt et al., 2013) that reduces floor effects of testing was used in the cognitive evaluation instead of MoCA.

2.6 | Covariates

Covariates were included for descriptive purposes, and to allow for adjustment for potential confounding factors. Identification of

potential confounders was based on previous literature. All covariates, except biometric measures, were self-reported. Sociodemographic covariates were age (continuous), sex (male, female), level of education (primary school, high school/vocational, college/university) and marital status (married, currently unmarried). Physical health covariates were hypertension (yes, no), body mass index (BMI; continuous), history of diabetes (yes, no), history of stroke (yes, no), history of myocardial infarction (yes, no), history of heart failure (yes, no), history of chronic obstructive pulmonary disease (COPD; yes, no), sleep apnea (never, rarely/sometimes, often), smoking (never, former, current), alcohol consumption (never, yearly, monthly, weekly) and physical activity (never, ≤ 1 times per week, ≥ 2 times per week). Mental health covariates were scored on the Hospital Anxiety and Depression Scale (HADS; Bjelland et al., 2002), divided into sub-scores (0–21) for depression (HADS-D) and anxiety (HADS-A). The genetic covariate was ApoE (carrier of ≥ 1 ε4 alleles, non-carrier). Hypertension was defined as having systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or using antihypertensive drugs. For HADS-A and HADS-D, personal mean imputation was used if one or two of the seven answers for a sub-score were missing. The two single nucleotide polymorphisms that determine ApoE were imputed from a joint reference panel, where 2201 HUNT participants were included. Genotyping and imputation of genes in HUNT are described elsewhere (Brumpton et al., 2022). As there were no education data in HUNT3, this variable was collected from HUNT4. Other covariates were collected at baseline.

2.7 | Analyses

Whereas complete case analyses are unbiased only if data are missing completely at random, analyses based on multiple imputation (MI) are unbiased under the less restrictive assumption of variables missing at random (Sterne et al., 2009). Thus, we performed MI using chained equations to replace missing values of predictor variables and MoCA score. We included all variables used in later analyses in the imputation model and created 20 imputed datasets. We used logistic regression to impute categorical variables and predictive mean matching, drawing values from the 10 closest subjects, to impute continuous variables (Austin et al., 2021). To account for potential interactions with ApoE, MI for ApoE-ε4 carriers and non-carriers was performed in separate datasets that we later merged after imputation. Variables derived from other variables were created before imputation and included in the imputation model as "just another variable" (Austin et al., 2021).

Descriptive statistics were recorded as means and standard deviations (SD) or percentages. Because imputed values may vary between imputations, categorical variables were recorded as mean percentages, not as counts. Sequentially adjusted binary logistic regressions were used to estimate odds ratios (OR) of having all-cause dementia or AD at follow-up by PID, DIS, DMS or EMA at baseline. Model 1 was unadjusted, Model 2 was adjusted for age and sex, and Model 3 was adjusted for age, sex, marital status, level of education, BMI, hypertension, history of stroke, history of diabetes, history of myocardial infarction, history of heart failure, history of COPD, sleep apnea, physical activity, smoking, alcohol consumption, HADS-D score, HADS-A score and ApoE. To assess whether PID, DIS, DMS and EMA were associated with cognition, we performed linear regression with total MoCA score as the outcome, adjusted in the same sequential way as in logistic regression. The results were recorded as unstandardized regression coefficients (*b*).

In additional analyses, we checked for interaction between ApoE and each of the insomnia variables (i.e. PID, DIS, DMS and EMA) on dementia risk, by adding interaction terms to the fully adjusted models.

As a sensitivity analysis we repeated all analyses without imputing missing values but using complete case analyses, and compared the results with the results from the MI analyses. Flow of the complete case study samples is presented in Supporting Information (Figure S1).

Stata version 17 was used for all analyses. In what follows, we report 95% confidence intervals (CIs) where relevant, and regard two-tailed *p*-values less than 0.05 to indicate statistical significance.

3 | RESULTS

3.1 | Descriptive statistics

Table 1 shows the baseline characteristics of our study participants ($n = 7492$), including mean MoCA score and prevalence of both dementia and AD at follow-up. Mean follow-up was 10.6 years, while mean age at the time of HUNT3 was 67.2 years (SD = 6.2). Females accounted for 55.5% of the sample, and 24.5% had completed post-secondary education. PID was present in 5.5%, DIS in 13.1%, DMS in 22.3%, and EMA in 13.9% of participants. At follow-up (HUNT4), 994 (13.3%) participants had dementia, of which 584 (7.8%) had AD. Baseline characteristics of the complete case sample appear in the Supporting Information (Table S1).

3.2 | Missing values before MI

Before MI, there were 1.6% missing values, and 19.7% ($n = 1479$) of the participants had at least one missing value. Three variables had ≥ 5.0% missing values: MoCA score (7.0%), sleep apnea (5.6%) and level of education (5.3%; Table S2). Participants with missing values for MoCA score, sleep apnea, level of education and all insomnia variables (i.e. PID, DIS, DMS, EMA) were significantly older and more likely to be female than their respective comparison groups without missing values (Table S3). Participants with missing MoCA were also more likely to have dementia, plausibly because all participants living in institutions with moderate to severe dementia were tested with SIB-8 instead of MoCA (Gjøra et al., 2021).

3.3 | PID, insomnia symptoms and risk of dementia

Probable insomnia disorder was not associated with all-cause dementia in any of the models (fully adjusted: OR = 1.03, 95%

TABLE 1 Characteristics of the sample at baseline (HUNT3 2006–2008), with total MoCA score, prevalence of dementia and prevalence of AD at follow-up (2017–2019), based on MI

Variables		Total $n = 7492$	PID		DIS		DMS		EMA	
			No ($n = 7079$)	Yes* ($n = 413$)	No ($n = 6510$)	Yes* ($n = 982$)	No ($n = 5823$)	Yes* ($n = 1669$)	No ($n = 6453$)	Yes* ($n = 1039$)
Female sex %		55.5	55.0	64.2	52.2	77.7	53.5	62.6	54.5	61.8
Age mean (SD)		67.2 (6.2)	67.3 (6.2)	66.7 (6.5)	67.2 (6.2)	67.2 (6.4)	67.3 (6.2)	67.0 (6.3)	67.2 (6.1)	67.7 (6.7)
In a marriage %		73.0	73.3	67.0	73.6	69.3	73.6	71.0	73.6	69.1
Education level %	College/University	24.5	24.4	26.2	25.2	19.9	24.5	24.6	25.2	20.4
	Primary school	30.6	30.6	31.0	30.0	34.6	30.6	30.9	29.7	36.5
BMI mean (SD)		27.7 (4.1)	27.6 (4.0)	28.5 (4.8)	27.6 (4.1)	27.8 (4.3)	27.5 (4.0)	28.1 (4.4)	27.7 (4.1)	27.6 (4.1)
Hypertension %		61.5	61.5	62.1	62.0	58.3	61.5	61.5	61.5	61.9
Diabetes %		6.6	6.5	8.3	6.6	6.4	6.4	7.2	6.6	6.4
Heart failure %		1.2	1.2	0.8	1.2	0.1	1.2	1.3	1.1	1.5
Myocardial infarction %		4.8	4.8	4.9	4.9	3.8	4.8	4.9	4.8	4.9
Stroke %		3.9	3.8	5.5	3.8	4.3	3.7	4.3	3.9	3.6
COPD %		4.0	3.8	8.3	3.6	6.8	3.7	5.3	3.9	5.1
Sleep apnea %	Sometimes	8.6	8.3	13.6	8.7	7.9	8.3	9.8	8.5	9.3
	Often	2.1	1.8	6.1	2.0	2.4	1.7	3.5	1.9	3.3
HADS-D score mean (SD)		3.6 (2.8)	3.5 (2.7)	5.9 (3.4)	3.4 (2.7)	4.7 (3.3)	3.4 (2.7)	4.4 (3.0)	3.4 (2.7)	4.9 (3.2)
HADS-A score mean (SD)		3.8 (3.1)	3.6 (3.0)	6.4 (4.0)	3.5 (2.9)	5.7 (3.7)	3.4 (2.9)	5.1 (3.6)	3.5 (2.9)	5.6 (3.7)
Physical activity %	Never	3.8	3.6	5.6	3.6	5.0	3.6	4.3	3.6	4.9
	Rarely	32.3	32.0	37.7	32.4	31.8	32.3	32.4	32.7	30.3
Smoking %	Former	41.9	41.7	46.2	41.9	42.2	40.5	46.8	41.3	45.6
	Current	15.7	15.8	14.6	15.1	19.6	16.8	11.9	16.2	12.7
Frequent alcohol consumption[a] %		18.1	18.1	18.5	18.4	16.1	17.6	19.6	18.3	16.9
ApoE-ε4 carrier %		29.8	29.8	29.7	30.4	26.4	30.6	27.1	29.9	29.6
MoCA score mean (SD)		22.6 (4.8)	22.6 (4.8)	22.8 (4.8)	22.6 (4.8)	22.7 (4.9)	22.5 (4.9)	22.9 (4.9)	22.7 (4.9)	22.0 (5.1)
Dementia %		13.3	13.2	14.7	13.3	12.8	13.6	12.0	12.9	15.5
AD %		7.8	7.7	8.6	7.7	8.3	8.1	6.7	7.5	9.6

Abbreviations: AD, Alzheimer's disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; EMA, early morning awakenings; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; MoCA, Montreal Cognitive Assessment; PID, probable insomnia disorder, according to DSM-5 criteria.

*Numbers of people with PID, DIS, DMS and EMA were estimated from mean percentages between imputations, and rounded to the nearest integer.

[a]Drinking 2–7 times per week.

TABLE 2 Analyses after MI ($n = 7492$)

	PID *n* PID[a] /*n* total = 413/7492			DIS *n* DIS[a] /*n* total = 982/7492			DMS *n* DMS[a] /*n* total = 1669/7492			EMA *n* EMA[a] /*n* total = 1039/7492		
Model	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Model 1	1.13	0.85–1.51	0.405	0.96	0.78–1.17	0.673	0.87	0.73–1.03	0.102	**1.24**	**1.03–1.50**	**0.025**
Model 2	1.21	0.88–1.65	0.242	0.91	0.73–1.14	0.411	0.87	0.72–1.04	0.125	1.13	0.92–1.38	0.239
Model 3	1.03	0.74–1.43	0.859	0.81	0.64–1.02	0.069	**0.81**	**0.67–0.98**	**0.031**	0.95	0.77–1.18	0.667
Interaction[b]			0.440			0.469			0.077			0.199

Note: OR, 95% CI and *p*-value (*p*) of all-cause dementia ($n = 994$) in HUNT4 70+ (2017–2019) by PID, according to DSM-5 criteria, DIS, DMS and EMA at baseline in HUNT3 (2006–2008). Sequentially adjusted models. Model 1: crude. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, marital status, education, BMI, hypertension, stroke, diabetes, myocardial infarction, heart failure, COPD, sleep apnea, physical activity, smoking, alcohol consumption, sub-scores for depression and anxiety on the HADS, and apolipoprotein E genotype.

Abbreviations: CI, confidence interval; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; EMA, early morning awakenings; OR, odds ratio; PID, probable insomnia disorder.

Bolding indicates statically significant associations at $p < 0.05$.

[a]Numbers of people with PID, DIS, DMS and EMA in the combined regression models were estimated from mean percentages between imputations, and rounded to the nearest integer.

[b]*p*-value of the interaction term, created as a product of apolipoprotein E genotype and each of the insomnia variables (i.e. PID, DIS, DMS, EMA), added to the fully adjusted model.

TABLE 3 Analyses after MI ($n = 7082$)

	PID *n* PID[a] /*n* total = 389/7082			DIS *n* DIS[a] /*n* total = 937/7082			DMS *n* DMS[a] /*n* total = 1581/7082			EMA *n* EMA[a] /*n* total = 977/7082		
Model	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Model 1	1.14	0.79–1.63	0.495	1.06	0.83–1.37	0.631	0.82	0.66–1.02	0.076	**1.31**	**1.04–1.66**	**0.022**
Model 2	1.21	0.82–1.79	0.331	0.97	0.74–1.26	0.809	0.79	0.63–1.00	0.051	1.17	0.91–1.50	0.212
Model 3	1.07	0.71–1.60	0.755	0.87	0.66–1.15	0.331	**0.73**	**0.57–0.93**	**0.012**	0.98	0.75–1.27	0.858
Interaction[b]			0.985			0.555			0.154			0.189

Note: OR, 95% CI and *p*-value (*p*) of AD ($n = 584$) in HUNT4 70+ (2017–2019) by PID, according to DSM-5 criteria, DIS, DMS and EMA at baseline in HUNT3 (2006–2008). Sequentially adjusted models. Model 1: crude. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, marital status, education, BMI, hypertension, stroke, diabetes, myocardial infarction, heart failure, COPD, sleep apnea, physical activity, smoking, alcohol consumption, sub-scores for depression and anxiety on the HADS, and apolipoprotein E genotype.

Abbreviations: CI, confidence interval; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; EMA, early morning awakenings; OR, odds ratio; PID, probable insomnia disorder.

Bolding indicates statically significant associations at $p < 0.05$.

[a]Numbers of people with PID, DIS, DMS and EMA in the combined regression models were estimated from mean percentages between imputations, and rounded to the nearest integer.

[b]*p*-value of the interaction term, created as a product of apolipoprotein E genotype and each of the insomnia variables (i.e. PID, DIS, DMS, EMA), added to the fully adjusted model.

CI = 0.74–1.43). Although DMS was not associated with all-cause dementia in the unadjusted model, in the fully adjusted model it was associated with a lower risk of all-cause dementia (OR = 0.81, 95% CI = 0.67–0.98). Meanwhile, EMA was associated with an increased risk of all-cause dementia in the unadjusted model, but the association disappeared when adjusted for age and sex. DIS was not associated with all-cause dementia in any models (Table 2).

Repeating the analyses with AD as the outcome yielded similar results. PID was not associated with AD in any of the models (fully adjusted: OR = 1.07, 95% CI = 0.71–1.60), DMS was associated with a lower risk of AD in the fully adjusted model (OR = 0.73, 95% CI = 0.57–0.93), EMA was associated with a higher risk of AD only in the unadjusted model, and DIS was not associated with AD in any of the models (Table 3).

3.4 | PID, insomnia symptoms and cognition

Using linear regression, PID was not associated with MoCA score in any of the models (fully adjusted: $b = 0.37$, 95% CI = −0.06 to 0.80). DMS was associated with a higher MoCA score in all models (fully adjusted: $b = 0.40$, 95% CI = 0.15–0.64). EMA was associated with a lower MoCA score in the unadjusted model, although not after full model adjustments. DIS was not associated with MoCA score in any of the models (Table 4).

TABLE 4 Analyses after MI ($n = 7492$)

	PID *n* PID[a] /*n* total = 413/7492			DIS *n* DIS[a] /*n* total = 982/7492			DMS *n* DMS[a] /*n* total = 1669/7492			EMA *n* EMA[a] /*n* total = 1039/7492		
Model	***b***	**95% CI**	***p***	***b***	**95% CI**	***p***	***b***	**95% CI**	***p***	***b***	**95% CI**	***p***
Model 1	0.23	−0.26 to 0.72	0.356	0.07	−0.26 to 0.40	0.681	**0.40**	**0.12–0.67**	**0.005**	**−0.64**	**−0.97 to − 0.31**	**0.000**
Model 2	−0.02	−0.46 to 0.42	0.940	−0.05	−0.35 to 0.25	0.745	**0.26**	**0.02–0.51**	**0.036**	**−0.49**	**−0.78 to − 0.19**	**0.001**
Model 3	0.37	−0.06 to 0.80	0.092	0.25	−0.04 to 0.55	0.091	**0.40**	**0.15–0.64**	**0.001**	−0.15	−0.43 to 0.14	0.312

Note: Unstandardized regression coefficient (*b*), 95% CI and *p*-value (*p*) of MoCA score in HUNT4 70+ (2017–2019) by PID, according to DSM-5 criteria, DIS, DMS and EMA at baseline in HUNT3 (2006–2008). Sequentially adjusted models. Model 1: crude. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, marital status, education, BMI, hypertension, stroke, diabetes, myocardial infarction, heart failure, COPD, sleep apnea, physical activity, smoking, alcohol consumption, sub-scores for depression and anxiety on the HADS, and apolipoprotein E genotype.

Abbreviations: CI, confidence interval; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; EMA, early morning awakenings; OR, odds ratio; PID, probable insomnia disorder.

Bolding indicates statically significant associations at $p < 0.05$.

[a]Numbers of people with PID, DIS, DMS and EMA in the combined regression models were estimated from mean percentages between imputations, and rounded to the nearest integer.

3.5 | Interaction with ApoE

The interaction terms showed no evidence of statistical interaction between ApoE and the insomnia variables (i.e. PID, DIS, DMS and EMA) on dementia risk (Tables 2 and 3).

3.6 | Complete case analyses

The directions of estimates of all significant associations found in MI analyses were reproducible in complete case analyses, although all models had smaller effect sizes, wider-ranging CIs and higher *p*-values. We found no other associations in the complete case analyses (Tables S4 –S6).

4 | DISCUSSION

4.1 | Summary of results

Among the results of our 11-year follow-up study, having PID was not associated with all-cause dementia, AD or MoCA score. No significant association was found for the two insomnia symptoms "difficulties initiating sleep" (DIS) and "early morning awakenings" (EMA). However, having "difficulties maintaining sleep" (DMS) was associated with a lower risk of all-cause dementia and AD, and with a higher MoCA score.

4.2 | PID and risk of dementia

Unlike past studies, we did not detect any significant associations between PID and all-cause dementia (de Almondes et al., 2016). Different follow-up periods may explain why. The pathological process leading to dementia begins several years before clinical symptoms of dementia manifest (Cunningham et al., 2015). The presence of insomnia in the 3 years prior to a diagnosis of dementia may be caused by the neuropathological process, so reverse causality could explain the risk observed in some studies (Chen et al., 2012; Hung et al., 2018).

Different study population characteristics and inclusion criteria may also complicate comparison of results. One study included only people with insomnia who used hypnotics concomitantly, which made it hard to determine whether the observed increased dementia risk derived from medication, insomnia or both, as the authors acknowledged (Chen et al., 2012).

As in similar studies (Cavaillès et al., 2022; Yaffe et al., 2015), we measured late-life insomnia. However, past findings indicate that insomnia's adverse effect on dementia risk may occur when sleep is disturbed earlier in life. Two studies have shown that insomnia (Sindi et al., 2018) and short sleep duration (Sabia et al., 2021) at the age of 50 years increase the risk of developing dementia decades later. Thus, using an earlier baseline measure of insomnia, for example at HUNT2 (1995–1997), could have yielded different results due to either the timing of exposure to insomnia or the longer follow-up period.

4.3 | DMS and risk of dementia

The observed risk-reducing effect of DMS on all-cause dementia and AD was surprising, for most other studies have shown either no association or an increased risk. Despite our relatively long follow-up period, reverse causality cannot be ruled out, and it is possible that participants with prodromal or early dementia at HUNT3 were less likely to experience or report DMS at baseline. However, other studies have produced findings similar to ours. In a French study, people with DMS at baseline had a reduced risk of developing dementia over the 8-year follow-up period (OR = 0.67, 95% CI = 0.49–0.90; Jaussent et al., 2012). A 12-year follow-up study with the same baseline sample was recently published and, although the association with dementia was no longer present (OR = 0.87, 95% CI = 0.75–1.03), the association between DMS and a lower risk of AD approached significance (OR = 0.84, 95%

CI = 0.69–1.02; Cavaillès et al., 2022). DMS has also been found to occur more frequently among ApoE-ε4 carriers than non-carriers in two studies that have assessed sleep characteristics among cognitively healthy older participants (Drogos et al., 2016; Kahya et al., 2017). An increased frequency of DMS among older ApoE-ε4 carriers with normal cognition could imply a protective effect of having this sleep pattern in regard to dementia risk.

4.4 | DMS and cognition

Difficulties maintaining sleep was also associated with a higher MoCA score, and this is consistent with the reduced risk of all-cause dementia and AD. Similarly to other studies about dementia, most comparable studies have presented either null findings or an association with impaired cognitive function. Two studies that have specifically assessed DMS revealed no association between DMS and cognitive decline (Brachem et al., 2020; Jelicic et al., 2002), whereas another study showed that DMS was the only insomnia symptom that predicted cognitive decline (Johar et al., 2016). Heterogenous results might be caused by different ways of measuring both insomnia and cognition (Sexton et al., 2020).

One large, cross-sectional study of 477,529 people found that having frequent insomnia symptoms was associated with a small but significant advantage in completing simple neurocognitive tasks (Kyle et al., 2017). The authors consider that the association may be explained by unmeasured personality traits among people with insomnia, including perfectionism. They also suggested that hyperarousal, which is closely linked to insomnia pathophysiology (Riemann et al., 2017), might enhance cognitive performance on brief tasks with low cognitive load but hinder performance on more cognitively challenging tasks (Kyle et al., 2017). However, in light of the observed association between DMS and the lower risk of all-cause dementia and AD in our study, we can conversely postulate that hyperarousal may boost cognitive reserves by increasing arousal in cognitive domains. This remains speculative and needs further clarification.

4.5 | Strengths and limitations

Our study had several strengths. First, it was a population-based study covering the general population in the former county of Nord-Trøndelag, including both home-dwelling individuals and people living in care homes. Second, the sample was large, and proportions of missing data were low. Third, by performing MI, we prevented the loss of power and reduced the risk of selection bias that often afflict complete case analyses. Variables in the imputation model predicted the missingness of important variables, which supported our assumption of variables not being missing completely at random (Sterne et al., 2009). Fourth, all degrees of dementia were included in the sample, and dementia was diagnosed by experienced clinicians using the *DSM-5* criteria. Fifth, the follow-up time was long, which reduced the likelihood of reverse causality. Sixth and last, our study benefited from access to a substantial amount of information about sociodemographic factors, physical comorbidities, psychiatric comorbidities, lifestyle factors and genetics, all of which allowed us to create extensively adjusted models and minimize the probability of residual confounding.

There are also some limitations. For one, PID has a specificity of 93% for definite insomnia, but a sensitivity of only 31% compared with diagnoses made using semi-structured face-to-face interviews (Filosa et al., 2020). Underestimated PID might have concealed true associations. Additionally, a large number of variables, including the insomnia variables (i.e. PID, DIS, DSM, EMA), were based on self-reporting, introducing a possible response bias. Moreover, despite MI, some selection bias likely occurred, as only 54.1% and 51.2% of people invited to HUNT3 and HUNT4 70+ participated. Non-participants in HUNT3 have been characterized as having lower socioeconomic status, a higher mortality rate, more insomnia, and a higher prevalence of several chronic diseases (Langhammer et al., 2012). Attrition from HUNT3 to HUNT4 was moderately higher among people with chronic disease and poor self-reported health (Åsvold et al., 2022), which may have also characterized attrition from HUNT3 to HUNT4 70+ and resulted in a sample that was healthier than the population. Another limitation was that we did not have access to information about use of prescribed sleep medication such as benzodiazepines. Because benzodiazepines are a well-known treatment for insomnia (Riemann et al., 2017) and a possible risk factor for dementia (Livingston et al., 2020), adjusting for use of benzodiazepines would be expected to affect any association between insomnia and dementia. Lastly, due to the exploratory nature of our study, correction for multiple testing was not performed, which raises the risk of spurious findings.

5 | CONCLUSION

In contrast to most previous studies, we found no association between PID and risk of dementia 11 years later. Conversely, we found an association between having DMS, lower risk of dementia, and better cognitive function. More research is needed to determine the relationship between insomnia disorder, insomnia symptoms and dementia risk, and future studies should explore if the associations vary across different subtypes of insomnia.

AUTHOR CONTRIBUTIONS

Selma Selbæk-Tungevåg, Geir Selbæk, Sverre Bergh and Linda Ernstsen were responsible for the conception and the design of the study; Selma Selbæk-Tungevåg, Stian Lydersen, Christian Myrstad and Linda Ernstsen contributed with the analysis of data; Selma Selbæk-Tungevåg wrote the first draft; Selma Selbæk-Tungevåg, Geir Selbæk, Bjørn Heine Strand, Christian Myrstad, Gill Livingston, Stian Lydersen, Sverre Bergh and Linda Ernstsen contributed to data interpretation and critical revisions of the manuscript.

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CONFLICT OF INTEREST

Geir Selbæk has participated in an advisory board meeting with Biogen. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data from the Trøndelag Health Study (HUNT) used in research projects are available upon reasonable request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). Information about accessing HUNT data (http://www.ntnu.edu/hunt/data) details the policy about data availability.

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