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Objective polysomnography-based sleep features and major depressive disorder subtypes in the general population

Geoffroy Solelhac [a,*], Mathieu Berger [a], Marie-Pierre F. Strippoli [b], Nicola Andrea Marchi [a], Aurélie Stephan [a], Jean-Marie Petit [c], Virginie Bayon [a], Théo Imler [a], Jose Haba-Rubio [a,d], Tifenn Raffray [a,d], Peter Vollenweider [e], Pedro Marques-Vidal [e], Gerard Waeber [e], Damien Léger [f], Francesca Siclari [a,g,h,1], Pierre A. Geoffroy [i,j,k], Martin Preisig [b,1], Raphaël Heinzer [a,1]

[a] Center for Investigation and Research in Sleep (CIRS), Lausanne University Hospital (CHUV), University of Lausanne, Lausanne, Switzerland
[b] Center for research in Psychiatric Epidemiology and Psychopathology (CEPP), Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Prilly, Switzerland
[c] Center for Psychiatric Neuroscience (CNP), Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[d] Florimont Sleep Center, Lausanne, Switzerland
[e] Department of Medicine, Internal Medicine, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland
[f] Université Paris Cité, VIFASOM, AP-HP, Hôtel-Dieu, Centre du Sommeil et de la Vigilance, Paris, France
[g] The Sense Innovation and Research Center, Lausanne and Sion, Switzerland
[h] Department of Clinical Neurosciences Lausanne University Hospital (CHUV), Lausanne, Switzerland
[i] GHU Paris - Psychiatry & Neurosciences, Paris, France
[j] Université de Paris, NeuroDiderot, Inserm, Paris, France
[k] Département de Psychiatrie et d'Addictologie, AP-HP, GHU Paris Nord, DMU Neurosciences, Hopital Bichat - Claude Bernard, Paris, France
[l] Netherlands Institute for Neuroscience, Amsterdam, Netherlands

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ABSTRACT

Insomnia and its opposite hypersomnia are part of the diagnostic criteria for major depressive disorder (MDD). However, no study has investigated whether the postulated sleep alterations in clinical subtypes of MDD are reflected in polysomnography (PSG)-derived objective sleep measures. The objective of this study was to establish associations between the melancholic, atypical and unspecified subtypes of MDD and objective PSG-based sleep features. This cross-sectional analysis included 1820 community-dwelling individuals who underwent PSG and a semi-structured psychiatric interview to elicit diagnostic criteria for MDD and its subtypes. Adjusted robust linear regression was used to assess associations between MDD subtypes and PSG-derived objective sleep measures. Current melancholic MDD was significantly associated with decreased absolute delta power and sleep efficiency and with increased wake after sleep onset. Remitted unspecified MDD was significantly associated with increased rapid eye movements density. No other significant associations were identified. Our findings reflect that some PSG-based sleep features differed in MDD subtypes compared with no MDD. The largest number of significant differences were observed for current melancholic MDD, whereas only rapid eye movements density could represent a risk factor for MDD as it was the only sleep measure that was also associated with MDD in remitted participants.

* Corresponding author at: Center d'Investigation et de Recherche sur le Sommeil (CIRS), center Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland.
E-mail addresses: Geoffroy.Solelhac@chuv.ch (G. Solelhac), Mathieu.Berger@chuv.ch (M. Berger), Marie-Pierre.Strippoli@chuv.ch (M.-P.F. Strippoli), nicola.marchi@unil.ch (N.A. Marchi), Jean-Marie.Petit@chuv.ch (J.-M. Petit), Virginie.Bayon@chuv.ch (V. Bayon), Jose.Haba-Rubio@chuv.ch (J. Haba-Rubio), Tifenn.Raffray@chuv.ch (T. Raffray), Peter.Vollenweider@chuv.ch (P. Vollenweider), Pedro-Manuel.Marques-Vidal@chuv.ch (P. Marques-Vidal), Gerard.Waeber@chuv.ch (G. Waeber), damien.leger@aphp.fr (D. Léger), Francesca.Siclari@chuv.ch (F. Siclari), Martin.Preisig@chuv.ch (M. Preisig), Raphael.Heinzer@chuv.ch (R. Heinzer).
[1] Co last authors: These authors contributed equally to the work

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1. Introduction

Sleep disturbances including insomnia and hypersomnia are part of the diagnostic criteria for major depressive disorder (MDD), and more than 90% of patients experiencing depression report sleep complaints (Ford and Cooper-Patrick, 2001; Geoffroy, 2018; Geoffroy et al., 2018; Geoffroy and Palagini, 2021; Tsuno et al., 2005). According to longitudinal studies, which suggest a bidirectional relationship between sleep complaints and MDD, sleep problems may not only be a marker of depressive episodes but could also represent a predisposing factor for depressive episodes (Baglioni et al., 2011; Blanken et al., 2020; Buysse et al., 2008; Chang et al., 1997; Franzen and Buysse, 2008; Jaussent et al., 2011; Paunio et al., 2015; Riemann and Voderholzer, 2003; Saitoh et al., 2022; Suh et al., 2013). Moreover, sleep complaints frequently persist after a depressive episode and increase the risk of recurrence (Lee et al., 2013).

During depressive episodes, objective changes in sleep patterns assessed by polysomnography (PSG) have primarily been observed in three domains: 1) slow wave sleep (SWS), illustrated by a reduction in the proportion of N3 sleep and delta wave activity (Borbély et al., 1984; Léger et al., 2018; Murphy and Peterson, 2015); 2) rapid eye movement sleep (REM) pressure, shown by a shorter REM sleep latency, and increases in the proportion of REM sleep and REM density (Baglioni et al., 2016; Benca et al., 1992; Kupfer and Foster, 1972; Palagini et al., 2013); and 3) sleep continuity, seen as increases in sleep onset latency and wake after sleep onset and decreases in total sleep time (TST) and sleep efficiency (Baglioni et al., 2016). A meta-analysis including data from nineteen studies per sleep feature confirmed the alterations in percentage of N3 sleep, REM latency, REM density, percentage of REM sleep, TST, and sleep efficiency in patients with MDD during depressive episodes (Pillai et al., 2011). The same meta-analysis also showed that there was an increase in REM latency, a decreased percentage of REM sleep, an increase in TST and sleep efficiency, and, surprisingly, a further decrease in percentage of N3 sleep after MDD remission (Pillai et al., 2011). A decreased proportion of N3 sleep and increased REM density were also reported in individuals at high risk for depression (Pillai et al., 2011).

Given the well-known heterogeneity of MDD, which may partially explain inconsistent results, attempts were made to subtype MDD, e.g. using the classic melancholic and atypical subtypes according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association 1994) or the DSM-5 (American Psychiatric Association, 2013; Bell, 1994). These subtypes have been shown to differ in course and responses to treatment and are postulated to differ with respect to sleep characteristics. Indeed, early-morning awakening is one of the diagnostic criteria for melancholic, whereas hypersomnia is part of the criteria for atypical depressive episodes. Moreover, both clinical and epidemiological studies have revealed that they are associated with different biological mechanisms. (Antonijevic, 2006; Musliner et al., 2016) including metabolic features, inflammation and stress hormones, which are also associated with sleep.

In a recent systematic review on electroencephaography (EEG) characteristics in melancholic patients, 10 studies were identified that included sleep EEG data (Bruun et al., 2021). In this review, four studies found increased REM latency in melancholic patients compared to non-melancholic people or healthy controls (Giles et al., 1990; Hubain et al., 1995; Rush et al., 1982; Sitaram et al., 1984) and two studies found higher REM density in melancholic MDD compared with healthy controls (Dippel et al., 1987; Sitaram et al., 1984). Two studies found a larger REM proportion in melancholic patients than in healthy controls (Iorio et al., 1994; Sitaram et al., 1984). However, not all studies found significant differences in REM sleep measures. Melancholic patients also exhibited decreased TST, decreased sleep efficiency, and earlier morning awakenings compared to control groups (Feinberg et al., 1982; Frank et al., 1992; Iorio et al., 1994; Rush et al., 1982). A recently published meta-analysis showed that patients with MDD and hypersomnia (close to the atypical MDD subtype) had an increased TST on ad libitum PSG without altered sleep efficiency compared to healthy controls (Plante et al., 2017).

To the best of our knowledge, no study has yet investigated whether PSG-derived objective sleep measures, including SWS, REM pressure and sleep continuity, could be documented in association with sleep alterations in patients with different MDD subtypes. We hypothesized that 1) the increase in REM sleep pressure (increase in REM density and percentage of REM sleep, decrease in REM latency), 2) the decrease in sleep stage N3 and delta power, 3) the alterations of sleep continuity measures are greater in participants with melancholic MDD subtype than in participants without MDD, and 4) certain characteristics, in particular decrease in delta power and increase in REM density, persist after the remission of melancholic episodes. Therefore, the aim of the present study was to investigate associations between MDD and melancholic, atypical and unspecified MDD subtypes with objective PSG-based sleep features relating to SWS, REM pressure and sleep continuity. To further determine whether PSG findings were dependent on the MDD state, associations were assessed for both current and remitted depressive episodes at the time of the PSG investigation.

2. Methods

2.1. Design and participants

This 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 was 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 study. This analysis included patients who had a PSG investigation with subsequent psychiatric evaluation to determine the MDD status at the time of the PSG. Individuals with any lifetime diagnoses of bipolar or schizoaffective disorders and/or schizophrenia were excluded. The CoLaus|PsyColaus and HypnoLaus studies were approved by the Ethics Committee of the Vaud Canton, and written informed consent was obtained from all individuals.

2.2. Polysomnography (PSG)-based sleep features

Participants performed a full night PSG at home (Titanium, Embla® Flaga, Reykjavik, Iceland). PSG were 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) for sleep.

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 (right and left eyes) channels 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, 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). 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. Absolute power spectral density in delta frequency band (1–4 Hz) was calculated on the F3 electrode using the Welch's method on artifact free consecutive, non-overlapping 6-second epochs (Hamming windows, 8 segments, 50% overlap). Absolute delta power spectral density was analyzed for non-REM (NREM) sleep stages N1, N2 and N3 together. The following objective PSG-based sleep features were analyzed, as defined in Table 1 SWS; REM pressure; and sleep continuity.

2.3. Psychiatric evaluation

Diagnostic information on mental disorders was collected 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 and subtyping of major depressive episodes relied on DSM-IV criteria. The specifier for depressive episodes with atypical features required at least two of the following symptoms: (1) increased appetite or significant weight gain; (2) hypersomnia; (3) leaden paralysis; and (4) interpersonal rejection sensitivity. The specifier for melancholic features required either a loss of pleasure in activities or a lack of reactivity to pleasurable stimuli and at least three out of the following five symptoms: (1) depression regularly worse in the morning; (2) early morning awakening; (3) psychomotor retardation or agitation; (4) anorexia or weight loss; and (5) excessive guilt. For the diagnosis of melancholic episodes, we could not take into account the criterion 'distinct quality of depressed mood' because it was not assessed in the DIGS.

MDD was subdivided according to the lifetime history of episodes with atypical or melancholic features into three subtypes: 1) MDD with atypical features only; 2) MDD with melancholic features only; or 3) unspecified MDD with neither atypical nor melancholic features or with combined atypical and melancholic features. The terminology "any MDD" was used when referring to analyses ignoring the subtypes of MDD. The DIGS also elicits information on the timing of depressive episodes, which allowed us to determine whether episodes were current or remitted at the time of PSG. Information about severity (depression Global Assessment of Functioning (GAF), percentage of recurrence and time in remission at PSG were collected during the DIGS interview.

Table 1
Objective polysomnography (PSG)-based sleep features.

Objective PSG-based sleep features	Definition
(1) Slow wave sleep	
Sleep stage 3 (N3)	Proportion of total sleep time spent in the N3 sleep stage
Delta power	Absolute delta spectral power (μV^2/Hz) in non-REM sleep
(2) Rapid eye movement pressure	
Rapid eye movement sleep	Proportion of total sleep time spent in the REM sleep stage
Rapid eye movements density	Number of rapid eye movements per minute of REM sleep
Rapid eye movement latency	Latency (min) to REM sleep after sleep onset
(3) Sleep continuity	
Sleep onset latency	Duration (min) between light off and first sleep onset
Wake after sleep onset	Duration (min) spent in wake after the first epoch of sleep
Total sleep time	Duration (min) spent in sleep during the recording
Sleep efficiency	Sleep efficiency (%) (TST*100/total recording time)

REM: rapid eye movement; TST, total sleep time.

2.4. 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) and weight was measured using a calibrated scale to within 0.1 kg (Seca); these values were used to calculate the body mass index (BMI in kg/m^2). Respiratory events were scored according to the 2012 AASM criteria (Berry et al., 2012) and periodic leg movements during sleep (PLMS) were scored according to the official World Association of Sleep Medicine (WASM) standards 2006 (Zucconi et al., 2006). The average number of apneas/hypopneas and PLMS per hour of sleep (apnea-hypopnea index [AHI] and PLMS index [PLMSI]) were calculated. Information on specific anxiety (generalized anxiety disorder, agoraphobia, social phobia, panic disorder) and substance use disorders (alcohol or drug abuse or dependence) was collected during the DIGS interview at the psychiatric investigation. Information on psychotropic treatment including anxiolytics, hypnotics and antidepressants was collected during the DIGS interview at the psychiatric investigation and during the interview the evening before the PSG.

2.5. Statistical analysis

Univariate comparisons were performed using Pearson's chi-square test for categorical variables and one-way ANOVA for continuous variables as appropriate.

Associations between MDD and its subtypes (independent variables) and PSG-derived sleep characteristics (dependent variables) were assessed using robust linear regression models for each PSG-based sleep feature. These robust linear regressions were preferred to multiple linear regression models because of the lack of normality of the residuals observed for multiple linear regression models and to reduce the influence of outliers. Models were adjusted for variables associated with MDD subtypes at a significance level of $p<0.20$ on univariate analysis. The models were adjusted for age, sex, BMI, current smoking status, use of antidepressants and anxiolytics (including hypnotics), AHI, PLMSI, anxiety disorders and substance use disorders.

An additional analysis was performed regarding the association between AHI and MDD subtypes adjusted for age, sex and BMI using robust linear regression model.

R (Version 4.0) software was used for all analyses. The 'lmRob' function from R package 'robust' (Version 0.7–0) was used for the robust linear regression model.

3. Results

3.1. Study population

PSG investigation was performed in 2162 patients, 1908 of whom had a subsequent psychiatric evaluation. After exclusion of patients meeting the exclusion criteria, the final sample included 1820 participants (Fig. 1). There were significant differences between different MDD subtypes with respect to age, sex, BMI, current tobacco consumption, use of antidepressants, use of anxiolytics and current anxiety disorders (Table 2). PSG-based sleep measures by MDD subtype status are shown in Table 3. For participants with remitted MDD, the time between remission and PSG was 5.30[1.17–14.05] years (median[IQR]). The course characteristics of MDD subtypes including severity assessed by GAF score, percentage of recurrence for current MDD and time in remission at PSG are described in Table 2. We did not find a significant association between the subtypes of MDD and AHI when adjusted for age, sex and BMI (Table 6).

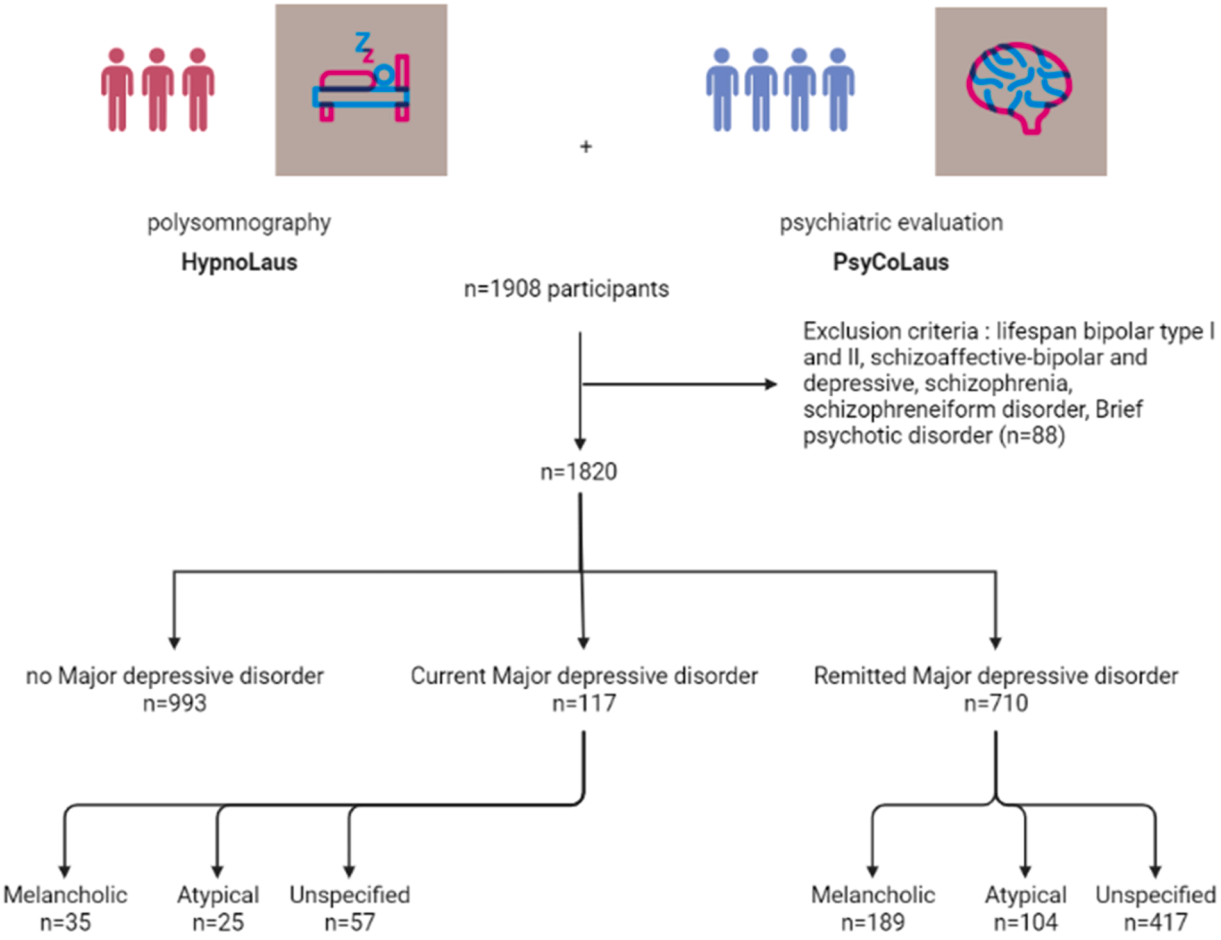

Fig. 1. Study flowchart.

3.2. Slow wave sleep

Current MDD participants showed a decreased in delta power compared to no MDD.

Regarding the subtypes of MDD, the decreased delta power was only significant for current melancholic MDD compared to no MDD participants (Fig. 2, Table 4). No differences were found between MDD subtypes compared to no MDD participants for sleep stage 3 percentage.

3.3. Rapid eye movement pressure

Remitted MDD participants showed an increase in rapid eye movement density compared to no MDD participants. According to MDD subtypes, the rapid eye movement density was significantly increased in unspecified remitted MDD compared to no MDD participants (Fig. 2, Table 4). No differences were found for rapid eye movement sleep percentage and rapid eye movement latency.

3.4. Sleep continuity

No difference was found regarding sleep continuity for current or remitted MDD compared to no MDD participants without taking regardless of MDD subtypes into account. According to MDD subtypes, a significant increase wake after sleep onset and decrease sleep efficiency were found for participants with current melancholic MDD compared to no MDD (Fig. 2, Table 5). No differences were found for total sleep time and sleep onset latency features.

4. Discussion

To the best of our knowledge, this is the first study assessing objective PSG-based sleep features in a large population-based study utilizing semi-structured diagnostic interviews to determine MDD subtypes, allowing determination of associations between sleep features and MDD subtypes as a function of the remission status of depressive episodes. Key findings were as follows: 1) the melancholic MDD subtype was associated with objective sleep alterations, including decreased absolute delta power and sleep efficiency and increased wake after sleep onset; 2) the atypical subtype was not associated with any changes in polysomnographic features; 3) the unspecified subtype was only associated with an increase in REM density; and 4) associations were not entirely explained by MDD state, given that the associations between the unspecified subtype and REM density were observed in individuals with remitted episodes.

4.1. Slow wave sleep

Regarding sleep macrostructure, the lack of change in N3 sleep proportion in individuals with versus without MDD contrasts with meta-analytical findings that reported a lower proportion of N3 sleep stage in patients with MDD compared with controls (Pillai et al., 2011). For sleep microstructure, the reduced absolute delta power associated with the current MDD melancholic subtype is partially in line with previous clinical data in patients with any MDD (Armitage et al., 2000; Plante et al., 2012). According to clinical studies, we observe an association between absolute delta power and any MDD (Pillai et al., 2011). The heterogeneity of this association in clinical samples could be due to the

Table 2
Characteristics of participants according to major depressive disorder subtype ($N = 1820$).

	Major depressive disorder subtype status								
	No MDD $N = 993$	Remitted Unspecified $N = 417$	Remitted Melancholic $N = 189$	Remitted Atypical $N = 104$	Current Unspecified $N = 57$	Current Melancholic $N = 35$	Current Atypical $N = 25$	*Stat*	*p*
Socio-demographic characteristics									
Age, mean (SD), y	59.7 (11.3)	57.2 (10.3)	58.5 (10.5)	55.7 (10.6)	51.8 (8.9)	54.0 (8.3)	53.5 (8.8)	F_6=9.8	**<0.001**
Women, n (%)	416 (41.9)	261 (62.6)	118 (62.4)	78 (75.0)	38 (66.7)	21 (60.0)	19 (76.0)	X^2=101.2	**<0.001**
Education level, n (%)								X^2=11.2	0.512
Low	516 (52.0)	195 (46.8)	85 (45.0)	52 (50.0)	25 (43.9)	20 (57.1)	14 (56.0)		
Middle	262 (26.4)	123 (29.5)	66 (34.9)	29 (27.9)	17 (29.8)	8 (22.9)	8 (32.0)		
High	214 (21.6)	99 (23.7)	38 (20.1)	23 (22.1)	15 (26.3)	7 (20.0)	3 (12.0)		
Behavioral characteristics n (%)									
Current smokers	149 (15.0)	88 (21.1)	40 (21.2)	14 (13.5)	12 (21.1)	12 (34.3)	7 (28.0)	X^2=20.0	**0.003**
Metabolic characteristics									
BMI, mean (SD), kg/m^2	26.2 (4.2)	25.8 (4.3)	25.6 (4.1)	27.0 (4.7)	25.9 (5.6)	25.2 (4.3)	28.3 (7.1)	F_6=2.9	**0.008**
Sleep events, mean (SD)									
AHI (events/h)	16.5 (16.6)	12.7 (13.0)	13.6 (14.9)	14.9 (15.2)	10.8 (13.2)	14.7 (15.8)	13.6 (19.4)	F_6=4.1	**<0.001**
AHI ≥15/h, n (%)	405 (40.8)	116 (27.8)	59 (31.2)	34 (32.7)	11 (19.3)	12 (34.3)	10 (40.0)	X^2=31.5	**<0.001**
PLMSI (events/h)	14.6 (25.2)	11.1 (18.6)	13.8 (21.7)	11.8 (22.9)	7.4 (15.5)	9.3 (13.5)	10.5 (18.5)	F_6=2.1	0.052
PLMSI ≥15/h, n (%)	295 (29.7)	103 (24.7)	57 (30.2)	28 (26.9)	9 (15.8)	9 (25.7)	5 (20.0)	X^2=9.3	0.158
Concomitant treatments, n (%)									
Antidepressants	34 (3.4)	35 (8.4)	30 (15.9)	18 (17.3)	20 (35.1)	11 (31.4)	11 (44.0)	X^2=167.9	**<0.001**
Anxiolytics	65 (6.5)	25 (6.0)	24 (12.7)	11 (10.6)	20 (35.1)	10 (28.6)	5 (20.0)	X^2=84.5	**<0.001**
Psychiatric comorbidities, n (%)									
Current anxiety disorders†	21 (2.1)	29 (7.0)	13 (6.9)	6 (5.8)	5 (8.8)	4 (11.4)	4 (16.0)	X^2=35.5	**<0.001**
Current substance use disorders*	32 (3.2)	19 (4.6)	8 (4.2)	1 (1.0)	2 (3.5)	0 (0.0)	3 (12.0)	X^2=10.2	0.117
Course characteristics									
GAF score, mean (SD)	79.7 (10.3)	46.8 (10.1)	44.3 (11.0)	46.2 (10.1)	51.3 (7.0)	49.7 (8.7)	49.3 (6.6)	F6=799.5	**<0.001**
Recurrent MDE, n (%)	–	145 (34.8)	85 (45.0)	48 (46.2)	28 (49.1)	18 (51.4)	14 (56.0)	X^2=521.6	**<0.001**
Time in remission at PSG, median (IQR), y	–	7.5 (3.2–17.1)	7.4 (2.5–18.4)	5.0 (2.6–10.5)	–	–	–	kw X^2=521.62	**<0.001**

Descriptive statistics are presented as mean (standard deviation) for continuous variables and n (percentage) for categorical variables. Pearson's chi-square test for categorical variables and one-way ANOVA for continuous variables were used as appropriate. (X^2, $F_{\text{degrees of freedom}}$). Kruskal Wallis non-parametric test for Time in remission (kw X^2).

† Generalized anxiety disorder, agoraphobia, social phobia, panic disorder;.

* Alcohol and drug abuse or dependence

BMI: body mass index, MDD: major depressive disorder, SD: standard deviation, y: years, AHI: apnea-hypopnea index, PLMSI: periodic leg movement during sleep index; GAF depression Global Assessment of Functioning; MDE: major depressive disorder; IQR: interquartile range.; PSG: Polysomnography.

proportions of individuals with the melancholic MDD subtype. The restriction of the association between absolute delta-power and the melancholic MDD subtype or any MDD to individuals with a current episode suggests that this is dependent on the MDD state.

4.2. REM sleep pressure

Any remitted MDD and remitted unspecified MDD were significantly associated with increased rapid eye movements density, which is considered as the most robust biomarker of elevated REM pressure in MDD (Wichniak et al., 2000). This finding is consistent with the result of clinical studies conducted in the 1970s supporting an increase in REM pressure in patients with depression (Kupfer and Foster, 1972). Although usual sleep characteristics such as REM latency, sleep efficiency, and proportion of N3 decrease with age and vary according to MDD severity, REM density has been shown to be stable across age and MDD severity (Lauer et al., 1991; Wichniak et al., 2000). Surprisingly, in our study, positive associations with REM density were observed only in individuals with any remitted or any unspecified MDD rather than current depressive episodes. Although the cross-sectional nature of our data did not allow us to determine the temporal relationship between the onset of depressive episodes and the beginning of alterations in REM density, we hypothesize that elevated REM density is a premorbid trait in individuals with unspecified MDD (Pillai et al., 2011).

4.3. Sleep continuity

We observed a significant increase in wake after sleep onset and a decrease in sleep efficiency in individuals with melancholic MDD, such an association was found only for current patients at the time of the PSG.

Table 3
Objective polysomnography (PSG)-based sleep features according to major depressive disorder subtype.

	Major depressive disorder subtype status						
	No MDD $N = 993$	Remitted Unspecified $N = 417$	Remitted Melancholic $N = 189$	Remitted Atypical $N = 104$	Current Unspecified $N = 57$	Current Melancholic $N = 35$	Current Atypical $N = 25$
Slow wave sleep							
N3 (%)	19.3 (8.3)	21.1 (7.9)	20.1 (8.3)	21.1 (8.5)	19.9 (9.1)	19.0 (7.5)	21.6 (11.0)
Delta power (μV^2/Hz)	117.5 (82.0)	124.5 (63.7)	133.8 (158.1)	134.8 (75.4)	147.1 (111.6)	105.6 (67.4)	123.8 (63.7)
Sleep continuity							
SOL (min)	16.5 (21.4)	17.4 (24.2)	21.4 (23.0)	15.7 (24.1)	20.7 (28.3)	15.9 (21.4)	18.1 (13.6)
WASO (min)	76.9 (57.5)	67.0 (50.1)	70.3 (53.3)	56.8 (50.0)	61.9 (55.5)	79.7 (59.7)	51.0 (47.7)
TST (min)	395.1 (67.4)	407.9 (71.0)	407.4 (71.0)	421.9 (80.8)	395.6 (78.9)	409.2 (76.1)	401.1 (67.1)
SE (%)	84.1 (10.9)	86.1 (9.6)	85.6 (10.3)	88.4 (9.6)	86.5 (13.2)	84.5 (9.8)	88.7 (10.2)
REM pressure							
REML (min)	89.5 (52.1)	92.6 (58.8)	96.0 (63.3)	97.1 (63.8)	118.7 (88.1)	127.1 (81.0)	103.5 (57.3)
REMD (/min)	3.0 (2.3)	3.6 (2.9)	3.4 (3.1)	3.1 (2.2)	3.2 (2.7)	4.0 (2.8)	3.1 (2.2)
REM (%)	21.7 (6.1)	22.4 (5.8)	22.9 (5.9)	22.0 (6.7)	20.9 (7.6)	21.2 (5.7)	21.2 (6.3)

Values are mean (standard deviation).
MDD: major depressive disorder, N3 (%): proportion of total sleep time spent in the N3 sleep stage, REM: rapid eye movement sleep, REMD: rapid eye movements density, REML: rapid eye movements latency, SE: sleep efficiency, SOL: sleep onset latency, TST: total sleep time, WASO: wake after sleep onset.

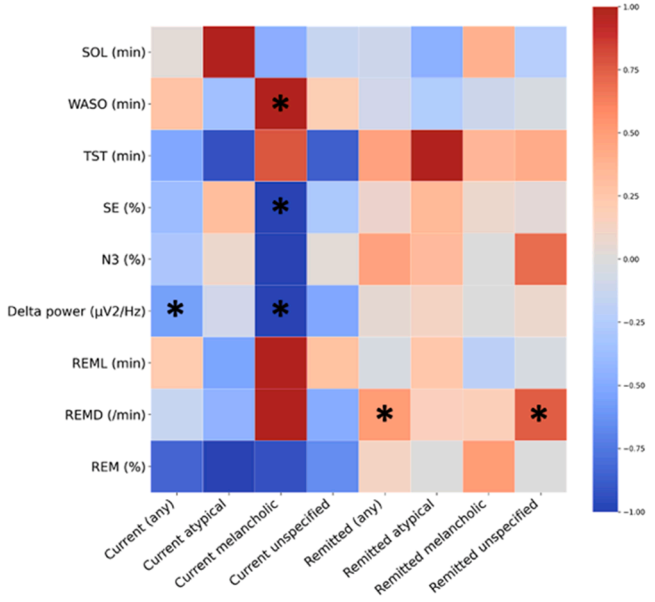

Fig. 2. Associations between major depressive disorder subtypes and polysomnography (PSG)-based sleep features according to multiple-adjusted robust linear regression models.
Adjustment for age, sex, body mass index, current smoking status, use of psychotropic drugs (antidepressants and anxiolytics), anxiety and substance use disorders.
The color scale (between –1 and 1) is a visual representation of the unstandardized beta coefficients for each PSG-based sleep features with respect to the mathematical signs. More intense red color indicates more positive unstandardized beta coefficient value for the corresponding PSG-based sleep feature; more intense blue color indicates more negative unstandardized beta coefficient value for the PSG-based sleep feature. *$p < 0.05$. N3 (%): proportion of total sleep time spent in the N3 sleep stage, SOL: sleep onset latency, WASO: wake after sleep onset, TST: total sleep time, SE: sleep efficiency; REML: rapid eye movements latency; REMD: rapid eye movements density; REM: rapid eye movement sleep.

These results are in line with previous studies investigating sleep and MDD (Pillai et al., 2011). Interestingly, these objective insomnia characteristics typical of the complaint of patients with melancholic MDD are no longer present in the remitted patients. No other associations between MDD subtypes and sleep continuity features were found, although we expected an increase in TST in individuals with atypical MDD and a decrease in those with other MDD subtypes. However, PSG may not be the optimal tool for assessing TST because it was performed over a limited time period (i.e., during the night) rather than over 24 h, thus potentially underestimating TST (e.g. in case of a daytime nap). Other potential explanations for the absence of associations between TST and MDD in our study were the milder severity of MDD in our population-based sample compared with clinical studies, and previously described discordance between subjective complaints of insomnia and objective EEG abnormalities (Andrillon et al., 2020; Castro et al., 2013; Zhang and Zhao, 2007).

4.4. Limitations

Our results need to be viewed in the light of several limitations. First, the cross-sectional nature of the data did not allow us to draw conclusions regarding the direction of the observed associations between MDD subtypes and sleep features. Second, we did not control for multiple comparison explaining that our analyses have an exploratory character and should first be confirmed in other samples. Thirdly, because the psychiatric assessment took place after the PSG investigation, inaccurate recall bias may have influenced the establishment of remission status at the time of the sleep investigation. However, this would have been most likely to underestimate the number of cases of MDD and reduce levels of statistical significance. Forth, despite the large size of the total sample, the number of individuals with current melancholic ($n = 35$) and current atypical ($n = 25$) MDD was small, raising the possibility that associations may not have been detected because of limited statistical power. Fifth, some participants were treated with psychotropic drugs that may influence sleep, but the models were adjusted for these medications. Sixth, we did not collect information on psychotherapy for sleep disorders. However, it seems unlikely to us that a significant proportion of the cohort was undergoing such treatment at the time of the PSG examination. Similarly, we do not have data on physical activity on the day of the PSG examination, which could have influenced the results.

4.5. Conclusion

Our findings revealed that even in individuals with a current depressive episode, there was only a small number of associations between MDD and PSG-based sleep features. In addition, these associations varied by MDD subtype and were most common in those with the melancholic subtype, providing some additional support to the pertinence of subtyping MDD. Interestingly, REM density was not dependent on MDD state (current vs. remitted) and could be a risk factor for the onset of MDD or a residual symptom of depressive episodes. In the future, prospective studies that analyze the predictive value of polysomnography on incident MDD subtypes are needed.

Table 4
Associations between major depressive disorder subtypes and slow wave sleep and rapid-eye movement pressure (multiple-adjusted robust linear regression models).

	Slow wave sleep				REM pressure					
	N3 (%)		Delta power (μV^2/Hz)		REML (min)		REMD (/min)		REM (%)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Current MDD (any)	−0.27	(−1.95,1.41)	**−16.74****	**(−27.89,−5.58)**	3.14	(−5.05,11.32)	−0.06	(−0.46,0.35)	−0.87	(−2.12,0.38)
Current atypical MDD	0.08	(−3.25,3.40)	−2.61	(−23.66,18.44)	−7.18	(−22.99,8.64)	−0.20	(−1.01,0.60)	−1.04	(−3.48,1.40)
Current melancholic MDD	−0.93	(−3.71,1.86)	**−30.05****	**(−48.86,−11.23)**	13.68	(−0.33,27.68)	0.45	(−0.29,1.18)	−0.96	(−3.06,1.13)
Current unspecified MDD	0.02	(−2.25,2.30)	−15.36	(−30.91,0.18)	3.97	(−7.17,15.11)	−0.22	(−0.78,0.34)	−0.69	(−2.41,1.03)
Remitted MDD (any)	0.43	(−0.37,1.24)	1.80	(−3.41,7.01)	−0.51	(−4.32,3.30)	**0.23***	**(0.03,0.42)**	0.13	(−0.47,0.74)
Remitted atypical MDD	0.31	(−1.35,1.97)	3.65	(−7.12,14.43)	3.32	(−4.40,11.03)	0.07	(−0.34,0.48)	0.01	(−1.23,1.25)
Remitted melancholic MDD	0.00	(−1.27,1.28)	0.10	(−8.17,8.38)	−2.65	(−8.73,3.44)	0.08	(−0.24,0.40)	0.52	(−0.43,1.48)
Remitted unspecified MDD	0.65	(−0.29,1.59)	2.36	(−3.69,8.42)	−0.36	(−4.80,4.08)	**0.34****	**(0.11,0.57)**	0.00	(−0.71,0.70)
No MDD (ref)	0 (ref)		0 (ref)		0 (ref)		0 (ref)		0 (ref)	

Adjustment for age, sex, body mass index, current smoking status, apnea-hypopnea index, periodic leg movements during sleep index, use of psychotropic drugs (antidepressants and anxiolytics), anxiety and substance use disorders.
95% CI: 95% confidence interval; MDD: major depressive disorder, N3 (%): proportion of total sleep time spent in the N3 sleep stage, REM: rapid eye movement sleep, REMD: rapid eye movements density, REML: rapid eye movements latency.
* $p < 0.05$;.
** $p < 0.01$.

Table 5
Associations between major depressive disorder subtypes and sleep continuity (multiple-adjusted robust linear regression models).

	SOL (min)		WASO (min)		TST (min)		SE (%)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Current MDD (any)	0.12	(−2.71,2.95)	6.40	(−2.10,14.91)	−6.54	(−20.93,7.85)	−1.40	(−3.18,0.38)
Current atypical MDD	4.44	(−0.13,9.01)	−7.72	(−23.95,8.50)	−12.04	(−39.80,15.71)	1.13	(−3.00,5.26)
Current melancholic MDD	−2.10	(−6.06,1.85)	**22.43****	**(8.51,36.34)**	10.09	(−14.47,34.64)	**−3.60***	**(−7.10,−0.11)**
Current unspecified MDD	−0.56	(−3.88,2.75)	4.43	(−6.96,15.82)	−11.33	(−30.76,8.10)	−1.03	(−3.91,1.84)
Remitted MDD (any)	−0.50	(−1.86,0.86)	−1.94	(−6.08,2.20)	6.21	(−0.78,13.19)	0.34	(−0.53,1.20)
Remitted atypical MDD	−2.03	(−4.38,0.32)	−5.46	(−13.72,2.81)	13.04	(−1.42,27.49)	1.24	(−0.83,3.31)
Remitted melancholic MDD	1.73	(−0.14,3.60)	−2.70	(−9.24,3.83)	4.62	(−6.41,15.65)	0.32	(−1.29,1.94)
Remitted unspecified MDD	−1.02	(−2.38,0.33)	−0.96	(−5.71,3.80)	5.39	(−2.77,13.56)	0.12	(−1.06,1.31)
No MDD (ref)	0 (ref)		0 (ref)		0 (ref)		0 (ref)	

Adjustment for age, sex, body mass index, current smoking status, apnea-hypopnea index, periodic leg movements during sleep index, use of psychotropic drugs (antidepressants and anxiolytics), anxiety and substance use disorders.
95% CI: 95% confidence interval; MDD: major depressive disorder, SE: sleep efficiency, SOL: sleep onset latency, TST: total sleep time, WASO: wake after sleep onset.
* $p < 0.05$;.
** $p < 0.01$.

Table 6
Associations between major depressive disorder subtypes and apnea hypopnea index (multiple-adjusted robust linear regression models).

	AHI (events/h of sleep)	
	β	95% CI
Current MDD (any)	−0.49	(−2.32,1.34)
Current atypical MDD	−1.07	(−5.02,2.88)
Current melancholic MDD	1.77	(−1.69,5.23)
Current unspecified MDD	−0.60	(−3.27,2.07)
Remitted MDD (any)	−0.14	(−1.06,0.78)
Remitted atypical MDD	1.46	(−0.56,3.48)
Remitted melancholic MDD	0.08	(−1.63,1.46)
Remitted unspecified MDD	−0.41	(−1.55,0.72)
No MDD (ref)	0 (ref)	

Adjustment for age, sex, body mass index. 95% CI: 95% confidence interval; MDD: major depressive disorder, AHI: apnea hypopnea index. *$p < 0.05$.

Authors contributions

GS, MB, MPS, MP and RH designed the study. GS performed statistical analysis. GS wrote the first draft of manuscript. All authors interpreted the data, critically reviewed the manuscript and approved the final version. GS is the guarantor of this work and, as such, had (with RH) full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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