Journal of Psychiatric Research 163 (2023) 325–336

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Objectively assessed sleep and physical activity in depression subtypes and its mediating role in their association with cardiovascular risk factors

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ARTICLE INFO

Keywords:
Depressive disorder subtypes
Atypical depression
BMI
Metabolic syndrome
Actigraphy
Epidemiology

ABSTRACT

The aims of this study were to investigate the associations of major depressive disorder (MDD) and its subtypes (atypical, melancholic, combined, unspecified) with actigraphy-derived measures of sleep, physical activity and circadian rhythms; and test the potentially mediating role of sleep, physical activity and circadian rhythms in the well-established associations of the atypical MDD subtype with Body Mass Index (BMI) and the metabolic syndrome (MeS). The sample consisted of 2317 participants recruited from an urban area, who underwent comprehensive somatic and psychiatric evaluations. MDD and its subtypes were assessed via semi-structured diagnostic interviews. Sleep, physical activity and circadian rhythms were measured using actigraphy. MDD and its subtypes were associated with several actigraphy-derived variables, including later sleep midpoint, low physical activity, low inter-daily stability and larger intra-individual variability of sleep duration and relative amplitude. Sleep midpoint and physical activity fulfilled criteria for partial mediation of the association between atypical MDD and BMI, and physical activity also for partial mediation of the association between atypical MDD and MeS. Our findings confirm associations of MDD and its atypical subtype with sleep and physical activity, which are likely to partially mediate the associations of atypical MDD with BMI and MeS, although most of these associations are not explained by sleep and activity variables. This highlights the need to consider atypical MDD, sleep and sedentary behavior as cardiovascular risk factors.

1. Introduction

Major depressive disorder (MDD) and cardiovascular risk factors (CVRFs) are major public health challenges (G. B. D. and Mortality-Collaborators, 2018). The rise in metabolic risks (i.e., high body mass index (BMI), high blood glucose, high blood pressure and high cholesterol) has the greatest cumulative impact on health (G. B. D. and Viewpoint-Collaborators, 2020), while MDD is among the leading causes of disability worldwide (G. B. D. et al., 2015). MDD and CVRFs are also highly comorbid, with previous studies showing associations between MDD and well-established CVRFs, such as overweight/obesity (Milaneschi et al., 2019; Silva et al., 2020), diabetes (Ditmars et al., 2021; Sartorius, 2018) and the metabolic syndrome (MeS) (Penninx and Lange, 2018; Vancampfort et al., 2014). Several mechanisms have been postulated to underlie this comorbidity, including also sedentary behavior and sleep (Otte et al., 2016; Penninx, 2017).

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https://doi.org/10.1016/j.jpsychires.2023.05.042
Received 31 October 2022; Received in revised form 23 March 2023; Accepted 15 May 2023
Available online 22 May 2023
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Physical inactivity, perturbed sleep and circadian rhythm disturbances are considered as modifiable risk factors for both depression and CVRFs. Indeed, there is increasing evidence for a strong association between sedentary behavior and depression in the general population (Schuch et al., 2017), and conversely, a large meta-analysis of prospective studies showed that higher physical activity levels were associated with a lower incidence of depression (Schuch et al., 2018). Moreover, both insomnia and hypersomnia are part of the diagnostic criteria for major depressive episodes. Insomnia could in fact be a driving factor in the onset of and a key target in the treatment of MDD (Riemann et al., 2020). Although hypersomnia may be a consequence of MDD, other factors such as low energy, overeating or physical inactivity may also influence hypersomnia in patients with depression (Lopez et al., 2017). Furthermore, irregular sleep-wake patterns have been documented in adults with depression (Difrancesco et al., 2019; Pye et al., 2021). Physical inactivity was also found to be a risk factor for CVRFs, such as diabetes, obesity and hypertension (Patnode et al., 2017). Previous studies have also shown that short sleep duration, poor sleep quality and sleep complaints were associated with increased risk of CVRFs and cardiovascular diseases (CVDs) (Hoevenaar-Blom et al., 2011; Troxel et al., 2010). Similarly, sleep irregularities, including irregular sleep duration and timing, have been found to increase the risk for CVDs (Huang et al., 2020). The associations between perturbed sleep and CVDs are likely to be attributable to the influence of sleep-wake patterns on disturbances in blood pressure and heart rate variability (Resnick et al., 2003; Silvani, 2019). Moreover, circadian rhythm disturbances have been shown to be associated to CVRFs and CVDs (Zimmet et al., 2019). However, data on the role of physical activity, sleep and circadian rhythm either as mediators, or as common etiological factors of the association between depression and CVRFs/CVDs are still scarce, which hinders the development of improved prevention and treatment strategies (Chaplin et al., 2021; Deschenes et al., 2019; Mezick et al., 2011; Riera-Sampol et al., 2021).

Heterogeneity of depression, in terms of symptoms, manifestations and course (Antonijevic, 2006; Ghaemi and Vohringer, 2011; Halbreich, 2006), is another understudied factor in research focusing on the role of physical activity and sleep in the association between depression and CVRFs and CVDs. Indeed, various presentations of depression may not necessarily share the same pathophysiological mechanisms (Buch and Liston, 2021), and based on their presentation may have differential associations with sleep and physical activity patterns. Associations between depression and CVRFs have been documented particularly for the atypical depression subtype. According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) (Association, 2013), depressive episodes with atypical features are characterized by mood reactivity and at least two of the following symptoms: increase in appetite/weight, hypersomnia, severe fatigue (leaden paralysis) and a long-standing pattern of interpersonal rejection sensitivity. Cross-sectional research supported associations between atypical depression and obesity markers (Cizza et al., 2012; Glaus et al., 2013; Lamers et al., 2013), diabetes (Glaus et al., 2013) or fasting glucose (Lamers et al., 2013), triglycerides (Lamers et al., 2013; Vogelzangs et al., 2014) and the MeS (Glaus et al., 2013; Lamers et al., 2013; Takeuchi et al., 2013), whereas melancholic depression was not associated with these markers (Cizza et al., 2012; Glaus et al., 2013; Lamers et al., 2013; Takeuchi et al., 2013; Vogelzangs et al., 2014). Prospective studies have confirmed associations restricted to atypical depression with obesity markers, glucose concentration and the MeS in the Dutch NESDA study (Lamers et al., 2016) and in our CoLaus|PsyCoLaus study (Lasserre et al., 2014, 2017). Inversely, elevated BMI predisposes also to subsequent onset of atypical depression, but not the other subtypes (Patel et al., 2018; Rudaz et al., 2017). Similarly, cross-sectional and prospective studies have provided evidence for a stronger association of atypical depression with inflammation markers than non-atypical or melancholic depression (Glaus et al., 2014, 2018; Lamers et al., 2013; Lasserre et al., 2017; Woelfer et al., 2019). Therefore, the investigation of mechanisms underlying the association, particularly of the atypical depression subtype with CVRFs, is of high scientific and clinical relevance.

Although self-reported measures have been the most widely used measure of sleep, physical activity and circadian rhythms in many large-scale population studies, there has been increasing use of wearable accelerometers that are non-invasive and unobtrusive, and, when worn continuously for multiple days, have been shown to provide objective estimates of physical activity, sleep, and circadian rhythms with high reliability (Acker et al., 2021).

The major goals of this paper were to: (1) investigate the associations of MDD and its subtypes (atypical, melancholic, unspecified and combined) with actigraphy-derived measures of sleep, physical activity and circadian rhythms; and (2) test the potentially mediating role of sleep, physical activity and circadian rhythms in the previously established associations of the atypical MDD subtype with BMI (Lasserre et al., 2014) and the MeS (Lasserre et al., 2017). In order to test whether the associations of MDD and its subtypes with sleep, physical activity and circadian rhythms reflect traits or states, MDD was subdivided into current versus remitted disorders. We hypothesized that: (1) the atypical MDD subtype is associated with long sleep duration and the melancholic subtype with short sleep duration, whereas all subtypes are associated with decreased sleep efficiency and lower levels of physical activity; (2) sleep variables and levels of physical activity are mediators of the associations between MDD and CVRFs.

2. Methods

2.1. Study sample

The sample of the present study stems from CoLaus|PsyCoLaus (Firmann et al., 2008; Preisig et al., 2009), a prospective cohort study designed to assess the associations between CVD/CVRFs and mental disorders in the community. The cohort of 6734 individuals aged 35–75 years was randomly selected between 2003 and 2006 from the population of the city of Lausanne according to the civil register. Data for the present paper stem from the second follow-up, which was conducted approximately 10 years after the baseline evaluation (May 2014 to April 2018). The second follow-up was the first to include actigraphy measures as a part of the physical evaluation.

Persons with schizophrenia, schizoaffective disorders or bipolar disorders were excluded from the present analyses, which included all 2317 participants with at least 7 valid days of actigraphy data (defined as $\geq$16 h per day of estimated wear time), who had data available on demographics, BMI, smoking and MDD, resulting in a total of 28,390 valid days for analysis (see Fig. 1 for the flow-chart). CoLaus|PsyCoLaus was approved by the Institutional Ethics' Committee of the University of Lausanne. All participants provided written informed consent for the study protocol.

2.2. Measurements

2.2.1. Sleep, physical activity and circadian rhythms

Sleep and physical activity were assessed using a wrist-worn triaxial accelerometer (GENEActiv, Activinsights Ltd., United Kingdom), a device that has been validated against reference methods (Esliger et al., 2011). The devices were pre-programmed with a 50 Hz sampling frequency and placed on participants' right wrists. Participants were requested to wear the accelerometer continuously during the 14 consecutive days following the physical evaluation in free-living conditions. The collected data were downloaded using the GENEActiv software version 2.9 (GENEActiv, Activinsights Ltd., United Kingdom) and collapsed into 60-s epoch files.

Moderate-to-vigorous physical activity (MVPA) was derived from accelerometry using standard count-per-minute threshold to classify the activity time. We used the R-package Actigraphy.R with the threshold of

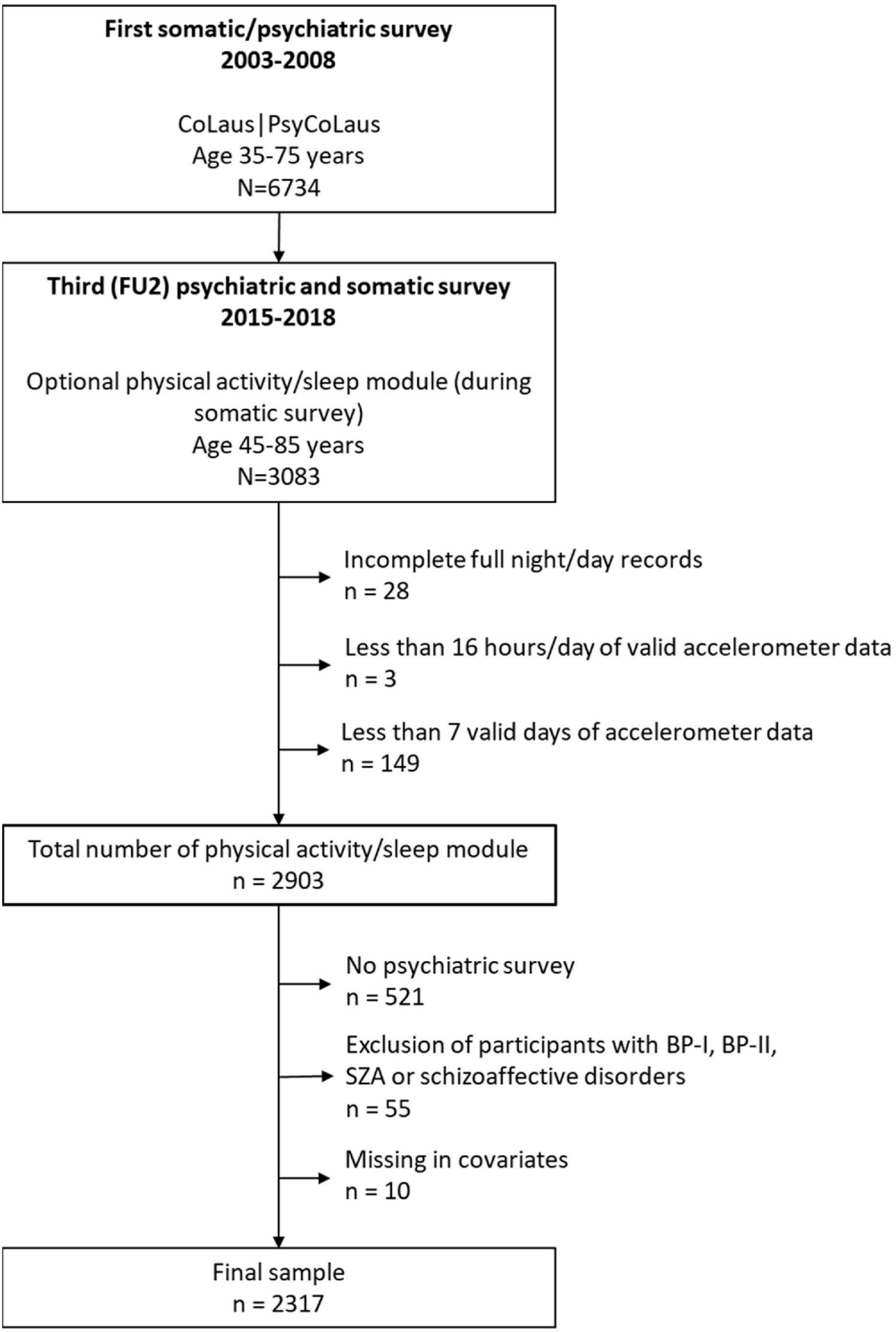

Fig. 1. Flow chart of the study for the association between mood disorders, sleep and physical activity with cardiovascular risk factors. Abbreviations: BP-I, Bipolar Disorder-I; BP-II, Bipolar Disorder-II; SZA, Schizophrenia.

100 (Buman et al., 2014; Di et al., 2019).

Objective sleep and circadian variables were derived from accelerometry with R-package (mMARCH.AC (Guo et al., 2022);) GGIR version 1.5–9 (http://cran.r-project.org) (Migueles et al., 2019; van Hees et al., 2015). These variables included sleep midpoint, duration, efficiency, relative amplitude and inter-daily stability. Both participant's average and variability (standard deviation of the day-level mean) across 14 days were calculated for each participant. Sleep midpoint was defined as the halfway point between the onset of sleep and the wake-up time. Sleep duration was characterized as time with no change in arm angle greater than 5° for 5 min or more during a wake-up to wake-up window using the WW file from the R-package GGIR (van Hees et al., 2015). Sleep efficiency, a proxy for sleep quality, was calculated as the percentage of sleep duration by time spent in bed.

Relative amplitude (RA) was calculated as the difference between the most active 10 h (M10) and the least active 5 h (L5) as follows: (M10-L5)/(M10+L5). Activity was normalized by their sum. Inter-daily stability (IS), a nonparametric metric of circadian rhythmicity that quantifies synchronization to day-night cycle, was calculated at the subject level using the average subject-specific profile.

2.2.2. Cardio-metabolic measures

The physical exam included measures of body weight, height, blood pressure (triplicate measure on the left arm after at least a 10-min rest in the seated position), and waist and hip circumference (Firmann et al., 2008). Additionally, venous blood samples were drawn after an overnight fast to measure levels of glucose, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides. BMI was calculated as the weight in kilograms divided by the height in meters squared. The MeS was diagnosed following the Adult Treatment Panel III criteria (De Hert et al., 2009), requiring three out of the following five criteria: (1) waist circumference (>102 cm for men and >88 cm for women), (2) blood pressure (>130/85 mm Hg), (3) HDL-cholesterol (<1 mmol/l for men and <1.3 mmol/l for women), (4) triglycerides (>1.7 mmol/l) and (5) fasting glucose (>6.1 mmol/l).

2.2.3. Socio-demographic characteristics and smoking

We collected information on age and sex, used as covariates, at the time of the somatic exam. A regular consumption of at least 10 cigarettes a day at the time of the somatic exam was used to define current smoking versus never or former smoking status.

2.2.4. Mental disorders

Information on MDD was collected using the mood disorder section of the French version (Leboyer et al., 1995) of the semi-structured Diagnostic Interview for Genetic Studies (DIGS), which was developed and validated by the National Institute of Mental Health (Nurnberger et al., 1994) in order to assess a wide spectrum of DSM axis I disorders. Both, the English and the French versions of the DIGS revealed adequate inter-rater and test-retest reliability for major mood and psychotic disorders (Preisig et al., 1999). The DIGS was completed using the anxiety disorder sections of the French version (Leboyer et al., 1991) of the Schedule for Affective Disorders and Schizophrenia-lifetime and anxiety disorder version (SADS-LA) (Endicott and Spitzer, 1978). Interviewers were required to be master-level psychologists and were trained over a 2-month period. Ongoing supervision throughout the study was provided by an experienced senior psychologist, who reviewed each interview and diagnostic assignment. MDD lifetime diagnoses were assigned according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Following the suggestion of Angst et al. definition (Angst et al., 2006), we did not use the five criteria of the specifier for atypical features according to the DSM-IV in a hierarchical way (i.e., mandatory requirement of mood-reactivity plus two additional symptoms according to the DSM-IV). Instead, we required any 3 out of the 5 DSM-IV criteria for atypical features. For the diagnosis of melancholic episodes, the DSM-IV specifier for melancholic features was applied. Again, following Angst et al. (2007) MDD was subdivided into four subtypes according to the lifetime occurrence of atypical and melancholic episodes: (1) atypical subtype (at least one atypical but no melancholic episode); (2) melancholic subtype (at least one melancholic but no atypical episode); (3) unspecified subtype (neither atypical nor melancholic episodes, MDD with atypical and melancholic features simultaneously); (4) combined subtype (at least one atypical and one melancholic episode). We defined MDD as current if criteria for this diagnosis were met at the time of the physical exam.

2.3. Statistical analysis

For the first study goal, we established the associations between lifetime, current, remitted MDD, and MDD subtypes with sleep, physical activity and circadian rhythm measures using linear regression models. Sleep measures included subject average and variability for sleep midpoint, duration and sleep efficiency. Physical activity measures included MVPA, and circadian rhythm measures included relative amplitude (RA), and inter-daily stability (IS). Sleep, physical activity and circadian rhythm measures were the dependent variables in the linear regression models. For each of these measures four models were run: one assessing the effect of lifetime MDD, one simultaneously assessing the effects of current and remitted MDD, one simultaneously assessing the effects of lifetime MDD subtypes, and one simultaneously assessing the effects of current and remitted MDD subtypes. Models were adjusted for age (continuous), sex, anxiety disorders (current and remitted), BMI (continuous), and current smoking. Models including MVPA variability as the dependent variable were also adjusted for mean MVPA levels.

For the second study goal, we tested whether sleep, physical activity and circadian rhythm measures were mediators of the previously established associations of the lifetime atypical MDD subtype with BMI and MeS (Lasserre et al., 2014, 2017) according to the four criteria postulated by Baron and Kenny (1986) and the definitions of MacKinnon, Krull and Lockwood (MacKinnon et al., 2000). According to these four criteria, mediation exists if: 1) independent (lifetime atypical MDD) and dependent variables (BMI and MeS) are associated, which has been previously demonstrated (Lasserre et al., 2014, 2017) and needed to be replicated in the present sample of participants that completed the actigraphy exam; 2) independent variable and mediators (sleep, physical activity and circadian rhythm measures) are associated (first study goal); 3) mediators and dependent variables are associated; and 4) after adjustment for the effects of mediators, mediators and dependent variables remain significantly associated but independent and dependent variables are either no longer associated (full mediation), or still associated but reduced in strength (partial mediation). For criterion 3, the associations of sleep, physical activity and circadian rhythm measures with BMI and MeS (dependent variables that were found to be significantly associated with lifetime atypical MDD according to criterion 1) were assessed using multiple linear and logistic regressions, respectively. For criteria 1 and 4 the associations of lifetime atypical MDD with BMI and MeS (dependent variables) without (criterion 1) and with adjustment for sleep, physical activity and circadian rhythm measures (criterion 4) were assessed using multiple linear and logistic regression models, respectively. For criterion 4, we added only potential mediators into the models that revealed a significant association with atypical MDD. All analyses were performed using SAS software (version 9.4) and *RStudio*, version 1.3.1093.

3. Results

3.1. Sample characteristics

The description of the sample of 2317 participants used for the assessment of the associations between MDD, sleep, physical activity, BMI, and the MeS is presented in Table 1. Almost half of the participants

Table 1
Sample characteristics (n = 2317).

		$n = 2317$	
Sex, *% (n)*			
Females		54.42	(1261)
Males		45.58	(1056)
Age, *mean (SD)*		61.79	(9.97)
MDD, *% (n)*			
MDD	Lifetime	49.76	(1153)
	Current	7.98	(185)
	Remitted	41.78	(968)
MDD subtypes, *% (n)*			
Atypical	Lifetime	9.02	(209)
	Current	2.16	(50)
	Remitted	6.86	(159)
Melancholic	Lifetime	13.16	(305)
	Current	2.11	(49)
	Remitted	11.05	(256)
Unspecified	Lifetime	25.77	(597)
	Current	3.71	(86)
	Remitted	22.05	(511)
Combined	Lifetime	1.81	(42)
	Remitted	1.81	(42)
Anxiety disorders, % (n)			
Anxiety disorders	Current	4.79	111
	Remitted	1.29	30
Sleep, ***mean (SD)***			
Midpoint *(hh:mm)*	Average	03:23	(01:01)
	Variability	01:00	(00:41)
Duration *(hh:mm)*	Average	06:44	(01:00)
	Variability	01:11	(00:31)
Efficiency *(%)*	Average	87.01	(5.51)
	Variability	5.42	(2.5)
Moderate-to-vigorous physical activity, ***mean (SD)***			
MVPA *(hours)*	Average	1.63	(1.03)
	Variability	0.64	(0.42)
Circadian rhythm, ***mean (SD)***			
RA	Average	0.82	(0.06)
	Variability	0.06	(0.03)
IS	Average	0.36	(0.09)
CVRFs, ***% (n)***			
BMI, *mean (SD)*		26.35	(4.75)
Metabolic Syndrome		24.44	(564)
Hypertension		43.57	(1009)
Diabetes		9.10	(210)
Dyslipidemia		39.66	(919)
Current smoking		17.31	(401)

Abbreviations: BMI, Body Mass Index; CVRFs, Cardiovascular Risk Factor; hh:mm, hours:minutes; IS, Interdaily Stability; MDD, Major Depressive Disorder; MVPA, Moderate-to-Vigorous Physical Activity; RA, Relative Amplitude; SD, Standard Deviation.

met lifetime criteria for MDD and 8% were in a current depressive episode at the time of the investigation. Among participants with lifetime MDD, approximately a fifth revealed atypical features, a quarter melancholic features, one out of 25 combined atypical and melancholic features, and more than a half were classified as unspecified. Participants had an average sleep midpoint after 3 a.m., slept almost 7 h per night and had a sleep efficiency of 87%. Concerning physical activity, participants showed an average of approximately 1 h and a half of MVPA per day. Additionally, participant showed relatively good balance with an average relative amplitude of 0.82 (sd = 0.06), whereas they had an average IS of 0.36 (sd = 0.09), which is considered as quite unstable (Rock et al., 2014). The mean BMI indicated a population being slightly overweight. Almost a quarter of the participants met criteria for the MeS, approximately 40% for hypertension or dyslipidemia, and almost 10% for diabetes. Around 17% were current smokers.

3.2. Associations of MDD and subtypes with sleep and physical activity

Both current and remitted MDD were associated with a later average sleep midpoint compared to participants with no MDD (Table 2). These associations were essentially attributable to the atypical and the unspecified subtypes. Indeed, lifetime and current but not remitted atypical MDD as well as lifetime and remitted but not current unspecified MDD were associated with a later sleep midpoint. Lifetime and remitted but not current MDD were also associated with lower MVPA levels, although the effect size for current MDD was even slightly larger than for remitted MDD. Similarly, lifetime and remitted but not current atypical and melancholic MDD were associated with lower MVPA levels. In addition, current unspecified MDD was also associated with lower MVPA levels. As to the circadian variables, lifetime and current but not remitted MDD as well as lifetime melancholic MDD were associated with low RA at the subject average. Moreover, lifetime and remitted MDD as well as lifetime and current atypical MDD were associated with low IS at the subject average. We did not find any significant associations of MDD with either subject average sleep duration or sleep efficiency.

Regarding variability within a person, results showed several associations of MDD and MDD subtypes with sleep, MVPA and circadian rhythms. Regardless of remission status, lifetime MDD was associated with higher variability in sleep duration, as well as lower variability in RA compared to participants with no MDD. Similarly, unspecified MDD regardless of remission status was associated with higher sleep duration variability. Current but not remitted atypical MDD was also associated with increase variability in sleep duration. Additionally, lifetime and current but not remitted melancholic MDD were associated with lower MVPA variability, whereas lifetime and remitted combined MDD were associated with lower MVPA variability. Finally, melancholic MDD regardless of remission status was associated with higher variability in RA, whereas only current but not remitted atypical and unspecified MDD were associated with higher RA variability. No significant associations were found between MDD subtypes with variability in sleep midpoint and sleep efficiency.

3.3. Role of sleep, physical activity and circadian rhythm in the associations of atypical MDD with BMI and MeS

Given that only the intra-individual averages of sleep midpoint, MVPA and IS were found to be associated with lifetime atypical MDD, analyses of associations with BMI and MeS were restricted to these three sleep, activity and circadian rhythm measures. Multiple regression models adjusted for age, sex and current smoking revealed highly significant associations of later sleep midpoint ($\beta = 0.38$, 95% C.I. 0.19–0.57; $p < .001$) and lower MVPA ($\beta = -1.05$, 95% C.I. −1.25 – (−) 0.85; $p < .001$) with higher BMI, whereas IS was not associated with BMI (($\beta = -0.49$, 95% C.I. −2.69–1.71; $p = .660$). Analogue logistic regression models also showed a highly significant association of MVPA with MeS (OR = 0.56, 95% C.I. 0.49–0.64; $p < .001$), whereas the associations of later sleep midpoint and IS with MeS did not reach the level of statistical significance (OR = 1.09, 95% C.I. 0.99–1.19; $p < .092$; OR = 1.23, 95% C.I. 0.40–3.76, $p = .716$, respectively).

Table 3 depicts the associations of lifetime MDD subtypes with BMI and MeS before (Model 1) and after adjustment for the three actigraphy-derived measures that revealed associations with lifetime atypical MDD. These were first modeled separately (Models 2–4) and then jointly added to the model (Model 5). Model 1 confirmed the previously published highly significant associations of lifetime atypical MDD with both a higher BMI and an increased likelihood of MeS also in the present sample (Lasserre et al., 2014, 2017). These associations remained significant after adding intra-individual average of sleep midpoint (Models 2), intra-individual average of MVPA (Models 3), IS (Model 4), as well as after simultaneously adding all three variables (Models 5). Adding intra-individual average of sleep midpoint to the model (Models 2), only slightly decreased the sizes of the associations of lifetime atypical MDD

Table 2
Associations between major depressive disorder (MDD) subtypes with sleep and physical activity (n = 2317).

	Sleep Midpoint				Sleep Duration					Sleep Efficiency			MVPA				Relative amplitude				Interdaily stability			
	Mean (SD)	Est[a]	95% CI	*p*	Mean (SD)	Est[a]	95% CI	*p*	%	Est[a]	95% CI	*p*	Mean (SD)	Est[a]	95% CI	*p*	Mean (SD)	Est[a]	95% CI	*p*	Mean (SD)	Est[a]	95% CI	*p*
AVERAGE																								
No MDD	03:19 (01:01)	REF.	–	–	06:41 (01:01)	REF.	–	–	86.58 (5.83)	REF.	–	–	1.62 (1.10)	REF.	–	–	0.82 (0.07)	REF.	–	–	0.36 (0.10)	REF.	–	–
Model 1																								
Lifetime MDD	03:27 (01:00)	**0.11**	**(0.02–0.20)**	***0.013***	06:46 (01:00)	0.04	(-0.05–0.12)	*0.403*	87.46 (5.13)	0.04	(-0.04–0.12)	*0.338*	1.63 (0.96)	**−0.12**	**(-0.20-(−) 0.04)**	***0.002***	0.83 (0.06)	**−0.09**	**(-0.17-(−) 0.01)**	***0.024***	0.35 (0.09)	**−0.09**	**(-0.17-(−) 0.01)**	***0.030***
Model 2																								
Current MDD	03:35 (01:11)	**0.22**	**(0.06–0.38)**	***0.008***	06:52 (01:08)	0.15	(-0.01–0.30)	*0.065*	86.68 (5.27)	−0.11	(-0.27–0.04)	*0.161*	1.62 (1.00)	−0.13	(-0.28–0.02)	*0.083*	0.82 (0.06)	**−0.18**	**(-0.32-(−) 0.03)**	***0.017***	0.35 (0.09)	−0.07	(-0.22–0.08)	*0.382*
Remitted MDD	03:25 (00:58)	**0.09**	**(0.00–0.18)**	***0.046***	06:45 (00:58)	0.02	(-0.07–0.10)	*0.701*	87.60 (5.09)	0.07	(-0.02–0.15)	*0.132*	1.63 (0.96)	**−0.12**	**(-0.20-(−) 0.04)**	***0.004***	0.83 (0.06)	−0.07	(-0.15–0.01)	*0.069*	0.35 (0.09)	**−0.09**	**(-0.18-(−) 0.01)**	***0.029***
Model 3																								
Lifetime MDD subtypes																								
Atypical	03:32 (01:00)	**0.18**	**(0.03–0.33)**	***0.020***	06:45 (01:02)	0.04	(-0.11–0.19)	*0.601*	87.27 (5.67)	−0.01	(-0.15–0.14)	*0.928*	1.58 (0.86)	**−0.16**	**(-0.30-(−) 0.02)**	***0.026***	0.83 (0.05)	−0.06	(-0.19–0.08)	*0.425*	0.34 (0.09)	**−0.17**	**(-0.31-(−) 0.02)**	***0.023***
Melancholic	03:19 (00:57)	0.01	(-0.12–0.13)	*0.939*	06:46 (00:58)	0.02	(-0.11–0.14)	*0.777*	87.61 (5.28)	0.06	(-0.07–0.18)	*0.355*	1.60 (0.89)	**−0.18**	**(-0.29-(−) 0.06)**	***0.003***	0.83 (0.06)	**−0.13**	**(-0.25-(−) 0.02)**	***0.025***	0.35 (0.09)	−0.08	(-0.20–0.04)	*0.184*
Combined	03:35 (00:53)	0.22	(-0.09–0.52)	*0.173*	06:50 (00:56)	0.12	(-0.18–0.43)	*0.425*	88.43 (4.42)	0.18	(-0.12–0.48)	*0.230*	1.77 (1.13)	−0.02	(-0.30–0.26)	*0.887*	0.83 (0.07)	−0.06	(-0.34–0.22)	*0.655*	0.35 (0.10)	−0.10	(-0.39–0.19)	*0.517*
Unspecified	03:28 (01:01)	**0.13**	**(0.03–0.23)**	***0.011***	06:46 (00:59)	0.04	(-0.06–0.14)	*0.453*	87.38 (4.90)	0.04	(-0.06–0.13)	*0.458*	1.66 (1.02)	−0.08	(-0.17–0.01)	*0.071*	0.83 (0.06)	−0.08	(-0.17–0.01)	*0.094*	0.35 (0.09)	−0.07	(-0.16–0.03)	*0.160*
Model 4																								
Current MDD subtypes																								
Atypical	03:54 (01:19)	**0.53**	**(0.24–0.81)**	***<.001***	06:49 (01:10)	0.16	(-0.12–0.45)	*0.251*	86.84 (4.92)	−0.06	(-0.33–0.22)	*0.689*	1.68 (0.97)	−0.06	(-0.31–0.20)	*0.657*	0.82 (0.06)	−0.13	(-0.39–0.13)	*0.324*	0.33 (0.09)	**−0.28**	**(-0.55-(−) 0.01)**	***0.043***
Melancholic	03:20 (01:04)	−0.02	(-0.31–0.26)	*0.865*	06:51 (01:08)	0.13	(-0.15–0.41)	*0.367*	86.62 (5.59)	−0.12	(-0.40–0.15)	*0.382*	1.73 (1.04)	−0.04	(-0.30–0.22)	*0.740*	0.82 (0.08)	−0.20	(-0.47–0.06)	*0.126*	0.36 (0.10)	0.06	(-0.21–0.33)	*0.676*
Unspecified	03:32 (01:05)	0.18	(-0.04–0.40)	*0.110*	06:53 (01:06)	0.15	(-0.07–0.37)	*0.177*	86.63 (5.35)	−0.13	(-0.35–0.08)	*0.218*	1.53 (1.00)	**−0.21**	**(-0.41-(−) 0.01)**	***0.036***	0.82 (0.06)	−0.18	(-0.39–0.02)	*0.071*	0.36 (0.09)	−0.02	(-0.23–0.19)	*0.869*
Remitted MDD subtypes																								
Atypical	03:26 (00:51)	0.08	(-0.09–0.24)	*0.383*	06:43 (00:59)	0.00	(-0.16–0.17)	*0.960*	87.40 (5.89)	0.00	(-0.16–0.17)	*0.962*	1.55 (0.82)	**−0.18**	**(-0.34-(−) 0.03)**	***0.017***	0.83 (0.05)	−0.04	(-0.19–0.12)	*0.652*	0.35 (0.09)	−0.13	(-0.29–0.03)	*0.114*
Melancholic	03:19 (00:56)	0.01	(-0.12–0.15)	*0.861*	06:45 (00:56)	−0.00	(-0.13–0.13)	*0.989*	87.80 (5.21)	0.09	(-0.04–0.22)	*0.181*	1.58 (0.85)	**−0.20**	**(-0.33-(−) 0.08)**	***0.001***	0.83 (0.06)	−0.12	(-0.24–0.00)	*0.055*	0.35 (0.09)	−0.11	(-0.23–0.02)	*0.102*
Combined	03:35 (00:53)	0.22	(-0.09–0.53)	*0.168*	06:50 (00:56)	0.13	(-0.18–0.43)	*0.414*	88.43 (4.42)	0.18	(-0.12–0.48)	*0.240*	1.77 (1.13)	−0.02	(-0.30–0.26)	*0.890*	0.83 (0.07)	−0.07	(-0.35–0.21)	*0.644*	0.35 (0.10)	−0.09	(-0.39–0.20)	*0.523*
Unspecified	03:27 (01:00)	**0.12**	**(0.02–0.23)**	***0.021***	06:45 (00:58)	0.02	(-0.08–0.13)	*0.682*	87.50 (4.82)	0.06	(-0.04–0.17)	*0.230*	1.68 (1.02)	−0.06	(-0.16–0.03)	*0.203*	0.83 (0.06)	−0.06	(-0.16–0.03)	*0.204*	0.36 (0.09)	−0.08	(-0.17–0.02)	*0.137*
VARIABILITY																								
No MDD	00:58 (00:37)	REF.	–	–	01:08 (00:31)	REF.	–	–	5.50 (2.60)	REF.	–	–	0.65 (0.47)	REF.	–	–	0.06 (0.03)	REF.	–	–				
Model 1																								
Lifetime MDD	01:02 (00:44)	0.07	(-0.01–0.15)	*0.100*	01:13 (00:31)	**0.13**	**(0.04–0.21)**	***0.004***	5.34 (2.40)	−0.02	(-0.11–0.06)	*0.624*	0.62 (0.37)	−0.05	(-0.10–0.00)	*0.065*	0.06 (0.03)	**0.12**	**(0.04–0.21)**	***0.004***				
Model 2																								
Current MDD	01:04 (00:42)	0.06	(-0.09–0.22)	*0.428*	01:19 (00:33)	**0.31**	**(0.15–0.47)**	***<.001***	5.50 (1.90)	0.04	(-0.12–0.20)	*0.585*	0.62 (0.35)	−0.07	(-0.17–0.03)	*0.163*	0.06 (0.04)	**0.27**	**(0.11–0.43)**	***<.001***				
Remitted MDD	01:01 (00:44)	0.07	(-0.02–0.16)	*0.107*	01:12 (00:31)	**0.09**	**(0.01–0.18)**	***0.035***	5.31 (2.49)	−0.03	(-0.12–0.06)	*0.472*	0.63 (0.37)	−0.05	(-0.10–0.01)	*0.097*	0.06 (0.03)	**0.10**	**(0.01–0.18)**	***0.026***				
Model 3																								
Lifetime MDD subtypes																								
Atypical	00:59 (00:35)	−0.02	(-0.17–0.12)	*0.748*	01:12 (00:28)	0.08	(-0.08–0.23)	*0.330*	5.24 (2.28)	−0.07	(-0.22–0.08)	*0.373*	0.64 (0.37)	0.02	(-0.07–0.11)	*0.662*	0.06 (0.03)	0.13	(-0.02–0.28)	*0.081*				
Melancholic	01:01 (00:42)	0.08	(-0.05–0.20)	*0.215*	01:12 (00:32)	0.12	(-0.01–0.25)	*0.070*	5.45 (2.62)	0.03	(-0.09–0.16)	*0.612*	0.60 (0.34)	**−0.08**	**(-0.16–0.00)**	***0.047***	0.06 (0.03)	**0.17**	**(0.05–0.30)**	***0.007***				
Combined	01:08 (01:12)	0.20	(-0.11–0.50)	*0.203*	01:13 (00:22)	0.09	(-0.22–0.40)	*0.550*	5.11 (1.57)	−0.11	(-0.42–0.20)	*0.473*	0.61 (0.36)	**−0.19**	**(-0.39–0.00)**	***0.046***	0.05 (0.03)	0.05	(-0.25–0.35)	*0.744*				
Unspecified	01:02 (00:44)	0.09	(-0.01–0.19)	*0.084*	01:13 (00:32)	**0.15**	**(0.05–0.25)**	***0.004***	5.33 (2.38)	−0.03	(-0.13–0.07)	*0.579*	0.63 (0.38)	−0.05	(-0.11–0.02)	*0.137*	**0.06 (0.03)**	**0.10**	**(0.00–0.20)**	***0.049***				
Model 4																								

(*continued on next page*)

Table 2 (*continued*)

VARIABILITY																				
Current MDD subtypes																				
Atypical	01:04 (00:31)	0.01	(-0.27–0.29)	*0.940*	01:23 (00:27)	**0.43**	**(0.14–0.71)**	***0.004***	5.42 (1.77)	−0.00	(-0.29–0.28)	*0.978*	0.69 (0.35)	0.05	(-0.13–0.23)	*0.562*	0.07 (0.03)	**0.33**	**(0.05–0.61)**	***0.021***
Melancholic	00:59 (00:30)	−0.06	(-0.34–0.22)	*0.689*	01:16 (00:33)	0.23	(-0.06–0.52)	*0.115*	5.62 (2.42)	0.10	(-0.19–0.38)	*0.515*	0.59 (0.28)	**−0.22**	**(-0.40-(−)0.04)**	***0.016***	0.06 (0.04)	**0.29**	**(0.01–0.57)**	***0.044***
Unspecified	01:06 (00:52)	0.16	(-0.06–0.38)	*0.151*	01:18 (00:35)	**0.28**	**(0.06–0.50)**	***0.013***	5.48 (1.64)	0.04	(-0.18–0.26)	*0.726*	0.59 (0.38)	−0.06	(-0.19-(−)0.08)	*0.413*	0.06 (0.04)	**0.22**	**(0.01–0.44)**	***0.043***
Remitted MDD subtypes																				
Atypical	00:58 (00:36)	−0.04	(-0.20–0.13)	*0.671*	01:08 (00:27)	−0.03	(-0.20–0.14)	*0.736*	5.18 (2.43)	−0.09	(-0.26–0.08)	*0.313*	0.62 (0.37)	0.01	(-0.10–0.11)	*0.864*	0.06 (0.03)	0.07	(-0.09–0.24)	*0.377*
Melancholic	01:01 (00:43)	0.11	(-0.03–0.24)	*0.123*	01:11 (00:31)	0.10	(-0.4–0.24)	*0.152*	5.42 (2.65)	0.02	(-0.11–0.16)	*0.747*	0.60 (0.36)	−0.05	(-0.14-(−)0.03)	*0.206*	0.06 (0.03)	**0.15**	**(0.02–0.29)**	***0.026***
Combined	01:08 (01:12)	0.20	(-0.11–0.50)	*0.204*	01:13 (00:22)	0.10	(-0.21–0.41)	*0.531*	5.11 (1.57)	−0.11	(-0.42–0.20)	*0.480*	0.61 (0.36)	**−0.20**	**(-0.39–0.00)**	***0.045***	0.05 (0.03)	0.05	(-0.25–0.36)	*0.727*
Unspecified	01:01 (00:43)	0.07	(-0.03–0.18)	*0.157*	01:12 (00:31)	**0.13**	**(0.02–0.23)**	***0.018***	5.30 (2.48)	−0.04	(-0.14–0.07)	*0.475*	0.64 (0.38)	−0.05	(-0.11–0.02)	*0.162*	0.06 (0.03)	0.08	(-0.02–0.18)	*0.124*

Abbreviations: Est, Estimate; CI, Confidence Interval; MDD, Major Depressive Disorder; MVPA, Moderate-to-vigorous Physical Activity. Models are adjusted for age, sex, anxiety disorders, body mass index and current smoking. Standardaized effect sizes are provided. For the models with MVPA variability as dependent variable, models were further adjusted for average MVPA levels. Statistically significant results are in bold. p-values are in italic.

[a] Linear regression models.

with BMI (2.9%) and MeS (1.2%). When intra-individual average of MVPA was added (Models 3), we found a more pronounced decrease in the sizes of the associations of lifetime atypical MDD with BMI (10.9%) and MeS (7.8%). In contrast, adding intra-individual average of IS to the model (Models 4), did not affect the effect sizes of the associations of lifetime atypical MDD with BMI and MeS. After simultaneously adding the intra-individual averages of sleep midpoint, MVPA and IS (Models 5), the effect sizes of the associations of lifetime atypical MDD with BMI (12.1%) and MeS (7.2%) only slightly decreased as compared to the models adjusted for the intra-individual average of MVPA alone. However, in Model 5 the intra-individual averages of sleep midpoint, MVPA and IS remained significantly associated with BMI, whereas only the intra-individual average of MVPA and IS revealed a significant association with MeS.

4. Discussion

The present study is the first to establish the associations between MDD and its subtypes with actigraphy-derived sleep, physical activity and circadian rhythm measures and to investigate the potential mediating role of sleep, physical activity and circadian rhythms in the well-established associations of the atypical MDD subtype according to DSM-IV criteria with BMI and MeS in the community. The main findings were that: (1) Current but also remitted MDD and its subtypes are associated with several actigraphy-derived variables including later sleep midpoint, decreased physical activity, lower stability of activity rhythm, lower balance of rest-activity status, and larger intra-individual variability of sleep duration; and (2) both later sleep midpoint and low physical activity, but not higher stability of activity rhythm are partial statistical mediators of the association between lifetime atypical MDD and BMI, whereas only low physical activity is a partial mediator of the association between lifetime atypical MDD and MeS.

4.1. Associations between MDD and MDD subtypes with actigraphy measures

Our observation that MDD is associated on the person's average level with later sleep midpoint and with increased sleep duration variability, but not with other sleep characteristics, partially contrasts with the results of a recent meta-analysis of population-based studies that among older adults also found bi-directional associations of depression with insomnia, poor sleep quality and sleep complaints (Bao et al., 2017). However, only two studies included in this meta-analysis were based on objective sleep measures. Although sleep midpoint was not studied in this meta-analysis, two recent studies supported associations between depression and sleep midpoint. Indeed, a population-based study including older adults using self-reported measures for both depressive symptoms and sleep revealed an association between a later sleep midpoint and more severe depressive symptoms (Lin et al., 2021). Moreover, a two-sample Mendelian randomization analysis relying on objective sleep measures provided evidence for a causal relationship between morning preference chronotype, which is likely to be related to early sleep midpoint, and a lower risk of depression (Daghlas et al., 2021). Up to this day, few studies have addressed the heterogeneity of depression (Cai et al., 2020) in relation to sleep measures and to the best of our knowledge, only the Dutch NESDA study used objective sleep measures (Difrancesco et al., 2021). However, the depression subtyping in the NESDA study relied on three factor-analytically derived symptom dimensions and not on MDD subtypes according to DSM-IV, which makes it difficult to compare the results of the NESDA study to ours. Whereas in our study associations with late sleep midpoints were restricted to the atypical and unspecified subtypes, in the NESDA study all three depression dimensions were linked to this sleep characteristic. The NESDA study further revealed an association between the somatic/vegetative dimension of depression, which is the closest to atypical depression, and a longer sleep duration. Surprisingly, we did no find an

Table 3
Association of lifetime atypical major depressive disorder with BMI and the MeS before and after adjustment for sleep midpoint and MVPA (n = 2317).

			BMI			MeS		
			Est[a]	95% CI	*p*-value	OR[a]	95% CI	*p*-value
Model 1		**Atypical MDD**	**2.39**	**(1.69–3.09)**	***<.001***	**1.66**	**(1.16–2.38)**	***0.005***
Average	**Model 2**	**Atypical MDD**	**2.32**	**(1.61–3.02)**	***<.001***	**1.64**	**(1.14–2.34)**	***0.007***
		Sleep midpoint	**0.33**	**(0.15–0.53)**	***<.001***	1.07	(0.97–1.18)	*0.149*
	Model 3	**Atypical MDD**	**2.13**	**(1.44–2.82)**	***<.001***	**1.53**	**(1.06–2.20)**	***0.022***
		MVPA	**−1.05**	**(-1.25-(−)0.85)**	***<.001***	**0.56**	**(0.48–0.64)**	***<.001***
	Model 4	**Atypical MDD**	**2.39**	**(1.68–3.09)**	***<.001***	**1.67**	**(1.17–2.39)**	***0.005***
		IS	−0.02	(-0.22–0.19)	*0.874*	1.03	(0.92–1.14)	*0.626*
	Model 5	**Atypical MDD**	**2.10**	**(1.41–2.79)**	***<.001***	**1.54**	**(1.07–2.22)**	***0.020***
		Sleep midpoint	**0.28**	**(0.09–0.47)**	***0.003***	1.05	(0.95–1.16)	*0.349*
		MVPA	**−1.08**	**(-1.29-(−)0.87)**	***<.001***	**0.54**	**(0.47–0.63)**	***<.001***
		IS	**0.26**	**(0.06–0.47)**	**0.013**	**1.15**	**(1.02–1.28)**	**0.017**

Abbreviations: BMI, Body Mass Index; Est, Estimate; OR: Odd Ratio; CI, Confidence Interval; IS, Interdaily Stability; MeS, Metabolic Syndrome; MVPA, Moderate-to-vigorous Physical Activity; MDD, Major Depressive Disorder.
Model 1: adjusted for sex, age and current smoking, melancholic, combined and unspecified major depressive disorders.
Model 2: Model 1 further adjusted for sleep midpoint.
Model 3: Model 1 further adjusted for moderate-to-vigorous physical activity (MVPA).
Model 4: Model 1 further adjusted for Interdaily Stability (IS).
Model 5: Model 1 further adjusted for sleep midpoint, MVPA and IS.
Statistically significant results are in bold. p-values are in italic.
[a] Linear regression models for BMI, and logistic regression models for the MeS. Standardized effect sizes are provided.

association between the atypical subtype and the intra-individual sleep duration even in those who were in a current episode at the time of the actigraphy measure, although hypersomnia is part of the criteria for atypical depressive episodes. In line with our findings, however, were those of previous research based on self-reported measures for chronotype that revealed a link between atypical depression and an evening preference, which is likely to be associated with a later sleep midpoint (Meliska et al., 2011). Our observed associations between atypical MDD and both a later sleep midpoint and increased variability of sleep duration were restricted to current episodes suggesting that these associations are state dependent. It is therefore unlikely that late sleep midpoint or an increased variability in sleep duration are a predisposing factor for the atypical MDD subtype. In contrast, the association between unspecified MDD and late sleep midpoint was also manifest in remitted participants indicating that late sleep midpoint could be a consequence of or a pre-existing risk factor for this type of MDD. To our knowledge, no previous studies have separately examined the associations between current and remitted depression subtypes with sleep midpoint and duration. One previous study showed an association between self-reported sleep disturbances with both the current and the remitted states of MDD in patients with mild cognitive impairment, suggesting that sleep disturbances might be a trait marker for MDD (Naismith et al., 2011). Future studies using objective measures for sleep in association with MDD subtypes are needed to replicate our findings.

Regarding activity levels, we observed an association between the lifetime overall MDD category and MVPA, which is in line with previous evidence showing depression to be linked with higher levels of sedentary behavior (Choi et al., 2019; Schuch et al., 2017), but also in term of reduced within-person variability. Moreover, the lifetime and remitted atypical and melancholic subtypes, as well as the current unspecified subtype were associated with lower levels of MVPA, which corroborates findings of the NESDA study revealing associations of all three depression symptom dimensions with objectively measured low levels of physical activity (Difrancesco et al., 2021).The melancholic subtype was not only associated with lower MVPA levels, but also with lower MVPA variability. The association of the current atypical and melancholic subtypes with lower levels of MVPA observed in remitted people, suggests that low levels of activity may be a trait marker in people with these MDD subtypes. In contrast to people with atypical and melancholic MDD, those with unspecified MDD only revealed low levels of activity during current depressive episodes suggesting state-dependence of this association.

Concerning circadian rhythms, the observed association of MDD with a lower person's difference between the most and the least active hours of a day corroborates findings on data of the UK Biobank (Lyall et al., 2018). Moreover, our observation that the association of MDD with low RA was restricted to people with current depressive episodes is consistent with Geoffroy et al. (2018), who suggested that RA could be influenced by current depressive symptoms. Among the MDD subtypes, only the melancholic subtype was significantly associated with low RA. Interestingly, the overall MDD category as well as all current subtypes were significantly associated with larger variability in RA. We also found MDD to be associated with low IS, which is in line with findings of at least two other cross-sectional population-based studies that revealed lower stability of rhythms with greater severity of depressive symptoms (Luik et al., 2015; Rykov et al., 2021). Our additional observation that current but not the remitted atypical subtype was associated with low IS, suggests that this instability may be limited to the depressive episode.

4.2. Sleep, physical activity and circadian rhythm as potential mediators of the associations of atypical MDD with BMI and MeS

Among the three measures associated with lifetime atypical MDD both later sleep midpoint and lower MVPA, but not IS were also significantly associated with BMI. Regarding MeS, only lower MVPA but not later sleep midpoint or IS, was significantly associated with this syndrome. Genome-wide association studies suggested that the associations of later sleep midpoint with BMI could at least partially be explained by common genetic vulnerability (Dashti and Ordovas, 2021). The established association of higher MVPA levels with decreased likelihood of BMI and MeS was expected and is in line with previous studies that assessed physical activity (Fiuza-Luces et al., 2018) or sedentary behavior (Duran et al., 2022).

The association of later sleep midpoint with BMI as well as those of low MVPA with BMI and the MeS remained all significant in the fully adjusted model. In these models also atypical MDD remained significantly associated with both BMI and MeS, although the effect sizes of the associations moderately decreased.

The observed significant associations of later sleep midpoint, and low levels of MVPA with both lifetime atypical MDD and BMI, as well as the still significant association of atypical MDD with BMI after adjusting the model for either sleep midpoint and low MPVA are compatible with partial statistical mediation of the association between lifetime atypical MDD and BMI by sleep midpoint and MVPA according to the criteria of

Baron and Kenny (1986). Considering that the association between atypical MDD and a later sleep midpoint was restricted to current depressive episodes, and given the generally rather short duration of these episodes, the attenuation of only 2.9% of the size of the association between lifetime atypical MDD and BMI after adjustment for sleep midpoint was not surprising. Given that obstructive sleep apnea has been shown to be associated with obesity in our own study (Hausler et al., 2019), and that it has been shown in one study that it may also be associated with morningness (Kim et al., 2015), we could hypothesize that this sleep disorder also might be involved in the attenuation of the association between lifetime atypical MDD and BMI.

Compared to sleep midpoint, MVPA was a stronger mediator of this association, which is likely to be attributable to the fact that the association between atypical MDD and low physical activity was not restricted to current episodes but mainly observed in people with remitted episodes. The observed significant associations of low levels of MPVA with both lifetime atypical MDD and MeS, as well as the still significant association of atypical MDD with MeS after adjusting the model for MPVA are again compatible with partial mediation of the association of lifetime atypical MDD with MeS by MPVA according to the criteria of Baron and Kenny (1986). However, the modest attenuation of 5–10% of the effect sizes after entering sleep midpoint and MPVA into the model also indicates that most of the associations of atypical MDD with obesity and MeS is not explained by these sleep and activity variables.

Although low IS was significantly associated with lifetime atypical MDD, no mediating effect of this circadian characteristic could be found given that it was not associated with BMI or MeS.

4.3. Limitations

The present study has to be considered in the context of several limitations. First of all, the results are based on cross-sectional data that did not allow us to determine the causal direction of the observed associations. The lack of information on the temporal sequence of depression onset, alterations in sleep and MVPA, as well as CVRFs, make interpretation of the observed statistical mediation difficult. Atypical MDD may indeed favor lack of physical activity, which is a well-known risk factor for metabolic disorders (Duran et al., 2022; Fiuza-Luces et al., 2018). Conversely, low physical activity could predispose to atypical MDD, which has been shown to prospectively increase the risk of weight gain and the MeS (Lamers et al., 2013; Lasserre et al., 2014, 2017). Only prospective cohort studies with multiple assessments could determine the temporal sequence between the studied conditions and therefore confirm whether the lack of physical activity is indeed a partial mediator of the associations of atypical MDD with increase in BMI and the MeS. Second, because of the population-based design, the sample size varied across MDD subtypes. There were approximately five times as many participants who were in remission at the time of the physical exam as there were participants who were in a current episode, resulting in large differences in statistical power to detect associations with actigraphy-derived variables across diagnostic groups. Third, the sample was derived from an urban area of Switzerland, which may in part explain the high prevalence of MDD. Fourth, because of the age of our sample, the findings may not be generalizable to younger populations. Future studies should test whether the findings of our study can also be replicated in youth samples. Fifth, since our analyses were exploratory, we did not adjust our findings for multiple testing. Therefore, results are to be interpreted in this context.

4.4. Conclusions

Our findings confirm significant associations of MDD and its subtypes with objectively measured characteristics of sleep, physical activity and circadian rhythm. However, only physical activity was also associated with both BMI and MeS, whereas sleep-midpoint was only associated with BMI and inter-daily stability was not associated with these two metabolic variables. Analyses also provided evidence for partial statistical mediation of the associations of atypical MDD with BMI by sleep midpoint and physical activity, as well as for partial statistical mediation of the associations of atypical MDD with MeS by physical activity. The potential mediation of the link between atypical MDD with CVRFs by physical activity can only be considered suggestive due to the cross-sectional nature of these data. Although these findings need replication in prospective follow-up data, the observed associations of the atypical subtype of MDD with objectively assessed sleep and activity as well as independent associations of the atypical subtype, sleep and activity measures with BMI and MeS highlight the need to pay particular attention in clinical settings to the atypical subtype of MDD as well as to sleep disturbances and sedentary behavior as risk factors for CVRFs.

Author statement

Jennifer Glaus: Writing- Original draft preparation, Writing- Reviewing and Editing; **Sun Jung Kang**: Data curation; **Wei Guo**: Data curation, Software; **Femke Lamers**: Writing- Reviewing and Editing; **Marie-Pierre F Strippoli**: Data curation; **Andrew Leroux**: Writing- Reviewing and Editing; **Debangan Dey**: Writing- Reviewing and Editing; **Kerstin J Plessen**: Writing- Reviewing and Editing; **Julien Vaucher**: Writing- Reviewing and Editing; **Peter Vollenweider**: Conceptualization, Methodology, Writing- Reviewing and Editing; **Vadim Zipunnikov**: Writing- Reviewing and Editing; **Kathleen R Merikangas**: Supervision, Writing- Reviewing and Editing; **Martin Preisig**: Conceptualization, Methodology, Supervision, Writing- Reviewing and Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The Colaus|PsyColaus study is a core site of the mobile Motor Activity Research Activity Consortium for Health (mMARCH) Network coordinated by the National Institute of Health Intramural Research Program (ZIA MH002954). mMARCH team completed the data extraction, analyses and standardization of the administration of the mobile technology in the study. The Colaus|PsyColaus study was supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (grants 3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, 33CS30-148401, 33CS30_177535 and 3247730_204523) and the Swiss Personalized Health Network (project: Swiss Aging Citizen Reference).

The authors would like to express their gratitude to the Lausanne inhabitants who volunteered to participate in the CoLaus|PsyCoLaus study, and to the collaborators who contributed to the coordination of the study and the collection of data. The authors would like to thank also all the investigators of the CoLaus|PsyCoLaus study, in particular Prof. G. Waeber and Prof. P. Marques-Vidal.

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