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Sleep disturbances and incident risk of major depressive disorder in a population-based cohort

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ABSTRACT

Sleep disturbances are well-known symptoms of major depressive disorder (MDD). However, the prospective risk of MDD in the presence of sleep disturbances in a general population-based cohort is not well known. This study investigated associations between both polysomnography (PSG)-based or subjective sleep features and incident MDD. Participants representative of the general population who had never had MDD completed sleep questionnaires ($n = 2000$) and/or underwent PSG ($n = 717$). Over 8 years' follow-up, participants completed psychiatric interviews enabling the diagnosis of MDD. Survival Cox models were used to analyze associations between sleep features and MDD incidence. A higher Epworth Sleepiness Scale and presence of insomnia symptoms were significantly associated with a higher incidence of MDD (hazard ratio [HR] [95 % confidence interval (CI)]: 1.062 [1.022–1.103], $p = 0.002$ and 1.437 [1.064–1.940], $p = 0.018$, respectively). Higher density of rapid eye movements in rapid eye movement (REM) sleep was associated with a higher incidence of MDD in men (HR 1.270 [95 % CI 1.064–1.516], $p = 0.008$). In women, higher delta power spectral density was associated with a lower MDD incidence (HR 0.674 [95 % CI 0.463–0.981], $p = 0.039$). This study confirmed the associations between subjective and objective sleep features and the incidence of MDD in a large community dwelling cohort.

1. Introduction

Major depressive disorder (MDD) is a major mental health problem and is the leading cause of mental health-related disability worldwide (Herrman et al., 2019). MDD is characterized by a broad range of symptoms and is not always easy to diagnose, with an estimated half of all cases missed in primary care (Mitchell et al., 2009). The identification of biomarkers for the early detection of depression is a pressing public health issue (Fekadu et al., 2022).

MDD is often associated with sleep-related complaints, including

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insomnia or hypersomnia (American Psychiatric Association, 2013; Bell, 1994). The sleep "target" seems to be an interesting way to assess the risk of developing MDD because it could be considered a modifiable parameter that might respond to appropriate intervention and management (Irwin et al., 2022; Pandi-Perumal et al., 2020; Riemann et al., 2020). Sleep complaints can be evaluated during medical interviews and the use of validated questionnaires, while objective sleep alterations can be evaluated by polysomnography (PSG) or actigraphy (Buysse et al., 1989; Gauld and Micoulaud-Franchi, 2022; Sateia, 2014).

Most studies investigating the relationship between sleep disturbances and the risk of depression have focused on insomnia (Riemann et al., 2020). Meta-analyses have shown that individuals reporting symptoms of insomnia have a higher risk of developing depression (Baglioni et al., 2011; Hertenstein et al., 2019a; Li et al., 2016; Zhang et al., 2022). Subjective sleep complaints other than insomnia (i.e., hypersomnia and excessive daytime sleepiness) were also associated with a higher risk of depression (Zhang et al., 2022). These associations are of interest because hypersomnolence complaints have been shown to predict future suicidal ideation in patients with MDD (Maruani et al., 2023). In Zhang's meta-analysis, only one of the 56 included studies evaluated objective sleep parameters using PSG (Zhang et al., 2022).

Despite growing interest in the relationship between sleep disturbances and depression, few general population studies have been performed. In a recent study by our group on 1820 community-dwelling adults from the CoLaus|PsyColaus cohort, we found that some PSG-based sleep features, such as electroencephalogram (EEG) delta power during non-rapid eye movement (NREM) sleep or rapid eye movement (REM) density (the number of rapid eye movements per minute of REM sleep) differed in some MDD subtypes compared to individuals without MDD (Solelhac et al., 2023). Using the same cohort, this study assessed associations between both subjective and objective sleep parameters features and the incidence of MDD during follow-up, and determined whether there were any variations in these associations based on sex. We hypothesized that daytime subjective sleepiness (Zhang et al., 2022), poor subjective sleep quality (Hertenstein et al., 2019b; Zhang et al., 2022), and higher REM density (Solelhac et al., 2023) would be associated with a higher risk of developing MDD.

2. Methods

2.1. Design and participants

The present study used data from the prospective CoLaus|PsyColaus cohort study, which assessed associations between mental disorders and cardiovascular risk factors in the community. The cohort initially included 6734 participants randomly selected from 35- to 75-year-old residents of Lausanne, Switzerland from 2003 to 2006 (Firmann et al., 2008). Participants underwent thorough physical and psychiatric evaluations at baseline and at three follow-up visits (Preisig et al., 2009). The PSG investigation took place between 2009 and 2013 (Heinzer et al., 2015), i.e. between the first and second follow-up of the CoLaus|PsyCoLaus study. The study timeline is represented in Fig. 1. After a subjective sleep assessment at the first CoLaus follow-up ($n = 5064$), a subset of 4233 participants completed psychiatric evaluations. Individuals with a lifetime history of MDD, bipolar disorder, schizoaffective disorder, schizophrenia, schizophreniform disorder or brief psychotic disorder, and those with current use of psychotropic medications (anxiolytics, hypnotics, antidepressants) were excluded (Fig. 2). The CoLaus|PsyColaus and HypnoLaus studies were approved by the Ethics Committee of the Vaud Canton, and written informed consent was obtained from all participants.

Baselines were set at the time of PSG recording and at the first follow-up (FU 1) of CoLaus for objective and subjective sleep analyses respectively as shown in the study timeline (Fig. 1).

2.2. Subjective sleep features

Subjective sleep features were assessed at the first physical follow-up of CoLaus|PsyColaus using validated questionnaires that measured sleep duration and quality (Buysse et al., 1989). Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a comprehensive questionnaire consisting of 19 items that assesses sleep patterns over the past month (Buysse et al., 1989). The questionnaire covers seven distinct domains, including sleep quality, latency, efficiency, duration, disturbances, daytime dysfunction, and use of sleep medications. Each domain is scored on a scale from 0 to 3, and the scores are summed to obtain the global PSQI score, ranging from 0 to 21. Higher scores on the PSQI indicate poorer sleep quality. Insomnia symptoms were defined using question 5a and 5b of the PSQI (participants reporting a sleep latency >30 min and/or wake up in the middle of the night or early morning awakening three or more times a week). The Epworth Sleepiness Scale (ESS) was used to evaluate daytime sleepiness (Johns, 1991). This scale asks participants to rate their likelihood of dozing off in various daily situations on a scale from 0 to 3; sores for the different items are added with the total ranging from 0 to 24 (higher scores indicate greater daytime sleepiness).

2.3. Polysomnography (PSG)-based sleep features

Participants underwent a full night PSG at home (Titanium, Embla® Flaga, Reykjavik, Iceland). PSG was performed according to the American Academy of Sleep Medicine (AASM) 2007 recommendations (Iber, 2007) and included: electroencephalography (EEG) leads (F3, F4, C1, C2, O1 and O2, 256 Hz sampling rate); electrooculography (EOG, left and right); electromyography (EMG, chin and *anterior tibialis* muscle); electrocardiography (ECG, one lead); oxygen saturation (SpO_2); airflow (nasal cannula); abdominal and thoracic respiratory efforts; snoring; and body position. PSG data were visually scored according to the AASM guidelines 2007 (Iber, 2007). Apneas and hypopneas were scored according to the 2012 AASM manual (Berry et al., 2012). Periodic leg movements during sleep (PLMS) were scored according to the World Association of Sleep Medicine/International Restless Legs Syndrome Study Group (WASM/IRLSSG) 2006 recommendations (Zucconi et al., 2006).

REM density was analyzed using an algorithm from the YASA library (Agarwal et al., 2005; Vallat and Walker, 2021; Yetton et al., 2016) in Python software (Version 3.9) to automatically detect rapid eye movements on the two EOG raw signal channels (right and left) in REM sleep. The following specifications were used for REM detection: between 50 and 325 microV for the amplitude; between 0.3 and 1.2 s for the duration; and between 0.5 and 5 Hz for the frequency. The variable calculated and used in the present analysis was the REM density,

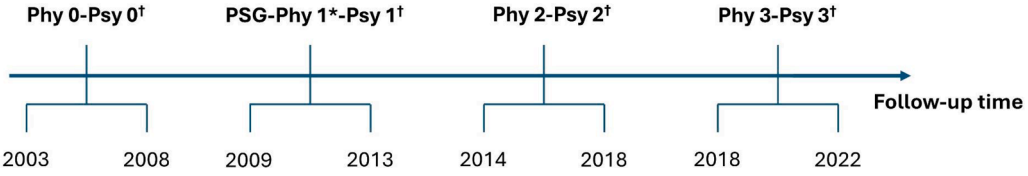

Fig. 1. Study Timeline. PSG: polysomnography, Phy: physical follow-up, Psy: psychiatric follow-up. †: average of approximately 1 year between physical and psychiatric follow-up; *: average of approximately 1 year between PSG and physical follow-up 1.

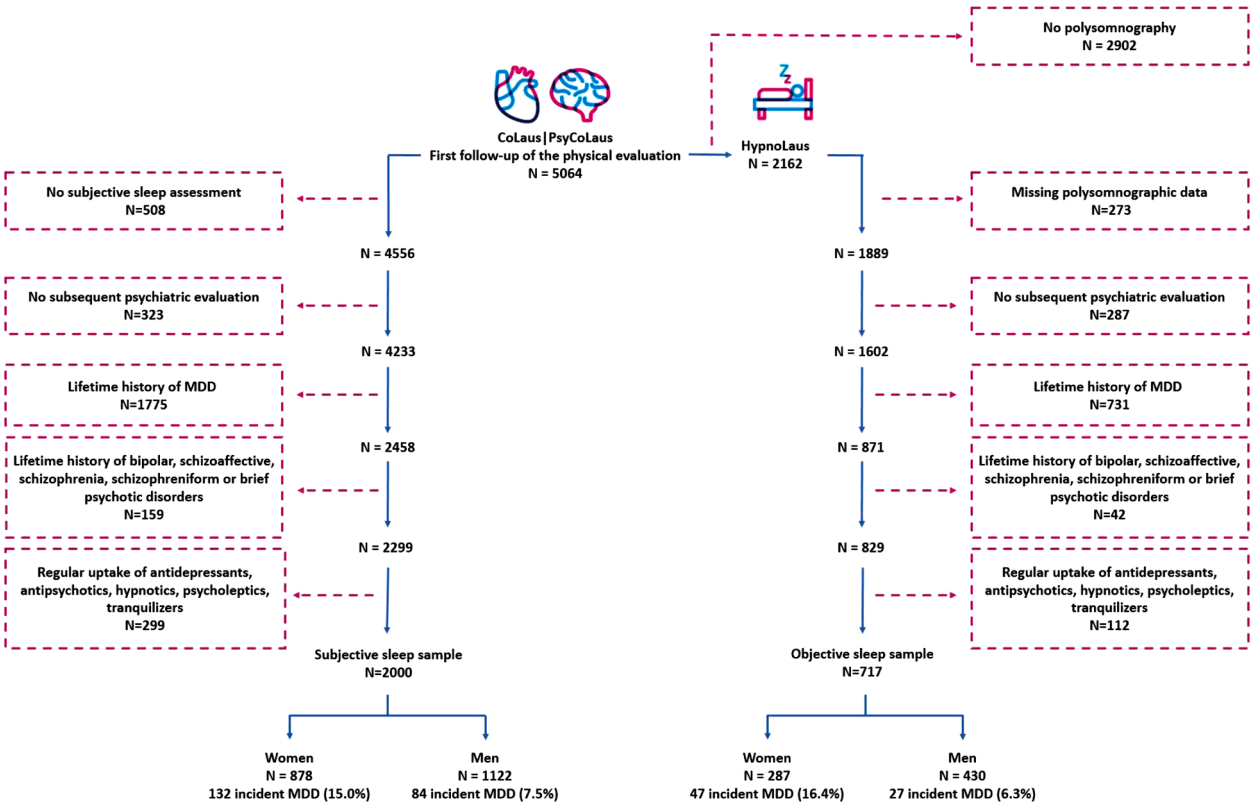

Fig. 2. Study flow chart. MDD=major depressive disorder. Selection and exclusion processes are shown in blue and dotted pink lines, respectively. * Among them 600 individuals (83.7 %) provided complete subjective sleep data.

corresponding to the number of REMs per minute of REM sleep.

The power spectral sleep EEG analysis has been previously described (Lecci et al., 2020). In brief, after an automatic rejection procedure, sleep EEG recordings were re-referenced to the average of the two mastoid channels and band pass filtered between 0.5 and 35 Hz with a finite impulse response. Based on literature according to the reduction of NREM EEG delta power in MDD (Armitage et al., 2000); we calculated absolute power spectral density in delta frequency band (1-4 Hz) using the Welch's method on artifact free consecutive, non-overlapping 6-second epochs (Hamming windows, 8 segments, 50 % overlap). The F3 electrode was selected for this analysis because previous studies have indicated that it is mainly frontal slow wave sleep that is associated with higher brain function, specifically memory and attention (Léger et al., 2018). Additionally, the superior quality of F3 electrode data in comparison to C3 in our dataset (due to less interpretable data due to EEG artifacts) was also a contributing factor in this choice. Absolute delta power spectral density was analyzed for NREM sleep stages N2 and N3 together. Previous publications showed that NREM EEG delta power was particularly reduced during the first part of the night in depression (Borbély et al., 1981; Carrier et al., 2001; Dijk et al., 1989; Svetnik et al., 2017), so we specifically focused on the first half of the total recording time of the PSG. To facilitate understanding of the article, we will refer to "delta power" throughout the manuscript.

To resume, the following objective PSG-based sleep features were analyzed: total sleep time (TST); sleep onset latency (SOL, time in min between light off and sleep onset); sleep efficiency (SE, TST*100/total recording time as a percentage); REM latency (time in min to REM sleep after sleep onset); REM (REM, proportion of TST spent in the REM sleep stage as a percentage), REM arousal (number of arousals during REM sleep stage [events/h]), apnea-hypopnea index (AHI in events/hour), PLMS index (PLMSI in events/hour), slow wave sleep (SWS, proportion of TST spent in the N3 sleep stage as a percentage); delta power in NREM sleep in μV^2/Hz for the first 50 % of the night), and REM density (number of rapid eye movements per minute in REM sleep stage [events/min]).

2.4. Psychiatric evaluation

Mental disorders including MDD were assessed at the psychiatric baseline and at the three follow-up evaluations using the French version (Leboyer et al., 1995) of the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). Interviews were carried out by trained master-level psychologists. A senior psychologist reviewed all interviews and assessments. Psychiatric diagnoses of major depressive episodes relied on DSM-IV criteria.

2.5. Covariates

Socio-demographic characteristics, education level and smoking history were assessed using a standardized interview during the physical investigation at the first follow-up. This investigation also included anthropometric measurements. Height was measured using a vertical stadiometer (Seca®, Hamburg, Germany) and weight was measured using a calibrated scale to within 0.1 kg (Seca®, Hamburg, Germany); these values were used to calculate body mass index (BMI in kg/m^2). Information regarding specific anxiety disorders (generalized anxiety disorder, agoraphobia, social phobia, panic disorder), psychotropic treatment and substance use disorders (alcohol or drug abuse or dependence) was obtained through DIGS conducted during the psychiatric evaluation at the first follow-up visit.

2.6. Statistical analysis

Adjusted Cox proportional-hazard models were used to determine the association between individual sleep features and MDD occurrence. These models were adjusted for age, sex, and current smoking status

Table 1
Baseline demographic characteristics of participants with sleep questionnaire data, overall and by sex.

	Overall (n = 2000)	Men (n = 1122)	Women (n = 287)
Socio-demographic characteristics			
Age (years)	57.3 [49.3; 66.7]	56.3 [48.5; 65.7]]	58.5 [50.3; 67.8]
Current smoker, *n* (%)	361 (18.0)	227 (20.2)	134 (15.3)
BMI (kg/m^2)	25.8 [23.1; 28.5]	26.4 [24.1; 28.9]	24.5 [21.6; 27.8]
Education level, *n (%)*			
Low	1069 (53.4)	569 (50.7)	500 (56.9)
Middle	500 (25.0)	279 (24.9)	221 (25.2)
High	431 (21.6)	274 (24.4)	157 (17.9)
Current dependence, *n (%)*[*]	61 (3.3)	57 (5.5)	4 (0.5)
Current psychiatric comorbidities, *n (%)*[#]	49 (2.7)	16 (1.6)	33 (4.1)
Subjective sleep features			
ESS score	5 [3; 8]	6 [4; 8]	4 [2; 7]
ESS score >10, *n (%)*	154 (8.7)	100 (10.1)	54 (6.9)
Insomnia symptoms[**], *n (%)*	478 (25.9)	245 (23.9)	233 (28.4)
PSQI score	3 [2; 5]	3 [2; 5]	4 [2; 5]
PSQI Component 1: Sleep quality, *n (%)*			
Very good	483 (28.9)	310 (29.6)	217 (26.0)
Good	1025 (61.2)	638 (61.0)	513 (61.4)
Bad	149 (8.9)	88 (8.4)	95 (11.4)
Very bad	17 (1.0)	10 (1.0)	10 (1.2)
PSQI Component 2: Sleep latency[†],*n (%)*			
Score 0	856 (52.7)	573 (56.3)	373 (46.3)
Scores 1–2	545 (33.5)	329 (32.3)	295 (36.6)
Scores 3–4	163 (10.0)	88 (8.6)	96 (11.9)
Scores 5–6	61 (3.8)	28 (2.8)	41 (5.1)
PSQI Component 3: Sleep duration, *n (%)*			
>7 hours	1287 (72.1)	770 (68.6)	663 (75.5%
6-7 hours	376 (21.1)	259 (23.1)	171 (19.5)
5-6 hours	106 (5.9)	79 (7.0)	41 (4.7)
<5 hours	15 (0.8)	14 (1.3)	3 (0.3)
PSQI Component 4: Sleep efficiency, *n (%)*			
>85 %	1176 (70.4)	771 (74.2)	560 (66.9)
75-84 %	298 (17.8)	154 (14.8)	169 (20.2)
65-74 %	102 (6.1)	55 (5.3)	59 (7.1)
<65 %	95 (5.7)	59 (5.7)	49 (5.9)
PSQI Component 5: Sleep disturbance[Δ], *n (%)*			
Score 0	95 (6.1)	68 (6.9)	42 (5.4)
Scores 1–9	1241 (79.1)	783 (79.4)	605 (78.0)
Scores 10–18	230 (14.7)	134 (13.6)	128 (16.5)
Scores 19–27	2 (0.1)	1 (0.1)	1 (0.1)
PSQI Component 6: Sleep medication, *n (%)*			
Not in the last month	1498 (90.4)	954 (92.2)	727 (87.9)
<1 time per week	77 (4.7)	35 (3.4)	52 (6.3)
1–2 times per week	34 (2.1)	17 (1.6)	26 (3.1)
5–6 times per week	48 (2.9)	29 (2.8)	22 (2.7)
PSQI Component 7: Daytime dysfunction[∏], *n (%)*			
Score 0	952 (58.5)	566 (55.3)	474 (58.9)
Scores 1–2	576 (35.4)	377 (36.9)	290 (36.0)
Scores 3–4	92 (5.7)	69 (6.7)	38 (4.7)
Scores 5–6	8 (0.5)	11 (1.1)	3 (0.4)

Values are median [interquartile range] or number of participants (%).
BMI=body mass index; ESS=Epworth Sleepiness Scale; PSQI=Pittsburgh Sleep Quality Index.

[*] Alcohol and/or drug abuse or dependence.

[#] Generalized anxiety disorder, agoraphobia, social phobia, panic disorder.

[**] Presence of insomnia was defined using PSQI questions 5a and 5b; participants reporting sleep latency of >30 min and/or waking in the middle of the night or early morning on three or more occasions per week were considered to have insomnia.

[†] Sleep latency: summation of PSQI question 2 (average sleep latency ≤15 mi n = 0, 16–30 mi n = 1, 31–60 min-=2, and >60 mi n = 3) and question 5a (frequency of sleep latency <30 min: not during the past month=0; less than once a week=1; once or twice a week=2; and three or more times a week=3).

[Δ] Sleep disturbance: summation of questions 5b to 5j (frequency of early awakening [5b], bathroom use [5c], difficulty breathing [5d], loud snoring or coughing [5e], feeling too cold [5f], feeling too hot [5g], having bad dreams [5h], having pain [5i], other [5j]: not during the past month=0; less than once a week=1; once or twice a week=2; three or more times a week=3).

[∏] Daytime dysfunction: summation of question 7 (during past month: frequency of trouble staying awake while driving, eating meals, or engaging in social activity) and question 8 (during the past month: how much of a problem has it been for you to keep up enough enthusiasm to get things done?): not during the past month=0; less than once a week=1; once or twice a week=2; three or more times a week=3.

because these are clinically recognized or historical MDD risk factors (Breslau et al., 1998; Kessler et al., 1994; Stordal et al., 2003; Weissman and Klerman, 1977). To investigate whether sleepiness was linked to OSA, we used a Cox model that included AHI and ESS adjusted for smoking status, age, and sex. Results were expressed as hazard ratio (HR) values with the 95 % confidence interval (95 % CI). The model assumptions were investigated using a Schoenfeld's test. To explore potential sex-specific effects, interaction terms between sleep features and sex were included in each individual model. Stratified analyses were conducted for models with a significant interaction.

Least Absolute Shrinkage and Selection Operator (LASSO) (Tibshirani, 1996) was then used to formulate multivariate models, while alleviating concerns of overfitting related to the restricted number of events (Simon et al., 2011) (using R package *glmnet* version 4.1.7). Given that the model was not chosen independently of the data, the R package *selectiveInference* was used to obtain valid *p*-values after variable selection as proposed by Tibshinari et al.(Tibshirani et al., 2019). For all statistical comparisons, two-sided *p*-values <0.05 were considered statistically significant.

To graphically represent the effect of the covariate(s) of interest on MDD incidence, we used the R package *simPH* (Gandrud, 2015). This package simulates parameter estimates and calculates quantities of interest such as hazard ratios following King *et al* approach (King et al., s. d.).

All analyses were performed using R software version 4.2.2 (R Foundation, Vienna, Austria) (R Foundation for Statistical Computing, s. d.)

3. Results

3.1. Study participants

Subjective sleep feature analyses included 2000 individuals (median age 59.4 years [interquartile range (IQR) 50.5; 67.6], 56.1 % men) and objective sleep features analyses (from PSG) included 717 individuals (median age 57.5 years [IQR 49.9; 68.5], 60.0 % men). Socio-demographic and subjective sleep characteristics for the total cohort and in men and women are reported in Tables 1 and 2. The mean follow-up durations for the subjective and objective sleep features analyses were 9.32 years (95 % CI 5.86–9.67] and 8.10 years (95 % CI 7.00–9.20), respectively.

3.2. Subjective sleep features

Overall, the mean interval between completion of the sleep questionnaire and the occurrence of MDD during follow-up was 4.08 years (95 % CI 1.55; 6.12). The incidence of MDD was higher in women than in men (15 % versus 7.5 %, $p < 0.001$).

In adjusted Cox regression models, a higher ESS score was significantly associated with an increased incidence of MDD (HR 1.062, 95 % CI 1.022–1.103; $p = 0.002$) (Table 3, Fig. 3). When fitting a Cox model that includes both ESS and AHI (adjusted for age, sex and smoking status), ESS score was significantly associated with a higher risk of developing MDD (HR 1.066, 95 % CI 1.004–1.133; $p = 0.037$) but not AHI (HR 1.005, 95 % CI 0.986 –1.025; $p = 0.589$). The presence of insomnia symptoms was significantly associated with MDD (HR 1.437, 95 % CI 1.064–1.940; $p = 0.018$) (Table 3, Fig. 4).

A significant interaction between sex and the PSQI score was identified ($p = 0.003$). In men, a higher PSQI score was significantly associated with MDD incidence (Table 3, Fig. 5); this association was mainly explained by the sleep quality, sleep duration, sleep efficiency and daytime disturbance individual components of PSQI. In women, the daytime disturbance component of PSQI was associated with MDD, but the global PSQI score was not (Table 3).

3.3. Objective PSG-based sleep features

For the cohort with valid PSG data ($n = 717$), the mean interval between the PSG investigation and the occurrence of MDD was 3.55 years (95 % CI 2.22–5.30) (Table 2).

In the Cox proportional hazards models, significant interactions with sex were identified for REM density ($p = 0.038$) and delta power($p =$

Table 2
Characteristics of participants with polysomnography data, overall and by sex.

	All ($n = 717$)	Men ($n = 430$)	Women ($n = 287$)
Socio-demographic characteristics			
Age (years)	57.5 [49.9; 68.5]	56.6 [49.0; 67.8]	58.3 [50.8; 69.4]
Current smoker, *n (%)*	95 (13.2)	60 (13.9)	35 (12.2)
BMI (kg/m^2)	25.8 [23.3; 28.2]	26.2 [24.2; 28.4]	24.5 [21.9; 27.7]
Education level, *n (%)*			
Low	355 (49.5)	197 (45.8)	158 (55.1)
Middle	205 (28.6)	122 (28.4)	83 (28.9)
High	157 (21.9)	111 (25.8)	46 (16.0)
Current dependence, *n (%)*[*]	20 (2.8)	18 (4.2)	2 (0.7)
Current psychiatric comorbidities, *n (%)*[#]	14 (2.0)	9 (2.1)	5 (1.7)
Objective sleep features			
TST (min)	398 [357; 438]	414 [376; 453]	388 [348; 427]
SOL (min)	9.8 [4.3; 18.8]	10.4 [4.7; 19.2]	9.0 [4.2; 18.5]
SE (%)	55.4 [34.0; 99.4]	53.6 [33.8; 98.2]	59.0 [34.5; 101.0]
PLMSI (events/h)	2.2 [0.0; 19.8]	2.7 [0.0; 21.1]	1.8 [0.0; 16.9]
AHI (events/h)	10.4 [4.2; 21.1]	15.4 [6.9; 26.1]	6.0 [2.5; 12.8]
Delta power (μV^2/Hz)	1.2 [0.8; 1.8]	1.5 [1.1; 2.1]	1.0 [0.7; 1.5]
Proportion of time spent in N3 sleep (%)	19.1 [14.2; 24.9]	21.5 [16.6; 26.1]	18.1 [12.9; 23.3]
REMD (/min)	2.4 [1.4; 3.7]	2.5 [1.5; 4.0]	2.3 [1.3; 3.7]
REML (min)	72.5 [57.0; 95.5]	73.0 [59.0; 99.0]	71.5 [56.0; 94.0]
Proportion of time spent in REM sleep (%)	22.2±5.87	21.7±6.06	23.0±5.51
REM arousal (events/h)	19.1 [12.5;29.3]	21.8 [14.8;32.0]	16.2 [10.4;24.5]

Values are median [interquartile range], mean ± standard deviation, or number of participants (%).
[*] Alcohol and/or drug abuse or dependence.
[#] Generalized anxiety disorder, agoraphobia, social phobia, panic disorder.
AHI, apnea-hypopnea index; BMI, body mass index; N3, non-rapid eye movement sleep stage 3; REM, rapid eye movement; REMD, rapid eye movements density; REML, rapid eye movements latency; SE, sleep efficiency; TST, total sleep time.

Table 3
Associations between major depressive disorder incidence and subjective sleep features (Cox proportional hazard models adjusted for age, sex and current smoking status).

	All		Men		Women	
	HR (95 % CI)	*p*-value	HR [95 % CI]	*p*-value	HR [95 % CI]	*p*-value
ESS score	1.062 (1.022–1.103)	**0.002**	-	-	-	-
ESS score >10	1.618 (0.964–2.718)	0.069	-	-	-	-
Insomnia symptoms	1.437 (1.064–1.940)	**0.018**	-	-	-	-
PSQI score	†	†	1.204 (1.111–1.305)	**<0.001**	1.023 (0.954–1.097)	0.523
Component 1: Sleep quality	†	†	1.748 (1.247–2.451)	**0.001**	1.179 (0.906–1.535)	0.221
Component 2: Sleep latency	†	†	1.112 (1.253–1.879)	**0.006**	1.002 (0.803–1.252)	0.983
Component 3: Sleep duration	†	†	1.427 (1.090–1.868)	**0.010**	0.857 (0.622–1.180)	0.344
Component 4: Sleep efficiency	†	†	1.301 (1.028–1.645)	**0.028**	0.878 (0.690–1.118)	0.292
Component 5: Sleep disturbance	†	†	0.854 (0.511–1.427)	0.547	1.246 (0.854–1.818)	0.255
Component 6: Sleep medication	†	†	1.309 (0.972–1.765)	0.077	0.912 (0.647–1.286)	0.600
Component 7: Daytime dysfunction	†	†	1.642 (1.213–2.223)	**0.001**	1.461 (1.125–1.898)	**0.004**

CI, confidence interval; ESS, Epworth Sleepiness Scale; HR, hazard ratio; PSQI, Pittsburgh Sleep Quality Index.
† Models with significant interaction between sex and predictor variable were stratified accordingly.

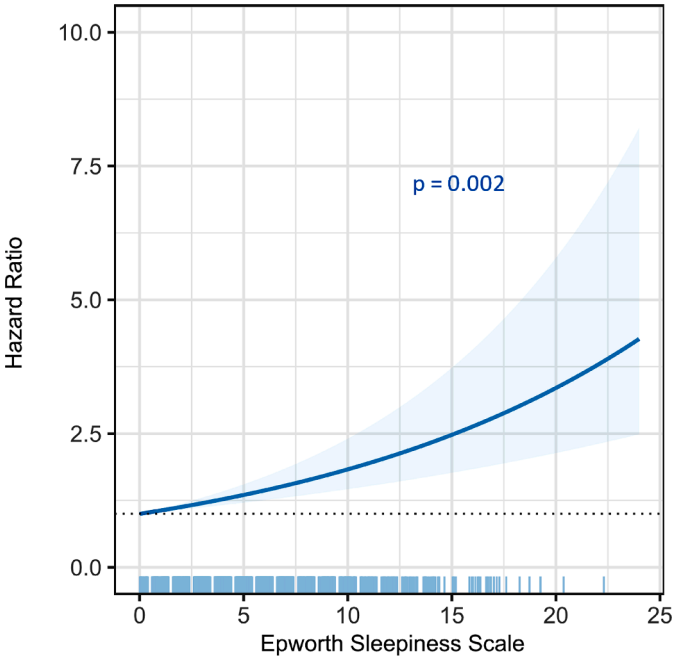

Fig. 3. Association between major depressive disorder incidence and the Epworth Sleepiness Scale. Data are multiple-adjusted Cox proportional hazards regression models showing simulated hazard ratio values with 95 % confidence intervals. Distribution of hazard ratio values are shown as a function of Epworth Sleepiness Scale and are derived from 1000 simulations using the approach described by King et al. (2000). Models are adjusted for age, sex, and current smoking status. Distribution of Epworth Sleepiness Scale values is shown on the rug plot along the *x*-axis. The *p*-value shown relates to the hazard ratio value in the original Cox proportional hazards regression model (1.062 [95 % confidence interval 1.022–1.103]).

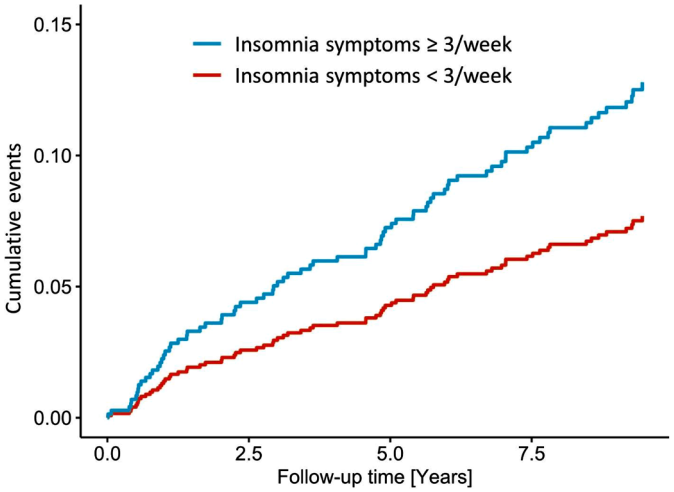

Fig. 4. Association between major depressive disorder incidence and insomnia symptoms. Multiple adjusted survival curves show the expected frequency of major depressive disorder based on presence of insomnia symptoms (sleep latency >30 min and/or wake up in the middle of the night or early morning early awakening) on more than 3 occasions each week. Models are adjusted for age, sex, and current smoking status. Hazard ratio value for insomnia symptoms ≥3 vs. <3 times per week: 1.437 [95 % confidence interval 1.064–1.940]; $p = 0.018$.

0.047). Elevated REM density values were significantly associated with MDD in men (HR 1.270, 95 % CI 1.064–1.516]; $p = 0.008$) (Table 4, Fig. 6). In women, higher delta power values were associated with a decreased incidence of MDD (HR 0.674, 95 % CI 0.463–0.981; $p = 0.039$) (Table 4, Fig. 7).

In men, the LASSO method identified the combination of age and REM density as the optimal model, with both showing statistically significant associations with the risk of MDD. In women, age, smoking status, delta power, sleep onset latency, and sleep efficiency were the components of the best-fitting model. In this LASSO-derived model Cox model, increasing delta power was associated with a lower incidence of MDD but this association was no longer statistically significant after addressing the post-selection inference bias.

4. Discussion

Our study shows that objective PSG-based sleep features are associated with risk of incident MDD in community-dwelling adults. Subjective sleep features like insomnia and sleepiness are also associated with an increased risk of developing MDD.

4.1. Subjective sleep features and MDD incidence

The ESS score was associated with an increased risk of developing MDD in our sample. Complaints of hypersomnolence are common in individuals with depression. Geoffroy and colleagues reported that hypersomnolence was present in about half of all patients with MDD (Geoffroy et al., 2018). In a recent meta-analysis, there was trend towards an association between excessive daytime sleepiness and depression (odd ratio 1.43, 95 % CI 1.00–2.05) (Zhang et al., 2022). One study analyzed ESS and the risk of depression with a one-year follow-up and also found an increased risk of incident depression when ESS was

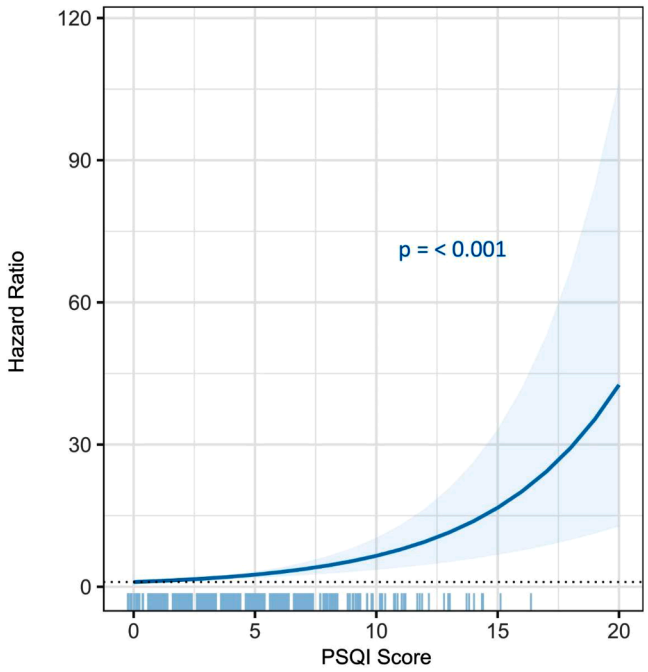

Fig. 5. Association between major depressive disorder incidence and the Pittsburg Sleep Quality Index (PSQI) score in men. Data are multiple-adjusted Cox proportional hazards regression models showing simulated hazard ratio values with 95 % confidence intervals. Distribution of hazard ratio values are shown as a function of PSQI score and are derived from 1000 simulations using the approach described by King et al. (2000) (King et al., 2000). Models are adjusted for age, sex, and current smoking status. Distribution of PSQI score values is shown on the rug plot along the *x*-axis. The *p*-value shown relates to the hazard ratio value in the original Cox proportional hazards regression model (1.204 [95 % confidence interval 1.111–1.305].

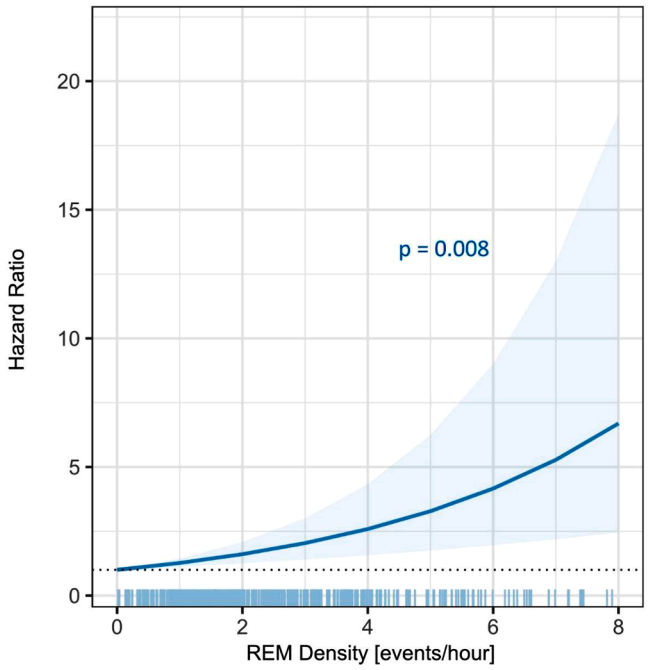

Fig. 6. Association between major depressive disorder incidence risk and rapid eye movements (REM) density in men. Data are multiple-adjusted Cox proportional hazards regression models showing simulated hazard ratio values with 95 % confidence intervals. Distribution of hazard ratio values are shown as a function of PSQI score and are derived from 1000 simulations using the approach described by King et al. (2000) (King et al., 2000). Models are adjusted for age, sex, and current smoking status. Distribution of REM density is shown on the rug plot along the *x*-axis. The *p*-value shown relates to the hazard ratio value in the original Cox proportional hazards regression model (1.270 [95 % confidence interval 1.064–1.516].

Table 4
Associations between major depressive disorder incidence and objective sleep features (Cox proportional hazard models adjusted for age, sex and current smoking status).

	HR (95 % CI)	*p*-value
Sleep efficiency (%)	1.022 (0.993–1.051)	0.136
SOL (min)	1.002 (0.983–1.021)	0.872
TST (min)	0.999 (0.996–1.003)	0.696
AHI (events/h)	1.005 (0.975–1.036)	0.729
PLMSI (events/h)	1.002 (0.986–1.020)	0.776
Proportion of time spent in N3 sleep (%)	0.999 (0.969–1.030)	0.950
REML (min)	0.998 (0.992–1.004)	0.460
Proportion of time spent in REM sleep (%)	0.997 (0.957–1.038)	0.888
REM arousal (events/h)	1.013 (0.994–1.032)	0.194
REMD (/min)[†]		
Men	1.270 (1.064–1.516)	0.008
Women	0.957 (0.820–1.116)	0.572
Delta power (μV^2/Hz)[†]		
Men	0.962 (0.595–1.557)	0.876
Women	0.674 (0.463–0.981)	0.039

[†] Models with significant interaction between sex and predictor variable were stratified accordingly.

AHI, apnea-hypopnea index; CI, confidence interval; HR, hazard ratio; N3, non-rapid eye movement sleep stage 3; REM, rapid eye movement; REMD, rapid eye movements density; REML, rapid eye movements latency; TST, total sleep time.

greater than 10 (Luo et al., 2018). Moreover, our results for AHI and ESS suggest that it is independent sleepiness, rather than OSA-associated sleepiness, that is associated with future incident MDD.

Insomnia symptoms are well-known risk factors for depression, with the overall hazard ratio for insomnia as a predictor of depression estimated at over 2 (Baglioni et al., 2011; Zhang et al., 2022). We also found an increased prospective risk of MDD related to insomnia symptoms with long follow-up based on DSM-IV criteria for diagnosing major depressive episodes.

4.2. *Objective PSG-based sleep features and MDD incidence*

A higher delta power in NREM sleep was associated with a lower risk of MDD for women. Reduced delta power is a known parameter of MDD status (Armitage et al., 2000). In our previous cross-sectional study, we observed this association in both melancholic and unspecified DSM subtypes of MDD. However, these associations were specific to an individual's current MDD status, and could not be extended to cases of remitted MDD (Solelhac et al., 2023). Furthermore, a meta-analysis reported a reduction in the percentage of slow wave sleep in individuals at high risk of depression compared with controls (6 studies) (Pillai et al., 2011). However, to our knowledge, the current study is the first to establish a prospective link between delta power and MDD incidence in a general population-based cohort. If REM sleep disinhibition parameters are frequently evoked in polysomnography reports, a more comprehensive analysis of delta power could provide a basis for suspecting a greater risk of developing MDD in patients undergoing sleep studies. It would be beneficial to include this information in a more systematic manner within our polysomnography reports.

Also, we showed that REM density was associated with a higher incidence of MDD in men. REM pressure is historically assessed by REM latency (objective-PSG difference between the onset of sleep and the onset of REM sleep) or the percentage of time spent in REM sleep. A reduction in REM latency or an increase of the proportion of REM sleep are considered as biomarkers of depression (Kupfer, 1976). However, these biomarkers are not specific to depression because they are found in

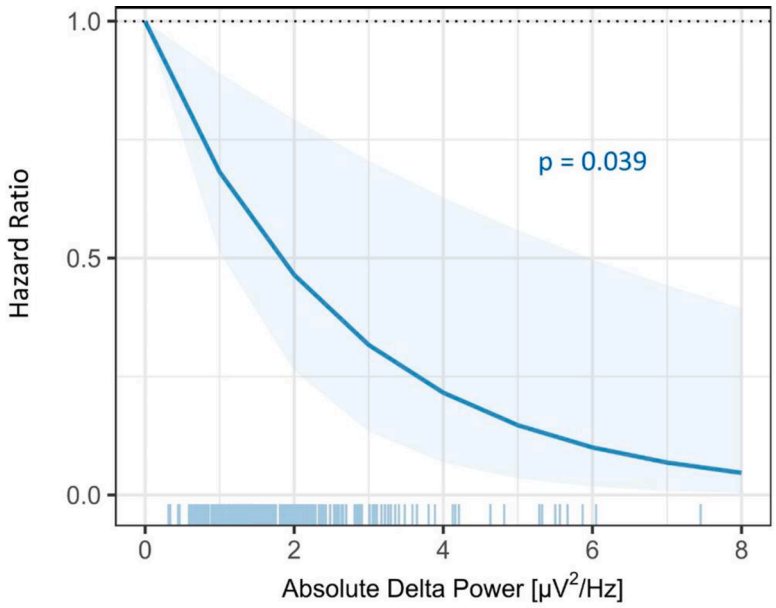

Fig. 7. Association between major depressive disorder incidence risk and delta power in non-rapid eye movement sleep in women. Data are multiple-adjusted Cox proportional hazards regression models showing simulated hazard ratio values with 95 % confidence intervals. Distribution of hazard ratio values are shown as a function of PSQI score and are derived from 1000 simulations using the approach described by King et al. (2000). Models are adjusted for age, sex, and current smoking status. Distribution of REM density is shown on the rug plot along the *x*-axis. The *p*-value shown relates to the hazard ratio value in the original Cox proportional hazards regression model (0.674 [95 % confidence interval 0.463–0.981].

other psychiatric conditions (Benca et al., 1992). REM density was then proposed as a biomarker of depression status, and has been shown to be a putative vulnerability marker for affective disorders and a predictor of treatment efficiency in depression (Clark et al., 2000; Friess et al., 2008; Modell et al., 2005; Palagini et al., 2013; Steiger and Kimura, 2010). According to another meta-analysis, patients with MDD have higher REM density than controls (Arfken et al., 2014). In our recent cross-sectional study, we found no difference in REM density between participants with current MDD and controls, but REM density was higher in participants with remitted MDD (Solelhac et al., 2023).

Our different findings for men and women are intriguing, but it is crucial to consider the unique sleep patterns associated with each sex. It is well known that men and women sleep differently, with women often reporting lower sleep quality and more frequent sleep disturbances (Mong et al., 2011). Numerous studies have shown a higher prevalence of insomnia in women compared with age-matched men (Zhang and Wing, 2006). This disparity is particularly pronounced during puberty and the menopausal transition, suggesting a strong influence of changes in ovarian steroid production (Camhi et al., 2000; Johnson et al., 2006; Lee et al., 2019; Mitchell and Woods, 1996; Morssinkhof et al., 2020; Owens and Matthews, 1998). The role of sex steroids in modulating sleep behaviors has been extensively reviewed (Lord et al., 2014), but it is still unclear what effect these hormones have on sleep and MDD. Knowing this, it seems essential to consider that the median age of our study cohort was 58.1 years for participants who did not develop MDD and 53.1 years for those who did. This age range is indicative of the menopausal stage in women, emphasizing the need for thoughtful consideration when examining our results. Regarding the increased REM density as a risk factor for depression in men and a higher delta power as a protective factor for depression in NREM for women, no study has really looked at sex differences in these two biomarkers in the prediction of MDD. However, it is known that women show greater delta power than men (Dijk et al., 1989). The different proportions of atypical and melancholic MDD subtypes by sex, which may be related to different objective PSG-based changes in sleep characteristics (Solelhac et al., 2023) may explain the difference between men and women in the risk of incident MDD associated with delta power. Overall, it is important to keep in mind that these sex differences cannot be clearly explained by this study and require further investigation.

4.3. *Strengths and limitations*

Our study has a number of strengths, such as the large number of participants representative of the general population, the acquisition of objective PSG variables, the use of DSM-IV criteria to diagnose MDD, and the longitudinal follow-up of over 8 years.

However, several limitations should be mentioned. Firstly, objective sleep assessment was conducted over a single night, potentially failing to capture representative sleep data due to the first night effect and night-to-night variability. However, it still the largest prospective cohort with objective PSG features. Secondly, the potential occurrence of covariates (e.g., life events, stressors, physical activity) during the follow-up period introduces uncertainty into the temporal relationship between sleep features and MDD. Thirdly the mean age of our cohort (approximately 57 years) may limit the generalizability of our findings. Given that MDD typically manifests at a younger age, our data from an older population might not fully capture the dynamics of MDD incidence in younger individuals. Finally, despite the evaluation of subjective sleep features through validated questionnaires, our study is limited by the absence of specific criteria for chronic insomnia disorder according to the International Classification of Sleep Disorders or the DSM-IV.

5. Conclusion

This study confirms the association between subjective complaints of insomnia and sleepiness and the risk of developing MDD in a large community dwelling cohort. In addition, we found that objective abnormalities such as REM density as risk factor and higher delta power as a protective factor for incident MDD. Hence, the successful management of sleep disturbances, particularly through cognitive behavioral therapy for insomnia seems essential and may also reduce the risk of developing MDD associated with these features.

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CRediT authorship contribution statement

Geoffroy Solelhac: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Théo Imler:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Marie-Pierre F. Strippoli:** Writing – review & editing, Methodology, Data curation. **Nicola Andrea Marchi:** Writing – review & editing. **Mathieu Berger:** Writing – review & editing. **Jose Haba-Rubio:** Writing – review & editing. **Tifenn Raffray:** Writing – review & editing. **Virginie Bayon:** Writing – review & editing. **Anne Sophie Lombardi:** Writing – review & editing. **Setareh Ranjbar:** Methodology. **Francesca Siclari:** Writing – review & editing, Methodology. **Peter Vollenweider:** Writing – review & editing, Data curation. **Pedro Marques-Vidal:** Writing – review & editing, Data curation. **Pierre-Alexis Geoffroy:** Writing – review & editing. **Damien Léger:** Writing – review & editing. **Aurélie Stephan:** Writing – review & editing, Methodology. **Martin Preisig:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Raphaël Heinzer:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare there is no conflict of interests.

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